Sreenivasa S. Jonnalagadda
Editor

Gastrointestinal Endoscopy

New Technologies and Changing Paradigms

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Preface

The art and science of gastrointestinal endoscopy is rapidly evolving and great strides have been made during the last decade. Initially introduced as a purely diagnostic tool, the endoscope has morphed into a conduit for tools with fascinating diagnostic and therapeutic applications. A deeper understanding of the pathophysiology of gastrointestinal diseases coupled with the changing epidemiology of diseases such as obesity and esophageal adenocarcinoma have stimulated this growth. As endoscopy transcends traditional boundaries, quantum leaps in imaging, power storage, wireless transmission and biomedical engineering, and advances in minimally invasive surgery have served as the foundation for fascinating improvements. Ultimately, patient preference for less invasive options to treat diseases traditionally in the surgical domain, and a desire to reduce morbidity and mortality arising from older management strategies have been at the heart of the gastrointestinal endoscopy revolution.

This comprehensive treatise on cutting edge tools and research provides a fascinating insight into the rapidly evolving field of diagnostic and therapeutic endoscopy. Accomplished international researchers and clinicians will discuss the latest endoscopic advances in diverse areas including obesity and associated metabolic syndromes, management of peripancreatic fluid collections, endoluminal suturing techniques, fistula closure, management of Barrett's epithelium, cholangioscopy, chromoendoscopy, high resolution manometry, and advances in endoscopic ultrasonography.

The authors aim to provide the reader with a comprehensive insight into the new endoscopic revolution that has captured the imagination of patients and physicians alike. This book encapsulates technologies that will leave an indelible mark on the evolving role of endoscopic management of gastrointestinal and metabolic diseases.

My family (Madhavi, Preeti, and Pallavi) has always encouraged my academic pursuits and shared the thrill of practicing cutting edge interventional endoscopy—I thank them for enjoying this exciting journey.

Sreenivasa S. Jonnalagadda, MD

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Barrett's Esophagus

Vijay Kanakadandi and Prateek Sharma

Introduction

Barrett's esophagus (BE) is defined as a condition of the esophagus, wherein the normal squamous mucosa of the distal esophagus is replaced by columnar epithelium with intestinal metaplasia [1–3]. It is a known complication of chronic gastro esophageal reflux disease (GERD). It is the only known premalignant condition that predisposes to the development of esophageal adenocarcinoma (EAC). Patients with Barrett's esophagus have 30–125 times the risk of developing EAC [4]. The diagnosis of BE requires the presence of endoscopic columnar lined esophagus proximal to the gastroesophageal junction and identification of intestinal metaplasia on biopsy. Endoscopic screening and surveillance of Barrett's esophagus is done to detect their progression to esophageal adenocarcinoma, a cancer with an abysmal 5-year survival of 15–20 % when detected late [5, 6].

Epidemiology and Risk Factors

The prevalence of Barrett's esophagus is higher in western countries when compared to Africa and Asia. In the west, prevalence of Barrett's in general population was estimated to be 1.3–5.6 % [7–9]. The prevalence of BE in patients with GERD is 10–15 % [10–12]. In China, BE was found in a 2.44 % of patients undergoing endoscopy in a review of published literature from 1989 to 2007 [13]. Two large prospective studies in Japan, Sendai Barrett's Esophagus Study (S-BEST) and the

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Far East Study (FEST), estimated the prevalence of BE to be 0.9–1.2% [14]. Data from Middle East and Africa are scarce. Reported rates of BE prevalence among patients referred for endoscopy range from 0.31% in Saudi Arabia to 10.6% in Sudan [15–17].

The known risk factors for Barrett's include GERD symptoms, age, male gender, Caucasian race, body mass index (BMI), waist circumference, and cigarette smoking. GERD was one of the earliest identified risk factors associated with Barrett's [18, 19]. Subsequent studies that showed association between Barrett's and GERD were not designed to estimate the risk in patients without GERD [20–22]. Further, up to 50% of the patients with esophageal adenocarcinoma do not have symptoms of reflux [23]. Therefore, the risk of Barrett's may not be as high as initially estimated. A recent meta-analysis estimated the odds of developing BE among patients with reflux symptoms to be 2.9, with the association being stronger with long segment Barrett's [24].

The prevalence of Barrett's esophagus increases with increasing age with a peak noted in the sixth decade of life [25, 26]. After adjusting for BMI, abdominal circumference and abdominal visceral adiposity have been found to be independent risk factors for Barrett's with the association being particularly strong with circumference greater than 80 cm [27–29]. In a large case-control series with 2502 participants, patients in the highest quartile of waist circumference were found to have 275% increase in the odds of developing BE [28]. It is postulated that increased intra-abdominal pressure that is seen with the increase in abdominal circumference may overcome the lower esophageal sphincter pressure and lead to increased reflux [30]. The association with BMI and Barrett's is weaker with some studies suggesting increased risk while others do not [31, 32]. A study based in northern California estimated the incidence of Barrett's to be the highest among nonHispanic whites (39/100,000 person years) followed by Hispanics (22/100,000), Asians (16/100,000), and Blacks (22/100,000) [25]. Several other studies have demonstrated increased risk of Barrett's among men with the estimated risk of developing Barrett's 1.5–2.6 times higher than women [25, 26, 33, 34]. Smoking has been associated with both Barrett's esophagus and esophageal adenocarcinoma. Both current and past smoking has been associated with Barrett's. Smokers have 1.67–2.41 times increased odds of developing Barrett's when compared to nonsmokers [35, 36]. Consumption of wine [37] and infection with H pylori [38] have been shown to decrease the risk of Barrett's.

Risk of Cancer in Barrett's Esophagus

Reflux of acid and bile results in inflammation of the distal esophagus. Immature squamous cells derived from stem cells replace damaged epithelium. Continued damage to stem cells induces differentiation into metaplastic columnar epithelium, also known as non-dysplastic Barrett's esophagus (NDBE), which is more resistant to refluxate. Mutations in p16, p53, and cyclin D are seen in low-grade dysplasia

(LGD) followed by aneuploidy, microsatellite instability and decreased apoptosis in high-grade dysplasia (HGD). Decreased cell to cell adhesion and migration leads to the development of esophageal adenocarcinoma (EAC) [39].

The risk of EAC among patients with NDBE has been estimated to be 0.1–0.33 % annually [40, 41]. Using a large Danish population-based registry, 11,028 patients were followed for a median of 5.2 years. After excluding prevalent cancers, 66 new EACs were detected yielding an incidence rate of 1.2 per 1000 person years or 0.12 % per year [40]. The relative risk of patients with BE developing EAC over general population was 11.3. In a subgroup analysis, the annual risk of patients with LGD was 0.51 % and NDBE was 0.1 %. The risk among those with Barrett's shorter than 3 cm has been estimated to be 0.19 % annually or 1 in 500 person years [41].

Due to poor interobserver agreement among pathologists in the diagnosis of LGD [42], the risk of EAC in this population is difficult to estimate. The pooled estimate in a large meta-analysis was 0.6 in 100 person years [43]. However, in a study where two expert pathologists confirmed the diagnosis, the risk was estimated at 1.2 per 100 person years [44]. In patients with HGD, the risk of concomitant EAC is 12.7 % [45] and the risk of progression to EAC is 6.6 per 100 person years [46].

Role of Endoscopy in the Diagnosis of Barrett's Esophagus

The diagnosis of Barrett's esophagus is made, when columnar epithelium with characteristic endoscopic appearance is found proximal to gastroesophageal junction and has intestinal metaplasia on pathology. The most widely accepted endoscopic landmark to detect the gastroesophageal junction is the most proximal extent of gastric folds [2, 3, 47]. Three types of columnar epithelia have been described at the gastroesophageal junction, gastric fundic, cardia, and intestinal. Intestinal metaplasia can be readily identified by the presence of goblet cells [48] and is the only type of metaplastic epithelium that has a known risk for progression to esophageal adenocarcinoma. Therefore, the intestinal metaplasia is considered a prerequisite for the diagnosis of Barrett's esophagus [2, 3].

Barrett's esophagus was classified as long segment and short segment based on the endoscopic extent (<3, ≥ 3 cm) of a visible columnar-lined esophagus. However, measuring the endoscopic maximal (M) and circumferential (C) extent of Barrett's esophagus is measured in centimeters, also known as the "Prague C & M criteria" is now currently recommended for all patients (Fig. 1) [49]. The Prague C and M criteria were found to have high validity among experts, Asian gastroenterologists who do not have extensive experience with Barrett's and gastroenterology trainees who were given a short educational course [49–51]. Visible lesions must be characterized by the Paris classification [52]. Endoscopically flat appearing mucosa can harbor dysplasia randomly distributed along the extent of Barrett's. Therefore, to detect dysplasia, rigorous and random sampling is necessary. One such protocol, "the Seattle protocol" is recommended for the diagnosis and surveillance of Barrett's esophagus. The protocol involves random four-quadrant biopsy every 1–2 cm

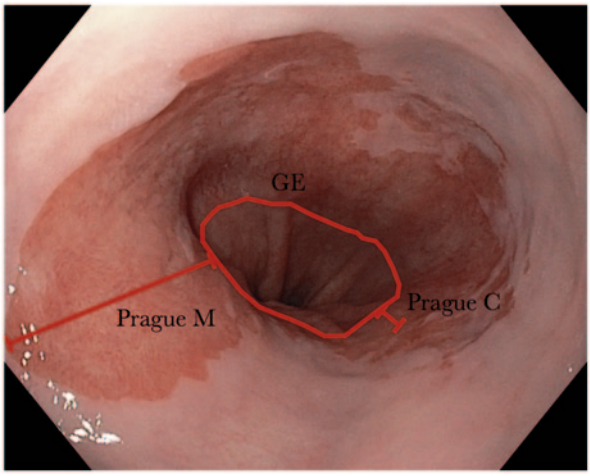

Fig. 1 Prague C and M criteria. Image demonstrates the gastroesophageal (*GE*) junction, Prague C and M measurements in BE

throughout the extent of columnar-lined esophagus in addition to biopsy of any visible lesions [3]. Systematic four-quadrant biopsy has shown to increase the yield of dysplasia by 13-fold [53] and a lack of adherence to such a protocol may lead to sampling error [54].

Role of Endoscopy in the Management of Barrett's Esophagus

Surveillance Endoscopy

Most published guidelines recommend endoscopic surveillance of BE. Surveillance for Barrett's is recommended on two grounds. One, to detect EAC in an early and curable stage; two, to improve overall mortality in EAC and BE patients. Although some studies have suggested that there is some benefit with surveillance; these are limited by lead-time and selection bias [55, 56]. Further, mortality among patients with Barrett's is equal to that of general population and most of them die from causes unrelated to EAC [57–59]. Presence of dysplasia requires confirmation with a second expert pathologist. Patients with no dysplasia undergo surveillance every 3–5 years, those with LGD every 6–12 months and those with HGD every 3 months if they do not undergo treatment (Fig. 2) [60–63].

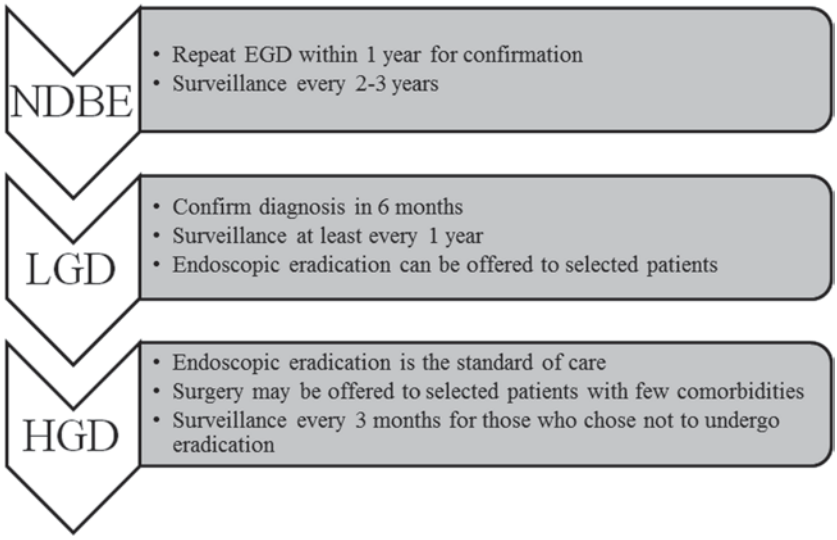

Fig. 2 Management algorithm for Barrett's esophagus

Advanced Imaging in Neoplasia Detection

High Definition White Light Endoscopy

Compared to the standard low-resolution endoscopes that produce images of 300,000 pixels, high definition white light endoscopy (HD-WLE) can produce images with 1 million pixels. They help in detecting the subtle mucosal and vascular changes that are not otherwise seen with standard endoscopes. They have now replaced low-resolution endoscopes as the standard of care. In a prospective multicenter study using a HD-WLE endoscope, inspecting the BE segment for longer time was associated with the increased detection of lesions suspicious for HGD/EAC [64]. Barrett's inspection time per centimeter correlated with detection of HGD and endoscopists with Barrett's inspection time (BIT) greater than 1 min/cm were more likely to detect visible lesions. HD-WLE alone has been shown to have a sensitivity of 79–85 % and is best used with another advanced imaging modality [65, 66].

Chromoendoscopy

Chromoendoscopy utilizes stains to visualize mucosal abnormalities that are not readily apparent. Lugol's iodine, acetic acid, and methylene blue have all been used as stains. Among these, methylene blue chromoendoscopy has been the most extensively studied. Light to absent staining and moderate to marked heterogeneity are associated with the presence of dysplasia [67]. While methylene-blue-directed biopsies

were found to be very sensitive for the detection of intestinal metaplasia, they did not improve overall yield of dysplasia or cancer [68–73]. Methylene-blue-directed biopsies were also found to have fewer yields when compared to random biopsies using Seattle protocol [74, 75].

Narrow-Band Imaging

Endoscopes that use narrow-band imaging (NBI) filter blue light corresponding to the absorption peaks of hemoglobin making the vascular pattern stand out in contrast to the mucosal pattern. NBI filters reflect light, and there is no need for adding dyes or intravenous contrasts, but the steep learning curve associated with it impedes widespread use. In a randomized crossover study, both HD-WLE and NBI detected the same number of patients with Intestinal metaplasia (IM), while NBI detected a greater number of patients with dysplasia and required a fewer number of biopsies [76, 77]. A pooled analysis of seven published studies showed that using NBI increased the yield of dysplasia detection in endoscopy by 34% [77]. Overall, the NBI has a sensitivity and specificity of 96 and 94% [78].

Autofluorescence Imaging

Certain endogenous molecules, such as collagen and elastin, known as fluorophores emit long-wavelength light when excited by shorter wavelength light. Autofluorescence imaging (AFI) utilizes this property and differentiates dysplastic epithelium from nondysplastic epithelium based on the differences in the intensities of their emitted light. The dysplastic epithelium is associated with decreased autofluorescence. Nondysplastic BE appears green while dysplastic BE appears blue or violet. Due to the range in color observed, standardized color scales have been used for the diagnosis [79]. It has been suggested that AFI be used as a broad field technique to mark areas that appear dysplastic. However, randomized crossover studies have shown a sensitivity of 40–60% and a high rate of false positives [65, 80]. To overcome this limitation, endoscopic trimodal imaging was performed. With this procedure, the esophagus was imaged using HD-WLE, followed by AFI. Visible lesion and abnormal areas were then further characterized by NBI. While adding AFI to HD-WLE led to the detection of increased number of patients and areas with dysplasia, NBI reduced the overall false positive rate [81, 82]. Again, these results were not seen in general practice [83].

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a technique that allows in vivo visualization of mucosa with up to 1000-fold magnification and to a depth of 250 μm. Intravenous sodium fluorescein is used as a contrast. It is available as a standalone

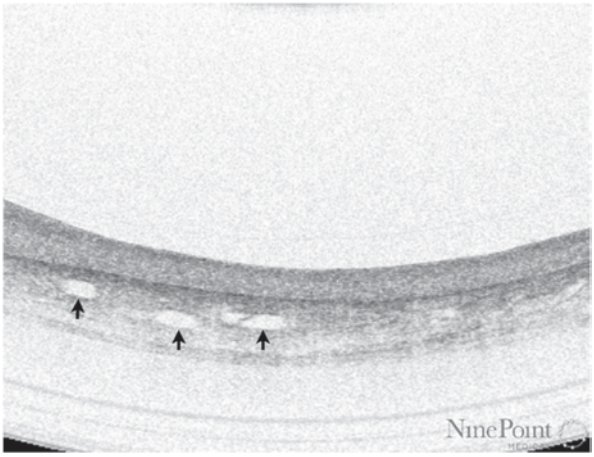

Fig. 3 Optical coherence tomography demonstrating submucosal glands (*arrows*)

endoscope (eCLE) or as a probe-based system (pCLE) that can be integrated into standard endoscopes. The eCLE endoscopes have a free working channel to take biopsies and the images produced are slightly higher in resolution, but the rate of acquiring images is slower. On the other hand, the pCLE system can be mounted on a regular endoscope and it produces more number of images, but the images produced are of lower resolution and the field of images produced is smaller. The prospective multi-center DONT BIOPCE trial demonstrated that pCLE was able to detect additional patients that were not detected by white light endoscopy or NBI [84]. The sensitivity of CLE ranges from 75–100 % and specificity from 83–98 % [85–89]. Using the Kansas city criteria for the diagnosis of dysplasia, after a short structured teaching session the combined accuracy of experts and nonexperts was 81 %, with a substantial inter-observer agreement ($\kappa = 0.61$) [90].

Optical Coherence Tomography

Optical coherence tomography (OCT) is a system similar to ultrasound, wherein the images are generated from magnitude of optical echoes detected from tissues. The advantage of OCT is, it provides real time images of esophagus up to a depth of 3 mm that would otherwise be undetectable by regular endoscopy (Fig. 3). The Nvision VLE™ imaging system (Nine Point Medical Inc., Cambridge, MA) uses an optical probe with a balloon at its distal end that is 25 mm wide and 6 cm long. The probe scans the portion of esophagus in contact with it over a period of 90 s and produces circumferential images with a resolution of 10 μm. An early pilot study demonstrated the feasibility of this technique [91]. A 1450 nm cautery marking laser light is integrated into the system, enabling visualization and marking of abnormal areas at the same time [92]. Diagnostic criteria for the detection of HGD/EAC have been shown to have a sensitivity of 83 % and specificity of 75 % [93].

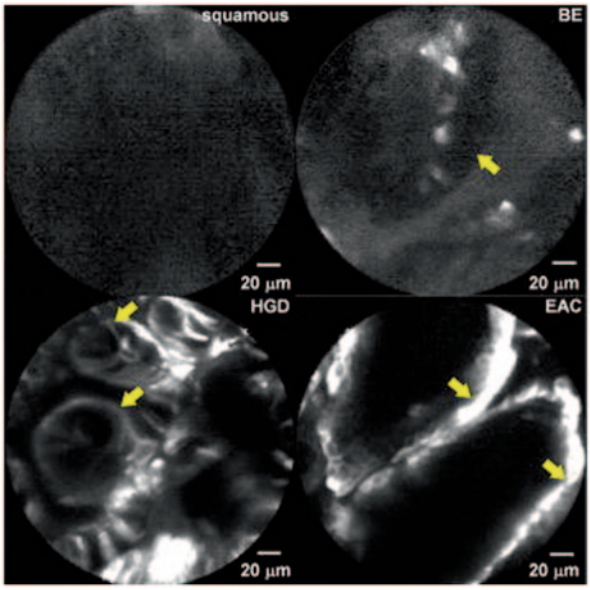

Fig. 4 Peptide-based imaging for Barrett's esophagus. Fluorescent imaging of squamous, nondysplastic Barrett's, high-grade dysplasia and esophageal adenocarcinoma

Investigational Imaging Techniques

Fluorescent tagged peptides and lectins are being used to mark dysplastic areas in the esophagus [94, 95]. Strum and colleagues used phage display technology to detect peptides that bind to EAC cells [94]. They isolated the peptide ASYNYDA that was found to have 5.3 times greater affinity for human H460 adenocarcinoma cells compared to non-neoplastic human Q-hTERT BE cells. The peptide was labeled with fluorophore FITC, and the fluorescent tagged peptide, now called ASY*-FITC was tested in ex-vivo specimens and human subjects. In resected esophageal specimens, the fluorescence intensities for HGD and EAC were found to be higher than NDBE and squamous epithelium (Fig. 4). The ASY*-FITC binding was tested in 25 subjects with the BE using confocal endomicroscopy. ASY*-FITC binding produced 3.8 times greater signal intensity for HGD and EAC compared to squamous epithelium and NDBE. A target-background (T/B) ratio was used to measure the intensity of fluorescence and a T/B ratio of 4.2 was found to have a sensitivity of 75% and specificity of 97% for the detection of neoplasia. Lectins are proteins that can bind to specific carbohydrate sequences. A progression from squamous epithelium to EAC is associated with the change in surface glycans. Using unsupervised clustering analysis, Bird-Lieberman et al. identified a group of lectins with high-binding affinity to squamous epithelium with progressively decreased binding to EAC [95]. One such lectin, the wheat germ agglutinin (WGA) was further tested in ex-vivo specimens. In the four resected esophagi, WGA fluorescence was associated with a degree of dysplasia with areas of HGD and EAC showing low WGA binding. The mean signal to background ratio for dysplasia was 5.2, compared to squamous epithelium enabling easy detection in the ex-vivo specimens.

Light incident on tissue is scattered due to vibration of the molecules it is composed of and causes a shift in the frequency of the scattered light. The change in the frequency of light differs with the composition of tissue and this property it utilized by Raman spectroscopy to differentiate neoplastic from non-neoplastic BE. Using confocal Raman spectroscopy, Bergholt et al. were able to differentiate HGD from LGD and NDBE with sensitivity of 87.0% (67/77), and a specificity of 84.7% (610/720) [96]. The performance characteristics of these techniques need to be evaluated in large population-based cohorts.

Role of Endoscopic Eradication Therapy in Dysplastic Barrett's Esophagus

Initially, the published surgical series reported rates of concomitant invasive cancer of 40% [97–99]. However, these studies did not use standardized criteria for cancer. Using strict criteria and definitions, the rate of invasive cancer is now estimated to be 5.58 per 100 patient years [46]. This has shifted the treatment approach away from esophagectomy that is associated with high operative morbidity and mortality in favor of endoscopic eradication therapy. The endoscopic eradication therapy of Barrett's is based on the premise that the removal of Barrett's epithelium using resection or ablation in conjunction with acid suppression results in replacement of columnar by "new" or neo-squamous epithelium. Described below are various methods used in ablation of Barrett's mucosa.

Multipolar Electrocoagulation

Multipolar electrocoagulation (MPEC) uses a thermal probe to ablate the squamous epithelium. The probe is placed in contact with the epithelium till the formation of white coagulum is observed. Multiple sessions are performed every 4–6 weeks till the entire Barrett's mucosa is ablated. Studies have demonstrated a reversal of Barrett's in 75–100% of patients [100–103].

Argon Plasma Coagulation

Argon plasma coagulation (APC) is a thermal coagulation method used to ablate Barrett's mucosa. The APC probe is passed down the biopsy channel and coagulation of the entire Barrett's mucosa is attempted if the length of BE is less than 3 cm. For longer segments of BE, 50% of circumferential mucosa is ablated to minimize the risk of stricture formation. Although complete ablation of Barrett's is reported initially, long-term eradication has been reported in 39–88% [100, 101, 104–109] with recurrence seen in up to 66% [106].

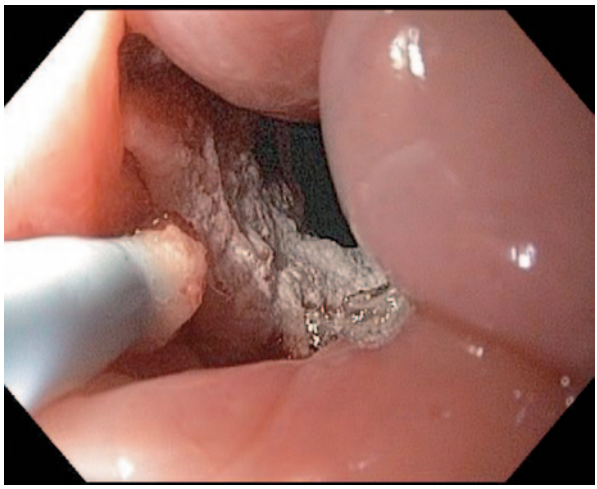

Fig. 5 Frost formed after cryotherapy

Photodynamic Therapy

Photodynamic therapy uses drugs that, upon exposure to light react with oxygen and produce tissue necrosis. These drugs are called photosensitizers and several compounds such as porphyrins, chlorins, benzoporphyrins, and pheophorbides have been used. They differ on their excitation wavelengths, absorption, clearance and skin photosensitivity. The light source has to deliver light uniformly to the entire tissue, which is a challenge given the peristalsis—movements associated with breathing and esophageal folds.

Cryotherapy

Cryotherapy involves rapidly freezing and slow thawing of tissues resulting in vascular thrombosis and ischemia. The two available devices use liquid nitrogen and carbon dioxide. The cryotherapy probe can be passed through the working channel of the endoscope. Low pressure liquid nitrogen (< 5 psi) at -196°C, or high pressure CO_2, (450–750 psi) is sprayed on the target tissue till a white frost is formed (Fig. 5) [110, 111]. The treatment is applied in doses ranging from two cycles of 20 s each to four cycles of 10 s. The treatment is repeated every 4–8 weeks till there is no evidence of residual BE [112, 113]. In a multi-center retrospective review, 98 patients with HGD were treated with cryotherapy for a mean 3.4 sessions per patient [114]. Sixteen patients completed the therapy, 58 (97%) had complete eradication of HGD, 52 (87%) had complete eradication of dysplasia and 34 (57%) had complete eradication of all intestinal metaplasia after follow up of 10.5 months. Other studies have reported a complete eradication of dysplasia in 78–96% of the cases [110, 112–116].

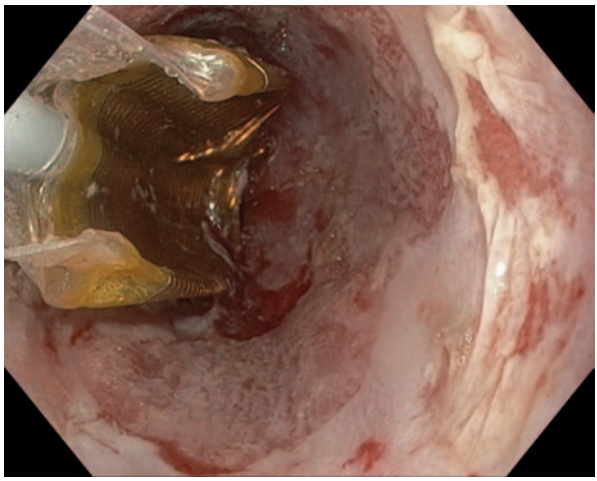

Fig. 6 Barrx™ 360 balloon (deflated) used for radiofrequency ablation in Barrett's esophagus

Radiofrequency Ablation

Radiofrequency energy can be delivered to the esophageal mucosa using a balloon that has electrodes mounted on it. A preset amount of energy can be delivered controlling the depth to which the tissue damage is limited. A soft sizing balloon is used to measure the diameter of the esophagus and a balloon device with a 3 cm mounted electrode is used to ablate 3 cm segments of BE. The circumferential ablation balloon (Barrx™ 360) is available in sizes of 18, 22, 25, 28, and 31 mm (Fig. 6). The procedure is repeated every 3 cm till the entire BE segment is ablated. A plastic cap at the end of facilitates cleaning of debris and tissue. Paddle-like electrodes that are mounted on the distal end of endoscope are available, if ablation of only a small region needs to be ablated. The Barrx™ 90 and 60 have electrodes sized 20 × 13 mm and 15 × 10 mm. An ultra-long (40 × 30 mm) catheter and a through-the-scope catheter 7.5 × 15.7 mm are also available.

The landmark Ablation of Intestinal Metaplasia (AIM) containing Dysplasia established radiofrequency ablation (RFA) as the preferred method of choice for eradicating dysplasia [117]. In this study, 127 patients with dysplasia were randomized to receive either RFA or sham therapy in a 2:1 ratio. Complete eradication of dysplasia was seen in 81% of patients with HGD and 91% of patients with LGD compared to 19% and 22% respectively seen in sham groups. At the end of 1-year follow-up of esophageal cancer developed in 19% of the sham group compared to 1% in the ablation group. After 3 years, dysplasia was eradicated in 98% and intestinal metaplasia in 91% of the patients [118]. Studies have reported rates of complete eradication of dysplasia ranging from 74–96% and the median time to eradication to be 22 months [117, 119–126]. Predictors of poor response to RFA include active reflux esophagitis, regeneration of endoscopic resection with BE, esophageal narrowing before RFA and years of neoplasia before RFA. However, recent reports indicate recurrence rates of up to 33% with dysplasia found in 22% of

those with recurrence [126, 127]. Factors such as longer BE segment, advanced age, and dysplasia have been found to be predictors of recurrence [126, 127]. Strictures seen in about 6 % of patients are the most common adverse event followed by pain (3 %) and bleeding (1 %) [126, 128].

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is a snare-based technique that involves mucosal excision. It is used both for diagnostic and therapeutic purposes. EMR is better at diagnosing the depth of invasion than endoscopic ultrasound and has better inter-observer agreement among pathologists than biopsy specimens [129]. Although EMR is currently recommended for visible lesions, almost a third of patients with HGD have change in their diagnosis irrespective of whether visible lesions were present [130]. EMR of visible lesions followed by RFA of the rest of the Barrett's epithelium used for resection led to the complete eradication of dysplasia in up to 100 % of the patients [121, 131]. Stepwise EMR can be done to completely eradicate dysplasia. In a prospective single-center study based in Germany, 349 patients with HGD were enrolled to undergo endoscopic resection [132]. Out of these, 337 (97 %) patients showed complete response and after a median follow up of 62 months, 330 (95 %) remained disease free. Other studies reported eradication rates of 97–100 % in patients undergoing this procedure [132–136]. Bleeding and perforation are seen in 1–3 % of patients and esophageal strictures are seen in up to 40 % of the patients.

Management of Nondysplastic Barrett's Esophagus

All patients with nondysplastic BE are enrolled into a surveillance program with endoscopies performed every 2–3 years (Fig. 2). Lack of a clear evidence of benefit, low rates of progression, increased costs, recurrent disease, and risks associated with treatment argue against endoscopic eradication of BE in this subgroup.

Management of Low-Grade Dysplasia

The management of patients with low-grade dysplasia is complicated by several factors. There is a significant variability in the diagnosis of low-grade dysplasia, even among expert gastrointestinal pathologists. The progression to EAC is variable and there is no evidence to suggest that endoscopic eradication prevents or reduces progression to EAC. The long-term durability of endoscopic treatment is unknown with a recent radiofrequency ablation registry study demonstrating a recurrence of 28 % [127]. A cost-utility analysis demonstrated that endoscopic eradication can be cost-effective if ablation of continued surveillance were not necessary [137]. However, the SURveillance vs. RadioFrequency ablation (SURF) study, a

randomized controlled trial where patients with LGD confirmed by two expert pathologists underwent either RFA or surveillance, showed complete eradication of dysplasia or intestinal metaplasia in 98 % of patients in the RFA arm with decreased rates of progression in the RFA arm (1.5 % versus 20.6 %) [138]. Therefore, the treatment of LGD is a moving target at this stage. In the absence of long-term data, surveillance is recommended with ablation reserved as a therapeutic option to be discussed with the patients. Rigorous surveillance with four-quadrant biopsy must be performed in all patients to detect early HGD/EAC.

Management of High-Grade Dysplasia

Due to the high rates of progression and prevalent EAC [45, 46], endoscopic eradication is recommended for patients with high-grade dysplasia. The recommended approach in patients with high-grade dysplasia is the removal of visible lesions using endoscopic mucosal resection followed by radiofrequency ablation of all visible Barrett's epithelium. Patients who have undergone eradication are enrolled into surveillance programs to detect recurrence of intestinal metaplasia or dysplasia. Due to the high efficacy of radiofrequency ablation, esophagectomy is now rarely used for patients with high-grade dysplasia. Most modern studies report an acceptable operative mortality of less than 5 % [139–146]. The advantages of esophagectomy include removal of the entire esophagus at the risk of developing recurrent dysplasia obviating the risk of sub-squamous metaplasia and removal of lymph nodes to which invasive cancer may have spread. This procedure must be therefore reserved for individuals with fewer comorbidities reducing the risk of perioperative mortality and complications.

Complications of Endoscopic Therapy

Strictures

This is the most common complication following endoscopic eradication therapy. Strictures are most commonly seen following EMR in 30–50 % of the patients [133–136]. The length of BE determines the risk of stricture formation; therefore, it is recommended that complete mucosal resection be reserved as a method for those with BE length less than C3 M5. Following RFA, strictures are seen in 5 % of the patients with higher rates reported in the series that used EMR in combination with RFA [118–124, 131]. Cryotherapy carries a 10 % risk of strictures while other modalities such as APC and MPEC carry a 2–3 % risk [114–116]. Esophageal strictures can easily be treated with balloon or bougie dilation.

Perforation and Bleeding

Perforation and bleeding are acute complications that are seen in the first 48 h. They are seen in about 1% of patients undergoing EMR and less than 1% of patients undergoing endoscopic therapies. Most of the patients with these complications can be managed appropriately. Death as a result of these or other endoscopic therapies is exceedingly rare.

Subsquamous Intestinal Metaplasia

Subsquamous intestinal metaplasia (SSIM) also known as buried Barrett's is the presence of intestinal metaplasia under squamous epithelium. It was previously assumed that this represented residual Barrett's epithelium over which squamous epithelium had grown following ablation. However, we now know that SSIM is present in patients before eradication. In the AIM dysplasia trial [117] and another study using EMR for eradication, they were found in a fourth of all patients [147]. However, since they are not detectable using most of the endoscopic techniques and due to the fact that our biopsies are inadequate in depth and orientation, we may be underestimating the true prevalence [148]. Recent reports have indicated that similar to surface metaplasia, SSIM has malignant potential and need to be carefully evaluated [149, 150]. 3D-optical-coherence tomography is one technique that allows visualization of esophageal mucosa up to a depth of 3 mm. Using this technique, one series demonstrated that SSIM can be seen in 72% of the patients before and 63% of the patients after ablation [151]. Further refinements in this technology as well as biopsy technique are necessary to explore this condition further.

Future Direction

Although endoscopic eradication has largely replaced surgical therapy for the treatment of HGD in BE, long-term data demonstrating efficacy at 5–10 years is lacking. We also do not know if endoscopic eradication will lead to reduction in the incidence of invasive cancer. Advanced imaging techniques such as fluorescent-tagged peptides and lectins need to be validated in large population-based cohorts. Biomarker panels are being developed to detect patients at the risk of progressing to EAC. Hypermethylation of CpG island promoter region has been shown to be associated with neoplastic progression in BE. Jin et al. performed a retrospective, double-blinded evaluation of methylation of eight genes (p16, HPP1, RUNX3, CDH13, TAC1, NELL1, AKAP12, and SST) to identify patients who progressed to dysplasia [152]. The combined eight-gene panel had an area under the receiver-operating curve (AUROC) of 0.840. Similarly, Avli et al. identified a hypermethylated four-gene panel (SLC22A18, PIGR, GJA12, and RIN2), and validated in both

retrospective and prospective cohorts. The four-gene panel had an AUROC of 0.988 with a sensitivity of 94% and specificity of 97%. Deoxyribonucleic acid (DNA)-based fluorescent in situ hybridization (FISH) is also being used to predict progression of BE. Using FISH analysis of brush biopsy specimens from BE patients, Her2/Neu, c-Myc, and 20q13.2 overexpression and aneuploidy of chromosomes 7 and 17 were used to differentiate HGD/EAC patients from NDBE [153]. A combination of these biomarkers was found to have an AUROC of 0.90 with a sensitivity of 88% and specificity of 100%. These panels are yet to be incorporated into routine clinical use.

Finally, genome wide association studies have identified 5 SNP loci associated with BE and EAC at 19p13, 9q22.32, 3p13, 16q24 and 6p21. These studies indicate significant polygenic overlap between EAC and BE [154, 155]. Further research in this area will provide insight into the development of BE and EAC.

Summary

The BE is a premalignant condition of the esophagus that leads to the development of esophageal cancer. It is seen in older Caucasian males with a large waist to hip ratio who smoke. It progresses through stages of NDBE, LGD and HGD before developing into invasive cancer. Endoscopy is necessary for diagnosis, treatment, and surveillance of these patients. The most commonly used endoscopic eradication technique is EMR of visible lesions followed by RFA of the remaining BE. Current studies indicate a recurrence rate of 30% for most eradication techniques and underscore the need for continued surveillance among these patients.

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Cholangioscopy

Takao Itoi

Introduction

The first report on peroral cholangioscopy (POCS) under duodenoscope guidance, the so-called mother–baby or mother–daughter system, was by Nakajima et al. in 1976 [1]. Since then, various mother–daughter systems, such as POCS, have been developed, not only for diagnostic endoscopy but also for therapeutic endoscopy [2–6]. At approximately the same time, Urakami et al. reported a direct-insertion system POCS, the peroral direct cholangioscopy (PDCS) [7]. However, PDCS did gain widespread acceptance because of technical difficulties compared with mother–daughter system POCS. In 2006, Larghi and Waxman published the first report of PDCS using a conventional ultra-slim video endoscope [8]. Recently several endoscopists have conducted diagnostic and therapeutic PDCS using standard and/or ultra-slim endoscopes [9–15]. In this chapter, we describe the role and practical application of current various POCS systems in biliary tract diseases.

Role and Practical Applications of Cholangioscopy in Biliary Diseases

Diagnostic Cholangioscopy

White-Light Cholangioscopy

POCS can directly observe intraductal lesions and is useful for depiction of indeterminate filling defects and biliary strictures. However, the usefulness of POCS

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depends on the characteristics of the lesions—intrinsic strictures can be diagnosed with a sensitivity of 66–76 % [16, 17]. In contrast, it is extremely difficult to diagnose extrinsic strictures (sensitivity 8 %) [16]. Thus, the use of POCS is best limited to intrinsic biliary lesions. Furthermore, it is well known that cholangiocarcinoma often shows superficial mucosal spread [18]. In particular, most papillary and about half of nodular-type cholangiocarcinomas have superficial mucosal cancerous spread. Thus, intraductal evaluation of superficial mucosal cancerous spread seems to be mandatory for curative resection. In contrast, hardly any flat infiltrative type cholangiocarcinomas have mucosal cancerous spread [18].

The cholangioscope in the mother–daughter system has a 1.2-mm working channel and can accommodate a 1-mm in diameter biopsy forceps. The tissue samples acquired with this forceps are often miniscule. In contrast, PDCS allows the use of a larger standard forceps or 2-mm in diameter biopsy forceps, potentially allowing for greater tissue yield from forceps biopsy.

Image-Enhanced Cholangioscopy

In gastrointestinal (GI) tract diseases, it is well known that chromoendoscopy with various dyes enables delineation of the tumor margins and enhancement of morphological findings of the tumor. In biliary tract lesions, one study reported the usefulness of POCS using 0.1 % methylene blue for superior visualization [19]. However, images are limited because of fiberoptic POCS. Brauer et al. have reported a case using video POCS with indigo carmine in a patient with intraductal papillary mucinous neoplasm of the bile duct [20]. Chromocholangioscopy has some potential for enhancing the visualization of biliary tract lesions, unless in the presence of mucus, exudate, and bile, which tend to obscure mucosal details and interfere with the ability to achieve adequate tissue staining.

Narrow-band imaging (NBI) enhances visualization of fine surface mucosal structures and mucosal capillary microvessels in various GI tract diseases compared with white light upper and lower GI endoscopy (Fig. 1; white-light imaging (WLI) & NBI). One prospective study revealed that the ability of NBI observation to identify both the surface structure and mucosal vessels was as good as or better than conventional observation although it could not differentiate benign and malignant etiology [21].

Cholangioscopic Findings in Benign and Malignant Lesions

Several investigators have identified characteristic cholangioscopic findings in various biliary-tract diseases (Table 1). The normal bile duct shows a flat surface, with or without shallow pseudodiverticulae, which represents the orifice of the bile duct gland and a fine network of normal thin vessels. In inflammatory diseases, e.g., chronic cholangitis and primary sclerosing cholangitis, irregular surface, scarring, and pseudodiverticulae with or without intradiverticulae are often seen [22].

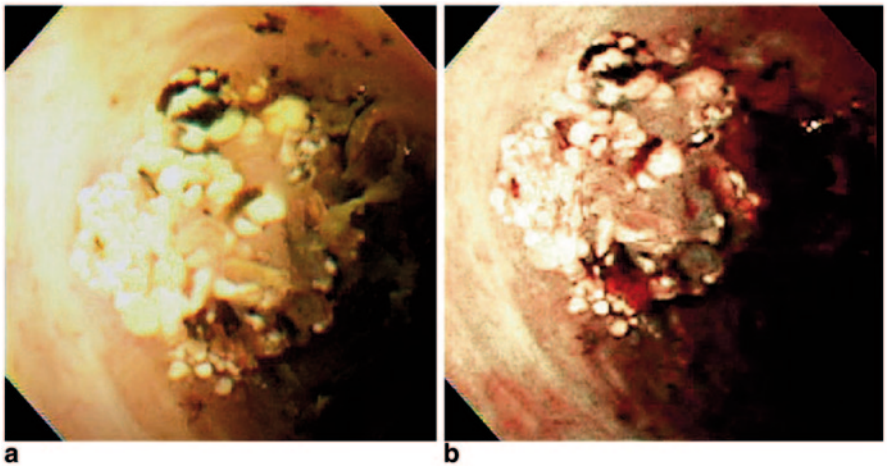

Fig. 1 Peroral video cholangioscopy. **a** white-light imaging, **b** narrow-band imaging

Table 1 Cholangioscopic findings in various biliary tract lesions

Lesions	Cholangioscopic findings
Normal	Flat surface with or without shallow pseudodiverticulae
	Fine network of normal vessels
Inflammatory lesions	Bumpy surface, pseudodiverticulae with or without intradiverticula stones
	Regular granular lesions (hyperplasia)
	Dilated or non-dilated tortuous vessels without encasement or fusion of vessels
	Scaring
Neoplasms	Irregularly papillary or granular lesions
	Nodular elevated lesions
	Friability and easily bleeding
	Dilated to non-dilated tortuous vessels
	Partially dilated vessels with or without encasement and fusion of vessels

Dilated tortuous vessels without encasement or fusion of vessels can be seen in immunoglobin G4 (IgG4)-related sclerosing cholangitis due to vascular congestion [22]. On the other hand, irregular papillary or granular lesions, and nodular elevated lesions are typical cholangioscopic findings that raise concern for biliary neoplasia. Friability of the lesions and easy bleeding are often seen with dilated or non-dilated tortuous vessels. In terms of typical neoplastic vessels, so-called "tumor vessels," either angiogenic or tumorigenic, are partially dilated vessels with encasement and fusion of vessels. We previously reported that the features of vessels were divided into four types: (1) sporadic fine vessels which are frequently seen in normal

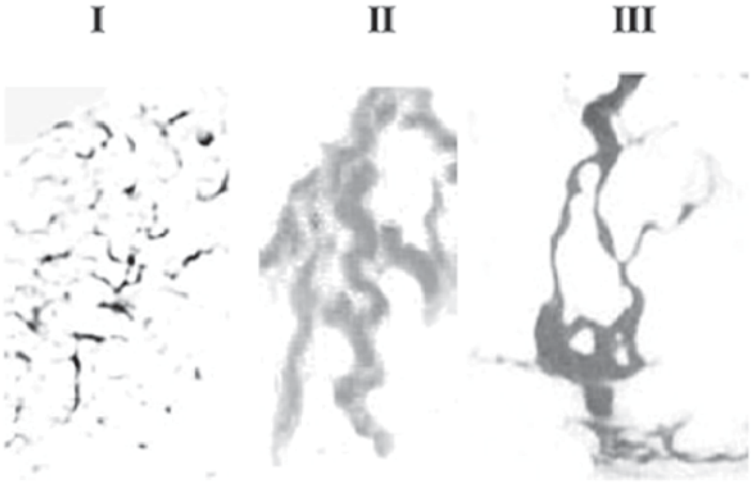

Fig. 2 Vascular patterns of bile duct mucosa

mucosa, (2) aggregated fine vessels without dilation which are frequently seen in chronic inflammation (Type I), (3) dilated and tortuous vessels without encasement or fusion of vessels (Type II), (4) partially dilated vessels without encasement and fusion of vessels (Type III; Fig. 2, Vessel patterns). Type I vessels are usually benign and Type III are typically malignant lesions. However, in the case of Type II vessels, such a differentiation between benign and malignant lesions poses a diagnostic dilemma given the cholangioscopic similarities.

Therapeutic Cholangioscopy

In a mother–daughter system, therapeutic interventions are limited by the size of the available 1.2-mm working channel. Devices which fit in this narrow-working channel include the 1.9-Fr electrohydraulic lithotripsy probe (Fig. 3) and holumium yttrium aluminum garnet (YAG) laser lithotripsy. On the other hand, in PDCS using ultra-slim endoscopes, which accommodate 5-Fr devices, various therapeutic interventions (Fig. 4) such as therapeutic drug injection, tumor resection, stone extraction, migrated stent removal, argon plasma coagulation (APC), and photodynamic therapy (PDT), are feasible.

Cholagioscopic Procedure and Outcome

Cholangioscopy procedures are performed with the patient in the prone position with intravenous anesthesia (propofol, 0.5 mg/kg) or with conscious sedation (intravenous midazolam, 0.05 mg/kg).

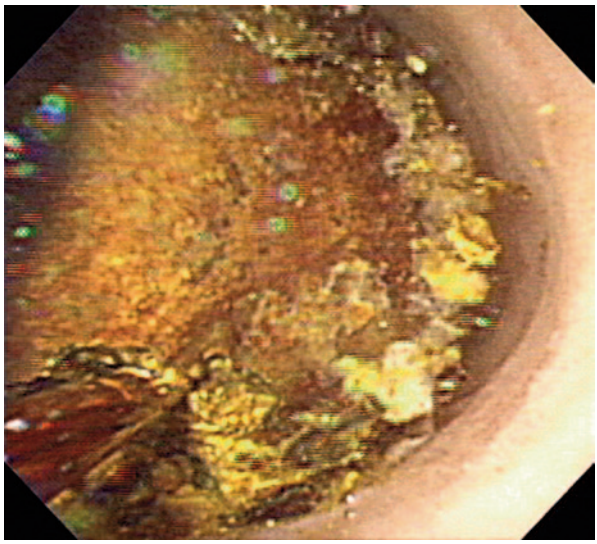

Fig. 3 Electric hydraulic lithotripsy for bile-duct stone (mother–daughter video cholangioscopy)

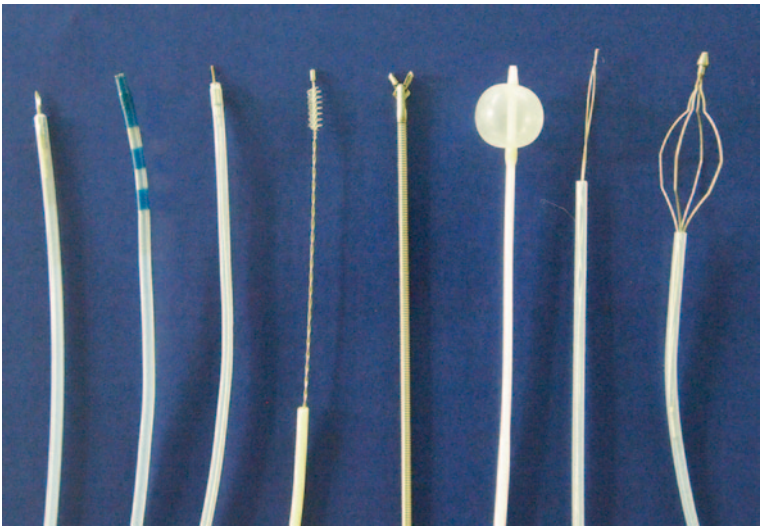

Fig. 4 5-Fr accessories for ultra-slim upper endoscopes

To improve visualization during cholangioscopy, regardless of the type of POCS used, either sterile saline solution or carbon dioxide insufflation has been used. One comparative study revealed that carbon dioxide insufflation provides better imaging and reduces procedure time compared to sterile-saline solution in almost all cases except in biliary protruding lesions [23].

Fig. 5 Mother–daughter video cholangioscopy system. **a** Actual procedure, **b** Tip of duodenal scope with daughter cholangioscope

Through-the-Duodenoscope Cholangioscopy

Mother–Daughter Type Cholangioscopy

Procedure The therapeutic duodenoscope, which is used as the mother scope has a 4.2-mm working channel, which helps to avoid kinking and damage to the cholangioscope. At present, several fiberoptic and video cholangioscopes (Fig. 5a, b) are commercially available in various countries. The specifications of the mother–daughter system video cholangioscopy are shown in Table 2. Two skilled endoscopists are required for effective control of the endoscopes and visualization.

Endoscopic sphincterotomy is a usually a prerequisite for mother–daughter system POCS to facilitate scope passage across the papilla and allow an escape route for saline and carbon dioxide used for insufflation and irrigation. The daughter

Table 2 Specification of daughter (baby) videocholangioscopy

	OLYMPUS	
	CHF-BP260	CHF-B260/B160
Angle of view, degrees	90	90
Observed depth, mm	3–20	3–20
Outer diameter, mm		
Distal end	2.6	3.4
Insertion end	2.9	3.5
Bending section, degrees		
Up/down	70/70	70/70
Right/left	NA	NA
Working length, mm	2000	2000
Working channel diameter, mm	0.5	1.2
Image-enhanced endoscopy	NBI	NBI

NA not available, *NBI* narrow-band imaging

cholangioscope is advanced through the 4.2-mm working channel of therapeutic duodenoscope into the bile duct either free hand or over a 0.025- or 0.035-in. guidewire. Utilizing the daughter cholangioscopes has 2-way deflections (up and down), and the mother duodenoscopes 4-way angulation, along with the elevator mechanism on the mother scope and the ability to vary from a long to short scope position; skilled endoscopists can obtain excellent controlled visualization of the entire biliary tree. An excessive use of the elevator mechanism of the mother duodenoscope can damage the daughter cholangioscope, in particular when the V-system duodenoscope (TJF-260V, Olympus medical systems, Tokyo, Japan; TJF-160V, Olympus America, Pennsylvania (PA)) is used. The video cholangioscope (CHF-B260/B160 and CHF-BP260, B260 and BP260, Olympus medical systems, Japan; B160, Olympus America) and the NBI system (CV-260SL, CVL-260SL/CV-180, CLV-180, light source, Olympus medical systems/Olympus America) should be used to highlight the vascular topography of intraductal lesions when needed.

After inspection with peroral video cholangioscopy (PVCS), the targeted biopsies from the lesions can be performed using a 3-Fr diameter ultrathin biopsy forceps (FB-44U-1, Olympus). However, with the slimmer PVCS (the CHF-BP260), a guide-wire or biopsy forceps cannot be used because of the small-working channel (0.5-mm in diameter).

Outcome The outcomes of large case series including three retrospective studies [24–26] and 1 prospective study [27] are described in Table 3. A mother–daughter system POCS in combination with tissue sampling provided high accuracy (94–98%), sensitivity (86–100%), specificity (87–92%), positive predictive value (88–99%), and negative predictive value (96–100%) for the diagnosis of indeterminate filling defects and biliary strictures, regardless of the use of fiberoptic or video POCS, retrospective or prospective analysis. In addition to determination of filling defects and biliary strictures, Kawakami et al. suggested that video POCS might be useful for the detection of mucosal spread of neoplasia and assists with the decision regarding extent of surgical resection in patients with cholangiocarcinoma [28].

Table 3 Summary of accuracy of mother-daughter type cohlangioscopy

Authors	n	Center	Study	Scope	Methods	Ac. (%)	Sen. (%)	Spe. (%)	PPV (%)	NPV (%)
Fukuda GIE 2007	97	Single	R	Fiber	ERC/ Tissue/ POCS	94	100	87	88	100
Shah CGH 2007	62	Single	R	Fiber	W/wo Tissue/ POCS	–	86	96	89	96
Itoi CGH 2010	144	Mum	R	Video	ERC/ Tissue/ POCS	98	99	96	99	96
Nishikawa GIE 2013	33	Single	P	Video	ERC/ Tissue/ POCS	97	100	92	96	100

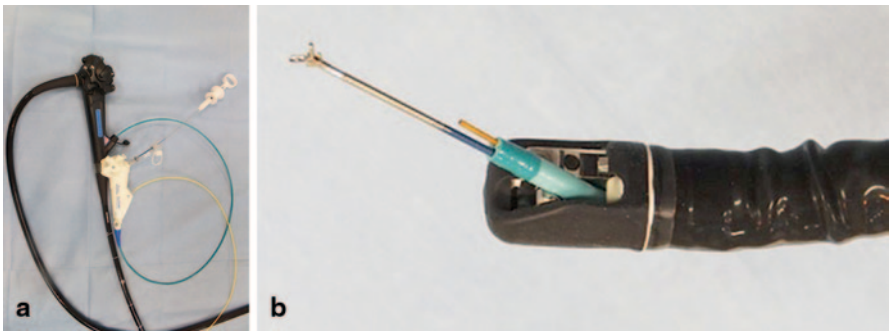

Fig. 6 Single-operator cholangioscopy system (SpyGlass). **a** Outside appearance. **b** Tip of duodenal scope with SpyScope and SpyBite

Single-Operator Fiberoptic Cholangioscopy

Procedure A single-operator system for cholagioscopy introduced recently by Bostoc Scientific has revolutionized the field of cholangioscopy. This technology incorporates a fiberoptic cholangioscopy which is to be strapped to the duodenoscope just below the working channel with a silastic belt, a pump, a light source, and a monitor, and three disposable devices: (1) a reusable 0.77-mm diameter optical probe (SpyGlass), (2) a 10F disposable 4-lumen catheter (SpyScope) consisting of a 0.9-mm channel for the SpyGlass fiber-optical probe, a 1.2-mm instrumentation channel and two dedicated 0.6-mm irrigation channels, and (3) a disposable 3F biopsy forceps (SpyBite) [29–32] (Fig. 6a, b). The modular system consists of 3 components: (1) a reusable 0.77-mm diameter optical probe (SpyGlass) for direct visual examination of the targeted duct, (2) a 10F disposable 4-lumen catheter (SpyScope) consisting of a 0.9-mm channel for the SpyGlass fiber-optical probe, a 1.2-mm instrumentation channel and two dedicated 0.6-mm irrigation channels, and (3) a disposable 3F biopsy forceps (SpyBite) for tissue acquisition in the pancreaticobiliary system [29, 30]. Since the SpyScope catheter has 4-way tip deflection, it provides good catheter maneuverability in the duct for diagnostic visualization and interventions. In contrast, the conventional mother–daughter POCS is capable of only 2-way tip deflection. Improvement of maneuverability (4-way tip deflection) may enable free-hand cholangioscope insertion without a guide-wire. Once the tip of the cholangioscope is advanced into the bile duct, irrigation of sterile saline is usually required for better visualization.

Outcome Experimental benchmark and clinical feasibility studies have already been described by Chen [29] and Chen and Pleskow [30]. To date, there are three prospective studies including one multi-center study and two single-center studies on the evaluation of SpyGlass in biliary diseases [32–34]. One single center study showed that the diagnostic accuracy of SpyGlass cholangioscopic impression was 89% although the diagnostic accuracy of SpyBite cholangioscopic biopsy was slightly lower at 82% [32]. A multi-center study revealed that the SpyGlass

cholangioscopic accuracy was 78%. In contrast, the diagnostic accuracy of SpyBite cholangioscopic biopsy was only 49%. These results suggest that visualization and targeted tissue acquisition are complementary during cholangioscopy. Others have reported greater success with targeted biopsy. For instance, Draganov reported that the diagnostic accuracy of POCS biopsy (85%) was superior to both cytology brushing (39%) and fluoroscopic standard forceps biopsy (54%) [34].

Peroral Direct Cholangioscopy

Urakami et al. first reported on the PDCS with a standard upper endoscope using the direct-insertion technique in 1977 [6]. However, as noted above, PDCS has not been widely adopted due to technical difficulties associated with direct peroral intubation of the bile duct with a standard upper endoscope. As a result, presently, the use of the mother–daughter system POCS has become widespread. The introduction of the single-operator cholangioscope system, has spurred efforts at direct peroral cholangioscopy. Recently, Larghi and Waxman reported a feasibility study of PDCS using a conventional ultra-slim upper video endoscope [7] (Table 4). Since then, several studies on the diagnostic and therapeutic PDCS have been published [8–15].

Procedure PDCS requires a skilled endoscopist for procedural success. Free-hand insertion of the endoscope, which is ideal for PDCS, is technically challenging and

Table 4 Direct peroral videochoangioscopy

Direct peroral videochoangioscopy					
	OLYMPUS			FUJINON EG-530NW/530N2	PENTAX EG-1690K
	GIF-XP160	GIF-XP180N	GIF-XP260N		
Angle of view, degrees	120	120	120	140	120
Observed depth, mm	3–100	3–100	3–100	4–100	4–100
Outer diameter, mm					
Distal end	5.9	5.5	5	5.9	5.4
Insertion end	5.9	5.5	5.5	5.9	5.3
Bending section, degrees					
Up/down	180/90	210/90	210/90	210/90	210/120
Right/left	100/100	100/100	100/100	100/100	120/120
Working length, mm	1030	1100	1030	1100	1100
Working channel diameter, mm	2	2	2	2	2
Image-enhanced endoscopy	NBI	NBI	NBI	FICE	i-Scan

NA not available, *NBI* narrow-band imaging, *FICE* flexible spectral imaging color enhancement

Fig. 7 Direct peroral cholangioscopy and anchoring balloon catheter

has a high rate of procedural failure [3], and even when performed over a guidewire, the success rates of ductal insertion remain disappointing. Endoscopists have described various techniques for intubation of the bile duct, including the overtube balloon technique [10, 11] and anchoring balloon technique [9, 14, 15, 35]. Of these techniques, anchoring balloon-assisted PDCS appears to be superior for bile duct intubation because of its simple technique and higher success rates.

The procedure of PDCS using an intraductal balloon catheter requires initial sphincterotomy of the major papilla followed by ballon sphincteroplasty with a 12–15 mm dilating balloon. PDCS is then performed using the over-the-wire technique, assisted by and an intraductal balloon catheter (5-Fr, B5-2Q; Olympus; Fig. 7). First, the endoscope is removed, leaving a 0.018–0.025-in. stiff guide-wire (Pathfinder®, Boston Scientific Japan, Tokyo, Japan, or VisiGlide®, Olympus) with the proximal end positioned in the intrahepatic bile duct. The ultra-slim endoscope (Table 4) is then advanced into the bile duct over the guide-wire to the papilla. Next, an intraductal balloon catheter is advanced up to the intrahepatic bile duct and inflated as an anchor. If the guide-wire access is lost during insertion of the ultra-slim endoscope, direct biliary cannulation and guide-wire insertion to the intrahepatic bile duct using a 5-Fr tapered catheter (PR-110Q, Olympus) is performed as previously described [36].

During the initial insertion of the cholangioscope into the lower bile duct, the floppy ultra-slim endoscopes usually acquires an “α” shape (extended scope position; Fig. 8a) or “reverse-J” shape (retracted position; Fig. 8b). For distal bile duct lesions, this limited access may prove adequate for diagnostic visualization or

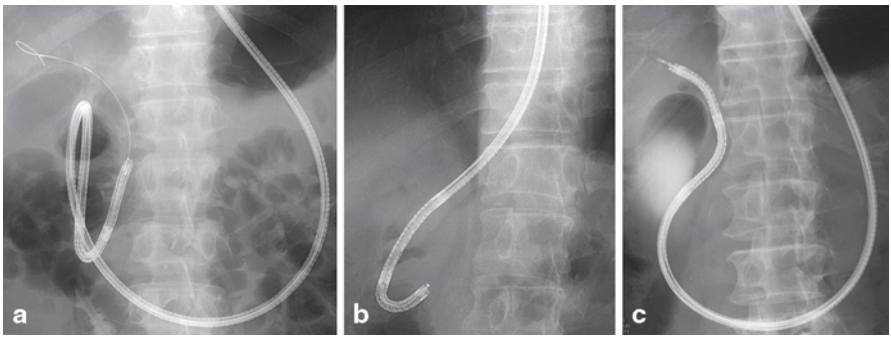

Fig. 8 Insertion patterns of peroral direct cholangioscopy. **a** α-type, **b** J-type, **c** U-type

therapeutic interventions. However, evaluation of the hilar portion of the bile duct, requires further advancement of the endoscope. "Pushing and pulling the scope" and/or "clockwise and counter clockwise" torque techniques are used in combination with the tension of intraductal anchoring balloon to gradually advance the endoscope up the biliary tree. The endoscope often shows a "U" configuration during these maneuvers (Fig. 8c).

Difficulties with scope insertion to the proximal biliary tree, resulted in the development of the first-generation dedicated PDCS prototype (first prototype) which had a short bending tip [37] and second-generation dedicated PDCS prototype (second prototype) which had a short and double bending tip and larger diameter of insertion portion of the endoscope (7 mm) [35, 38]. The second prototype can more reliably provide access to the distal portion of the bile duct for evaluation and interventions.

Previously, POCS has been performed mainly in patients without a history of surgically altered foregut anatomy due to the near impossibility of access in patients with a long afferent loop, for instance, following is Whipple resection or Roux-en Y reconstruction procedure. Recently, several endoscopists have reported the usefulness of PDCS in patients with surgically altered GI anatomy [39, 40]. If the endoscope can reach the papilla or anastomotic site, the scope insertion is technically not as difficult, because the insertion angle is not as acute.

Outcome Technical success rates reported in the literature range from 46 to 96% (Table 5; Fig. 9a, b). Although the criteria of "technical success" were unclear in each study, the successful insertion of the scope in the distal bile duct was relatively high regardless of the use of a balloon overtube or intraductal anchoring balloon catheter. There have been several anecdotal reports of therapeutic interventions during PDCS: tumor ablation using APC, PDT, EHL, laser lithotripsy, migrated stent removal, residual stone removal, and stent placement [7–12, 37, 38].

The use of PDCS in patients with surgically altered anatomy, not only diagnostic but also therapeutic PDCS has been reported [39, 40]. An ultra-slim upper endoscope was directly advanced up to the hilum in 80% of patients with altered surgical anatomy in one series [40].

Table 5 Outcome of peroral direct chaoangioscopy

Author (year)	*n*	Assistant devices	Technical success (%)
Larghi (2007)	15	GW	78
Choi (2009)	12	Balloon-overtube	83
Moon (2009)	11	GW	46
	21	AB	95
Tsou (2010)	14	Balloon-overtube	93
Pohl (2011)	25	AB	72
Moon (2012)	48	AB	96
Itoi (2013)	41	Free-hand, GW and/or AB	72
	7	Free-hand	0
	34	GW and/or AB	88

GW guide-wire, *AB* anchoring balloon

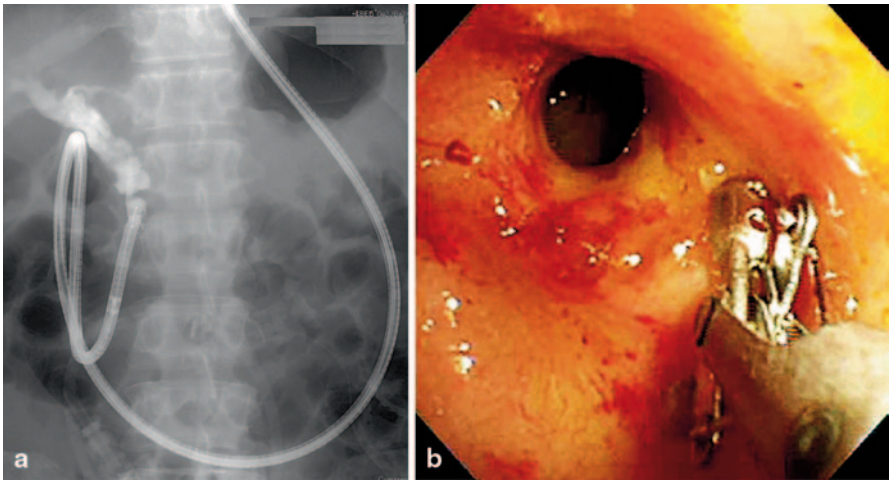

Fig. 9 Direct peroral videocholangioscopy-guided biopsy for indeterminate biliary stricture. **a** direct bile duct insertion using an ultra-slim endoscope, **b** forceps biopsy was performed under direct inspection

Adverse Events and Limitations of POCS

Regardless of the technique used, mother–daughter POCS, single-operator POCS, or PDCS, adverse events can occur. One study from a high volume center revealed that POCS appears to be associated with a significantly higher rate of cholangitis, possibly because of intermittent intraductal saline irrigation required during the procedure [41]. In addition to cholangitis, air embolism is an extremely rare, but fatal adverse event. A recent case report described air embolism with resultant left hemiparesis after direct cholangioscopy performed with an intraductal balloon

anchoring system [42]. Therefore, POCS-related procedures should be performed using minimal CO_2 insufflation rather than room air, although the potential for embolism still exists.

Conventional mother–daughter system POCS has the following limitations: (1) the procedure requires two skilled endoscopists, (2) the daughter cholangioscope is easily damaged and repairs are expensive, (3) small 1.2-mm working channels limit therapeutic interventions. These limitations to the technology have limited the use of conventional mother–daughter cholangioscopy to a few tertiary care centers.

The single operator cholangioscope system has broadened the availability of cholangioscopy in the community. However, there continue to be several limitations to the currently available technology. Firstly, devices such as the biopsy forceps come out of the working channel at different positions circumferentially at the tip of the device, rendering it difficult to target visualized lesions for biopsy or laser lithotripsy. Secondly, while the single-operator system is amenable to cholangioscopy by a single operator, dual operators can make the procedure even easier. Furthermore, when performing any intervention, a single-operator system may be both difficult and time-consuming depending on the circumstances.

PDCS also has several limitations: (1) special techniques are required for scope insertion, i.e., no standard insertion technique is yet established, (2) PDCS is not stable in the bile duct; in particular, it is comparatively unstable in the distal bile duct, (3) no dedicated direct cholangioscope is commercially available.

An easy to perform direct cholangioscopy will open new avenues for the broader endoscopy community. Presently, given the technical and technique-related drawbacks, the evaluation of ductal abnormalities with new techniques such biliary chromoendoscopy, confocal microendoscopy, and targeted biopsy of intraductal lesions have remained within the domain of tertiary referral centers. In conclusion, the recent evolution of POCS has provided high resolution white-light imaging in combination with NBI, a single-operator system and direct cholangioscopic system using an ultra-slim endoscope. However, there is still no “all-in-one” POCS system, meaning easy insertion, observation, intervention, and distinct imaging although each system has several merits and demerits. Therefore, we believe in the necessity of establishing an “all-in-one” POCS system in the near future.

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Peripancreatic Fluid Collections and Walled-Off Pancreatic Necrosis

Faris M. Murad and Sreenivasa S. Jonnalagadda

Pancreatic fluid collections (PFCs) arise as a consequence of pancreatic injury. Acute pancreatitis can lead to inflammatory changes in the pancreas, and if severe enough, may lead to ductal injury and possibly necrosis. PFCs arise from pancreatic ductal injury. Depending on the severity and etiology of the pancreatitis, ductal disruption can occur from the main pancreatic duct, side branches, or a combination of both. The most common form of pancreatic fluid collections arise from acute injury of the pancreas (acute pancreatitis, trauma to the pancreatic duct, surgical resection, or iatrogenic injury including post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and inadvertent injury during surgery of nearby organs). PFCs may also arise from chronic pancreatitis and this is usually due to the ductal obstruction (stones, strictures).

The management of PFCs has seen an evolution from surgical management to minimally invasive approaches including percutaneous drainage by interventional radiologists, video assisted retroperitoneal debridement via percutaneous tract, and endoscopic management by interventional gastroenterologists. The endoscopic management utilizes a transmural approach at drainage and/or transpapillary approach to manage duct disruption or stricture/obstruction of the main pancreatic duct. This chapter focuses on the endoscopic management of PFCs.

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Nomenclature

At the heart of proper management of PFCs, it is important to ensure that correct terminology is utilized in classifying PFCs. The classification was created to provide common terminology and help define the severity of the disease. Many PFCs are improperly labeled as "pseudocyst" while in reality, there is an evidence of pancreatic necrosis from the areas of nonenhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT) and the appropriate terminology is walled-off pancreatic necrosis. The Atlanta classification was initially created to provide common terminology and severity of acute pancreatitis and has been recently revised as our understanding of acute pancreatitis and PFCs have evolved [1] (Table 1). PFCs classification is based on history, timing of acute pancreatitis, and CECT scan imaging. Improper terminology may result in suboptimal treatment regimens and poor outcomes.

In approaching patients with PFCs, a proper history and physical examination is important. In the absence of a prior history of pancreatitis, a neoplastic etiology should be considered more a pseudocyst and management changes from a therapeutic drain-

Table 1 Terminology based on revised Atlanta classification

Terminology	Definition	CECT findings
Acute peripancreatic fluid collection	Peripancreatic fluid occurring in the setting of interstitial edematous pancreatitis within the first 4 weeks of acute pancreatitis	Homogeneous fluid adjacent to the pancreas confined by fascial planes with no recognizable wall
Pancreatic pseudocyst	An encapsulated, well defined collection of fluid, but no or minimal solid components which occur >4 weeks after the onset of interstitial edematous pancreatitis	Well-circumscribed, homogeneous, round or oval fluid collection. No solid components. Well-defined wall. Occurs only in interstial edematous pancreatitis
Pancreatic abscess collection	Similar to a pancreatic pseudocyst, but infected. Typically occurs after bacterial or fungal contamination	Similar to pancreatic pseudocyst. Occurs because of bacterial or fungal contamination of a fluid collection. Typically occurs in the setting of pancreatic duct leak/disruption after contamination
Acute necrotic collection	A collection of both fluid and solid components (necrosis) occurring during necrotizing pancreatitis. These are immature collections <4 weeks after the onset of severe acute pancreatitis	Heterogeneous, varying of nonliquid density. No encapsulating wall. Intrapancreatic and/or extrapancreatic
Walled-off pancreatic necrosis	A mature, encapsulated acute necrotic collection with a well-defined inflammatory wall. These tend to mature >4 weeks after the onset of necrotizing pancreatitis	Heterogeneous liquid and nonliquid density. Well-defined wall. Intrapancreatic and/or extrapancreatic

CECT contrast-enhanced computed tomography

age procedure to a diagnostic fine needle aspiration. Cross-sectional imaging with CECT scan will help define the contents of the PFC (liquid, solid, or both), whether there is evidence of pancreatic necrosis, if the cyst wall is well-formed and amenable to endoscopic intervention. Liquefied collections are easily drained transmurally or via a transpapillary approach. The transmural approach involves transmural enterotomy creation (transgastric or transduodenal) and placement of polyethylene stents. On the other hand, collections with solid debris require larger transmural enterotomies and placement of large caliber stents and possible endoscopic debridement.

Delineation of ductal anatomy and communication with the PFC may require magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography (EUS). While ERCP will also clarify this issue, there is a risk for infection and an ERCP is typically performed with therapeutic intent. The management approach to a PFC can be formulated only after these issues are ascertained.

Unfortunately, the term pancreatic pseudocyst is commonly misused to describe walled-off pancreatic necrosis (WOPN). When mischaracterized as a pancreatic pseudocysts (PC), patients with the WOPN may develop secondary infection, as the devascularized solid material cannot be evacuated via the small caliber stents typically placed to drain a PC. The Atlanta classification was intended to help define pancreatic and peripancreatic fluid collections accurately and guide appropriate management.

Liquefied Pancreatic Fluid Collections

Acute peripancreatic fluid collections (APFCs) are immature fluid collections that develop in the early phase of interstitial edematous acute pancreatitis. APFCs lack a true wall. They are mainly confined to the retroperitoneal space. These APFCs are usually sterile. They may get infected spontaneously or following iatrogenic contamination at ERCP. The APFCs usually resolve without intervention. APFCs that persist for >4 weeks are likely to develop into a pseudocyst.

PCs arise from focal disruption of the pancreatic duct in which amylase-rich pancreatic fluid becomes surrounded by a well-defined nonepithelialized wall. PCs contain to minimal solid material. PCs may develop following acute pancreatitis or in a setting of chronic pancreatitis. In chronic pancreatitis, a stricture in the main pancreatic duct or obstructing pancreatic calculus may result in the formation of a PC. The pancreatic ductal hypertension and resultant blowout of the pancreatic duct (leak) are believed to result in a PC.

Indications for Drainage of Liquefied Pancreatic Fluid Collections

Patients who develop liquefied collections do not necessarily require drainage. Drainage of these liquefied collections is driven by symptoms and/or because of infection. Infection, bleeding, and perforation occur infrequently following the drainage of PCs and these potential risks outweigh the benefit of drainage in an as-

ymptomatic patient. Symptoms associated with large PCs are abdominal pain, early satiety with weight loss, gastric outlet obstruction, or obstructive jaundice.

Previously PCs that were >6 cm were referred for drainage even if asymptomatic. Size is, however, no longer used as sole criteria for drainage. There is a chance that PCs will resolve spontaneously over time. In a retrospective review of 68 patients with a walled-off pancreatic fluid collection followed conservatively, 63% either had spontaneous fluid collection resolution or remained well without symptoms or complications at a mean follow-up of 51 months. However, patients need to be counseled that observation alone does carry risks. In the same series, there was a 9% incidence of serious complications, typically during the first 2 months after the diagnosis. Complications included pseudoaneurysm formation, free perforation, and spontaneous abscess formation. An additional third of the patients underwent elective surgery due to increasing size of the fluid collection and pain [2]. In another series of 75 patients, significant abdominal pain, complications, or progressive enlargement of a fluid collection led to surgery in 52% of the patients. The remainder of the patients who were followed conservatively had no symptoms, with either persistence of their fluid collections or a gradual decrease in size. While walled-off pancreatic fluid collections were smaller in the conservatively managed group than in patients requiring surgery, neither the etiology of the fluid collection nor the computed tomography (CT) criteria could predict successful outcome with a conservative approach [3]. The decision regarding conservative approach versus an intervention should be tailored individually to the clinical scenario.

In assessing whether a patient needs drainage, a proper pre-drainage evaluation needs to be performed, are a number of cystic lesions that may mimic a PFC. The patient's history is critically important in establishing a history of pancreatitis and possible etiologies (trauma, recent surgery, alcohol use, and gallstones). If there is no history of pancreatitis, then one must consider other lesions that may mimic a PFC (cystic neoplasm of the pancreas, pseudoaneurysm, lymphocele, cystic degeneration of a neoplastic lesion).

The review of cross-sectional imaging for solid components and collateral vessels will help determine the feasibility of drainage. A pseudoaneurysm is generally considered to be an absolute contraindication to endoscopic drainage and has to be addressed by an arterial embolization prior to endoscopic therapy. Unexplained gastrointestinal bleeding, sudden increase in size of collection, and unexplained sudden anemia may be clues to a bleeding pseudoaneurysm. An magnetic resonance imaging (MRI) or a triple-phase or dynamic bolus CT-scan with early imaging during the arterial phase should be performed in all patients prior to a pseudocyst drainage procedure to avoid catastrophic bleeding from a pseudoaneurysm that may occur following decompression of the pseudocyst. In a series of 57 patients referred for endoscopic drainage of pancreatic walled-off pancreatic fluid collections, five pseudoaneurysms were detected prior to the drainage procedure.[4]

The pre-procedure evaluation should also include assessment of the coagulation profile. Patients who are cirrhotic or are hemophiliacs might not be suitable for drainage due to the risks of bleeding. A patient on anticoagulation will also need to have the medications discontinued and possibly reversed. Some of the newer anti-

coagulation medications do not have reversal agents and will need sufficient time half-life before transmural drainage is performed.

Drainage of Liquefied PFCs

Liquefied PFCs may be drained by transpapillary approach, transmural approach, or a combination of these. After careful evaluation of cross-sectional imaging, a decision can be made based on the size and location of the collection, adherence to the gastric wall or duodenum, and whether the collection is in continuity with the pancreatic duct. It is extremely important that the PFC is adherent to the gastrointestinal (GI) tract if transmural drainage is to be performed. Nonadherence to the GI tract can result in leakage of cystic contents into the retroperitoneal space and perforation once the cyst is decompressed. A general practice is to allow the PFC to mature for at least 4 weeks and visualization of a mature wall/peel around the cyst on cross-sectional imaging. There is one report of using a fully covered self-expanding metal stent (fcSEMS) for PFCs with indeterminate adherence. A cyst resolution was achieved in 78 % of patients.[5]

Transpapillary Drainage

Collections that are small (≤ 6 cm) and communicate with the main pancreatic duct, can be drained by ERCP with the placement of a polyethylene pancreatic duct endoprosthesis. This might be the safest approach in collections that are not adherent to the GI tract. If there is obstruction of the main pancreatic duct from stones or strictures, it is important that the guide-wire is advanced upstream of the obstruction for successful placement of an endoprosthesis. If an obstruction downstream to the PFC cannot be traversed with a guide-wire, transpapillary drainage will not be successful.

In patients undergoing transpapillary drainage, a pancreatic duct sphincterotomy is usually performed, but is not absolutely necessary. The size of the pancreatic duct stent placed is based on the duct diameter. A larger pancreatic duct diameter can accommodate a larger diameter stent. It is important to choose a stent of appropriate caliber to minimize stent-induced changes in the normal pancreatic ducts. Depending on the caliber of the pancreatic duct, 5 F, 7 F, 8.5 F, or even 10 French stents may be used in this situation.

Transmural Drainage

Transmural drainage of liquefied PFCs is a well-established technique. The majority of transmural drainage of PFCs are performed with EUS guidance. Drainage of PCs can be performed at the site of maximal bulge without EUS guidance. How-

ever, as noted below, EUS guidance provides information which probably enables a safer technique and may alter the approach, particularly if a large amount of previously unrecognized solid debris is present within the PC.

EUS has several important advantages to non-EUS guided approaches. The first and the most important advantage is endosonographic visualization of intervening vessels between the gastric/duodenal wall and the PFC. [6, 7] (Figs. 1 and 2) The ability to guide the EUS needle into the collection while avoiding intervening vessels minimizes the risk of bleeding. Secondly, EUS-guided approaches can assess adherence of the PFC to the GI tract and the distance between the gastric mucosa and the cyst wall. The third advantage is that a number of PFCs do not form extrinsic compression on the GI tract, so the EUS guidance is critical in evaluating and identifying the location of the PFC. Finally, EUS will clarify the consistency of cyst contents.

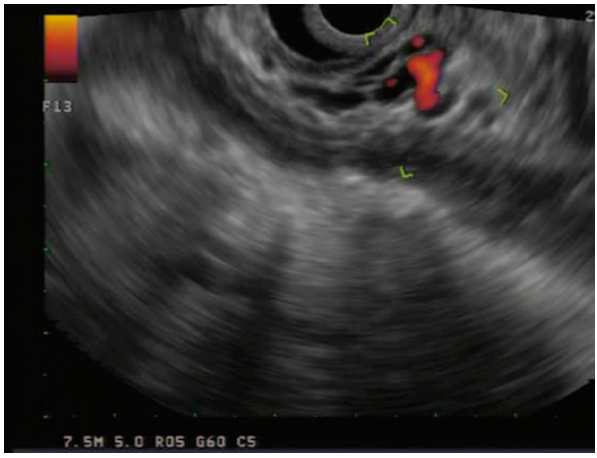


Fig. 1 EUS evaluation of gastric wall of WOPN. Multiple collateral vessels sonographically visualized precluding transmural drainage. *EUS* endoscopic ultrasonography, *WOPN* walled-off pancreatic necrosis

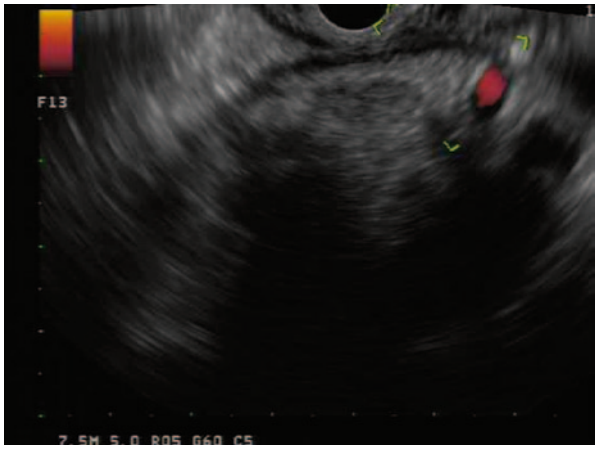


Fig. 2 EUS evaluation of gastric wall of WOPN. Multiple collateral vessels sonographically visualized precluding transmural drainage. *EUS* endoscopic ultrasonography, *WOPN* walled-off pancreatic necrosis

Technique

EUS-guided drainage of a PFC is performed with a therapeutic linear echoendoscope, which typically accommodates 10 French accessories and has Doppler capabilities. Utilizing a linear echoendoscope, one-step drainage is possible of PFCs. This has been reported successful in >94% of cases [8, 9]. As liquefied PFCs contain no or minimal solid material, the drainage through transgastric or transduodenal punctures with placement of multiple 10 Fr stents will result in successful drainage of most PCs. (Figs. 3 and 4)

The linear echoendoscope is passed to the level of the PFC. Once the PFC is endosonographically identified, the optimal point for entry should be carefully evaluated. The site is evaluated for a maximal point of adherence and intervening blood vessels. Once the optimal site is identified, a 19 G endoscopic ultrasonography fine needle aspiration (EUS-FNA) needle is passed under endosonographic guidance into the collection. A 19 G needle is utilized as it allows passage of a 0.035 in. guide-wire. Fluid is initially aspirated using a suction syringe from the PFC. The fluid aspirated can be sent for a cell count and differential, gram stain and culture. The suction syringe is then removed and a long 0.035 in. guide-wire is advanced down the EUS-FNA needle. The guide-wire is then visualized endosonographically and fluoroscopically to coil within the collection. (Fig. 5) The passage of the guide-

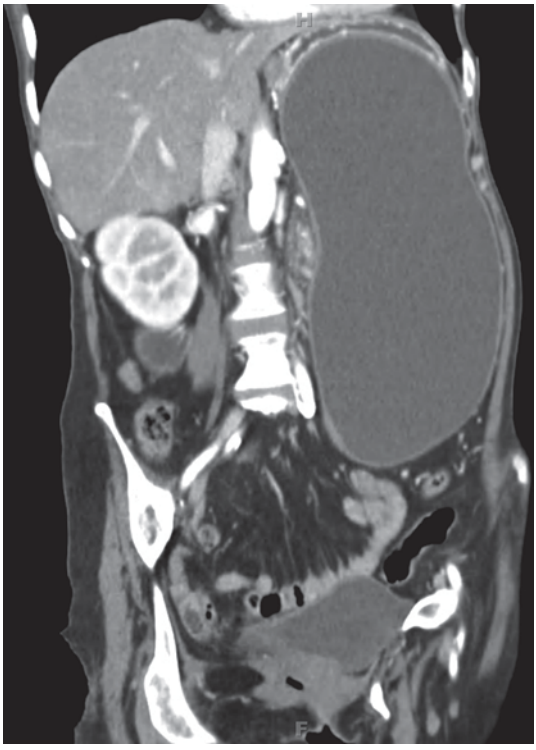


Fig. 3 CECT scan revealing large pseudocyst. The large PFC is causing significant extrinsic compression of the stomach. *CECT* contrast-enhanced computed tomography, *PFC* pancreatic fluid collections

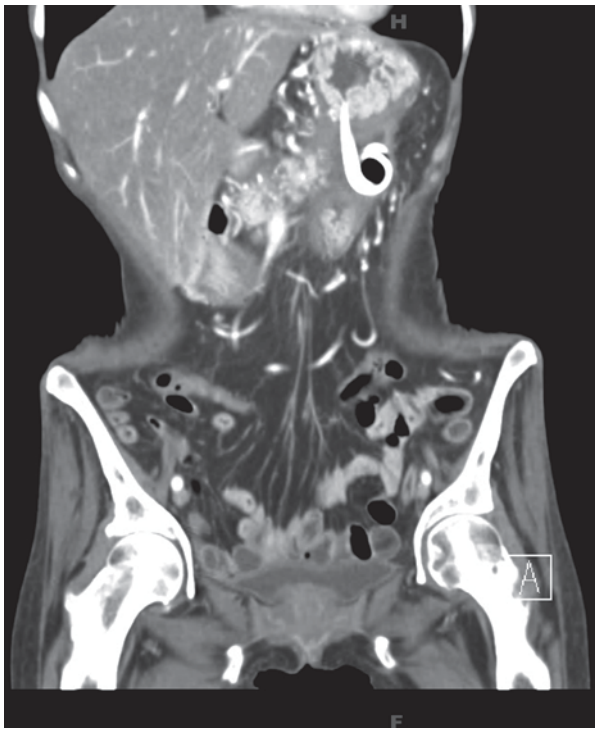


Fig. 4 CECT scan after transmural drainage of pseudocyst. The pseudocyst has completely collapsed after drainage. Two double-pigtail stents noted across the gastric wall. *CECT* contrast-enhanced computed tomography

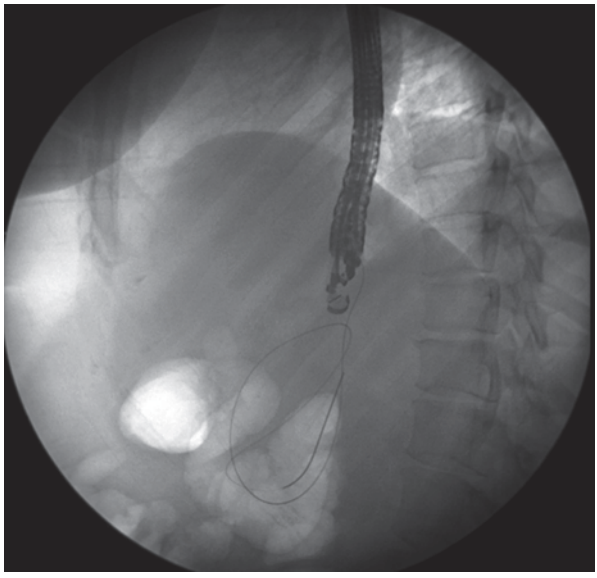


Fig. 5 Fluoroscopic image of a therapeutic linear echo-endoscope and guidewire coiling within PFC. *PFC* pancreatic fluid collections

wire into the PFC secures access and the needle is removed, leaving the wire in place. This next step is creating a small tract across the GI tract to allow the passage of a dilating balloon. This can be achieved using "hot" access or "cold" access. A hot access utilizes current across a metal wire to help create the tract. A needle knife with a "bent" needle can be passed over the guide-wire and used to create the enterotomy tract to allow passage of a dilating balloon. The major risk of using a needle-knife is bleeding. This technique is especially useful, if the GI tract is fibrotic from previous PFC drainage or previous surgery. A cold access utilizes small dilating balloons or tapered dilating catheters to create the initial enterotomy tract, so that larger dilating balloons can pass across the tract. Once the enterotomy tract is established, the enterotomy can be dilated to 10 mm. It is not necessary to create an enterotomy greater than 10 mm as liquefied collections should easily drain across a 10 mm enterotomy tract. Control and suction of fluid as it evacuates from the cyst into the stomach is crucial to avoid pulmonary aspiration. Aspiration of evacuating fluid can be minimized by intubating the patient for the procedure and/or slowly deflating the initial dilating balloons and prompt suctioning the evacuating fluid as it enters the stomach. This method of partially deflating the balloon over several minutes in the tract will help avoid the sudden entrance of a large volume of fluid into the stomach.

Once the enterotomy is dilated to 10 mm, the use of double pigtail stents rather than straight stents are recommended to provide ongoing drainage. The pigtails on either end will minimize the chance of spontaneous migration across the enterotomy and additionally, as the collection collapses when the fluid drains, the pigtail within the collection will not impact on the wall within the collection and cause injury/bleeding. Straight stents will have a higher chance of spontaneous migration into or out of the collection and might impact on the wall of the collection. The use of long fcSEMS, while reportedly successful, are not typically utilized for liquefied PFCs due to the prohibitive costs and concern for bleeding from within the cavity as the collection collapses. The newer Axios lumen apposing fcSEMS by Xlumena (Figs. 6, 7, 8) might avoid the issues with impaction on the opposite wall. The Axios stent might also have a role in PFCs with suspected nonadherence[5, 10] (Fig. 9).

Fig. 6 Xlumena Axios delivery catheter

Fig. 7 Xlumena Axios delivery catheter with guide-wire

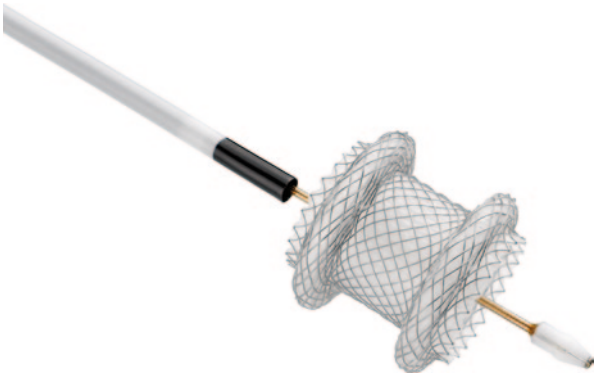


Fig. 8 Xlumena Axios stent

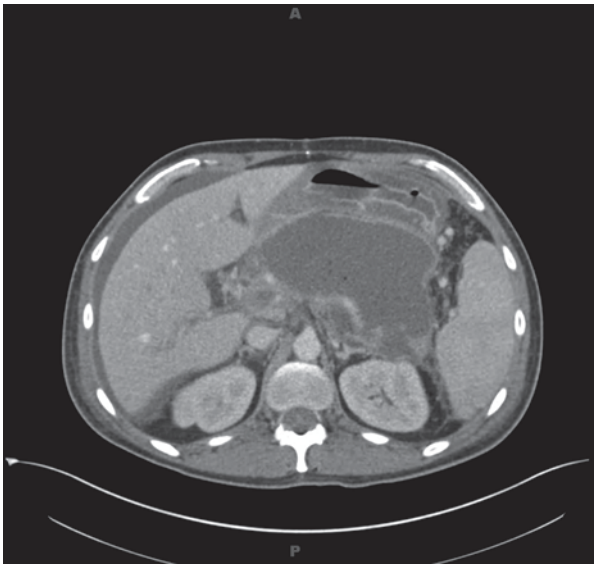


Fig. 9 CECT revealing indeterminate adherence of WOPN and gastric wall. *WOPN* walled-off pancreatic necrosis

Pancreatic Necrosis

The WOPN represents the mature phase of an acute necrotic collection. The hallmark of pancreatic necrosis is areas of nonviable and devascularized pancreatic tissue. There may be associated peri-pancreatic fat necrosis. Pancreatic necrosis is identified on CECT in which the areas of nonenhancement of the pancreas represent the areas of necrosis. (Fig. 10) Pancreatic necrosis is frequently associated with pancreatic duct disruptions/leaks. WOPN collections typically contain both solid and liquid components. The liquid within the collection is a combination of pancreatic juice from the pancreatic duct disruption/leak, inflammatory mediators, and peri-pancreatic fat necrosis. The solid components that are typically within the collection are varying amounts of parenchymal necrosis and peri-pancreatic fat necrosis.

It may be difficult to discern the WON if a CT scan is performed without intravenous contrast. Even with a CECT scan, it may be difficult to appreciate the amount of parenchymal necrosis. On CECT, the WOPN collections are typically homogeneous and the solid debris might not be easily appreciated. A high level of suspicion for solid debris based on the imaging characteristics is important for pre-procedure recognition of solid debris in the collection. If the WOPN is mislabeled

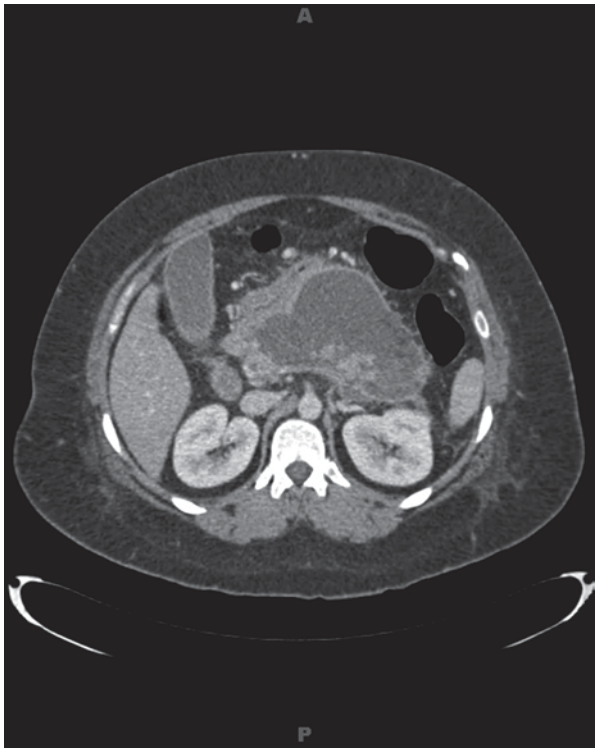


Fig. 10 CECT revealing large WOPN and limited viable pancreas. Only a small area of viable pancreas enhances within the walled off collection. *CECT* contrast-enhanced computed tomography, *WOPN* walled-off pancreatic necrosis

as a pseudocyst, then the drainage of the fluid via multiple typical 10 French stents will be inadequate and could lead to secondary infection of the necrotic material.

The timing of drainage of WOPN is debatable. Most WOPN collections are sterile unless there has been previous manipulation (percutaneous guided aspirate of the fluid, ERCP with pancreatography, EUS-guided FNA of the fluid, or transmural drainage of the fluid). Sterile collections do not require drainage or decompression unless the patient is symptomatic. Infected collections of WOPN are absolute indications for drainage. Drainage of acute necrotic collections is not recommended, as the collection has not had a chance to mature and contain itself. Transmural access of an acute necrotic collection (ANC) should be avoided as the risk of perforation is markedly increased. WOPN are defined as pancreatic necrotic collections that have evolved over 4 weeks of time from the initial onset of pancreatitis. Symptomatic WOPN collections and infected WOPN are indications for drainage and possible debridement.

There are a number of modalities to manage WOPN surgical management, percutaneous drainage by interventional radiology, endoscopic management, or a combination approach. Endoscopic methods for management of WOPN are technically more difficult than transmural drainage of liquefied PFCs. There is a higher risk of adverse events with endoscopic management of WOPN. This is partly due to a larger enterotomy that must be created, increased risk of bleeding and perforation, and current limitations on endoscopic tools available to manage solid debris within the collection.[8] Previously, surgery was the gold standard for management of WOPN. Over the last 15 years, there has been a strong movement away from the surgical management to minimally invasive techniques due to better outcomes with nonsurgical approaches. The most common methods include placement of percutaneous drainage catheters, video-assisted retroperitoneal debridement via an established percutaneous tract, endoscopic management with flexible endoscopic instruments, or a combination of both.

Techniques

This section focuses on endoscopic methods rather than percutaneous and surgical methods. Endoscopic management evolved from endoscopic techniques initially created to manage liquefied PFCs. The methods are very similar initially, but differ in that solid necrotic material needs to be evacuated from the collection. Transpapillary drainage is not feasible for the WOPN, as this will not allow the drainage of solid material. Transgastric drainage of WOPN is the standard approach in endoscopic management.

Transmural drainage of WOPN is initially identical to the previously described endoscopic management of liquefied PFCs. Using EUS-guidance with a therapeutic linear echoendoscope, the WOPN is endosonographically examined. Once a suitable point of entry is identified, then a 19-G EUS-FNA needle is passed across the gastric or duodenal wall into the collection. It is important that a sample of the fluid is sent for microbiological analysis. After the long 0.025 or 0.035 in. guide-wire is

coiled within the collection, the enterotomy is created. The enterotomy is dilated sequentially from an initial dilation of 10 mm, to a goal of 18–20 mm. Suctioning of fluid as it enters the stomach is important for the prevention of aspiration and maintaining a clear field of view. The larger enterotomy allows the better evacuation of solid material from the collection and passage of a flexible gastroscope into the collection. Once the enterotomy is dilated to an appropriate size, then the enterotomy tract is secured with the placement of a 10 Fr by double pigtail stent. At this point, the therapeutic linear echoendoscope can be exchanged for an adult gastroscope or therapeutic gastroscope. The therapeutic adult gastroscope has a larger working channel and will not get clogged easily. It will also allow the passage of additional 10 Fr double pigtail stents. Once the gastroscope has been passed into the WOPN collection, the visual inspection is performed to assess the collection. The necrotic tissue can be assessed (Figs. 11, 12 and 13), the presence of intracavitary vessels visualized (Fig. 14), and any remaining fluid can be aspirated. The direct endoscopic pancreatic necrosectomy (DEPN) can then be performed. There are limited tools available for DEPN. Multiple endoscopic tools have been tried including Roth Net (US endoscopy), graspers, forceps, and snares. The most efficient tool is a braided (spiral) snare. The braided snare has the advantage of being able to grip the necrotic material more reliably without slippage, and the necrotic material can easily be deposited in the GI tract. The Roth net can grasp necrotic debris, but will not release the debris due to the consistency of the necrotic material. A forceps will grab necrotic material easily, but there is a risk grabbing a small intracavitary vessel with resultant bleeding. The goal of manual debridement is to evacuate as much necrotic material as possible. The granulation tissue lining the collection marks the extent to which debridement should be performed. It may take 2–4 sessions to completely debride a collection of WOPN with each session lasting up to 1–2 h.

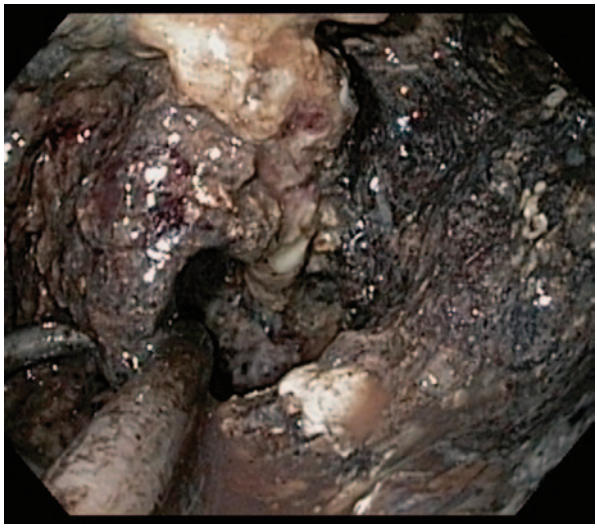


Fig. 11 Endoscopic images of necrotic material within WOPN. *WOPN* walled-off pancreatic necrosis

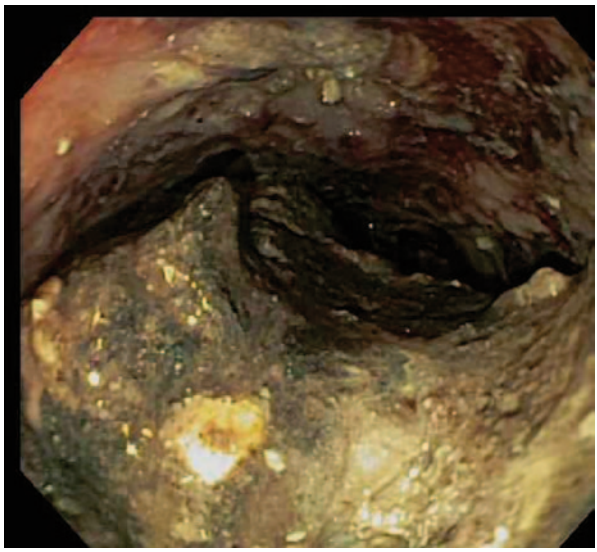


Fig. 12 Endoscopic images of necrotic material within WOPN. *WOPN* walled-off pancreatic necrosis

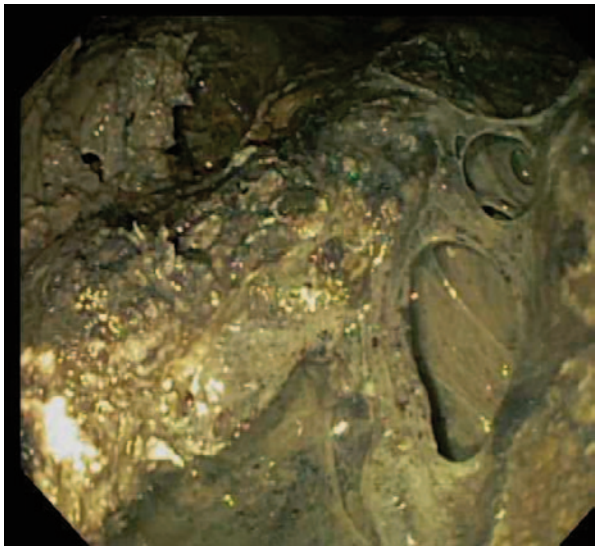


Fig. 13 Endoscopic images of necrotic material within WOPN. *WOPN* walled-off pancreatic necrosis

There have been a number of studies evaluating combined endoscopic and percutaneous approaches. Percutaneous methods place large bore drainage catheters into the collection. At the same time, an endoscopic transmural access is obtained into the collection. This combined approach utilizes multiple drain sites with a goal of flushing the collection until resolution is obtained. Up to 60 cc of normal saline is flushed through the catheters every 2–4 h initially. The collections are evaluated with CECT every few weeks until resolution of the collection is identified [8, 11–13].

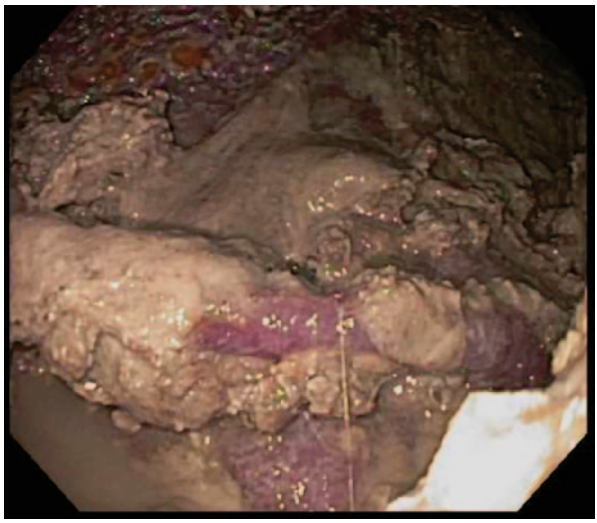


Fig. 14 Endoscopic image of intracavitary vessel within WOPN collection. *WOPN* walled-off pancreatic necrosis

Irrespective of the method utilized to manage WOPN, multiple procedures are typically required. The enterotomy will typically close down around the stents and will need to be redilated. This is especially true of a transgastric access as the gastric wall is thick, muscular, and has an excellent vascular supply. Time constraints also limit the amount of time that can be spent on endoscopic debridement during each session. The timing of repeat procedures is dictated by the clinical status of the patient and/or findings on cross-sectional imaging.

Broad spectrum antibiotics are usually recommended in patients undergoing drainage of WOPN. A fluid aspirate from the collection may help to guide the choice of antibiotics. Antibiotics are not useful in clearing infection of necrotic material as the necrosis is devascularized. Antibiotics likely play a bigger role in minimizing bacteremia especially during DEPN.

A new lumen apposing fcSEMS is available which might be useful in expediting resolution of WOPN. The Axios stent is shaped like a dumbbell and comes in multiple diameters (8, 10, 15, and soon 20 mm). This device may allow for better egress of solid material within the collection and entry of gastric acid that may aid in the breakdown of necrotic material.

Outcomes of Endoscopic Management of PFCs

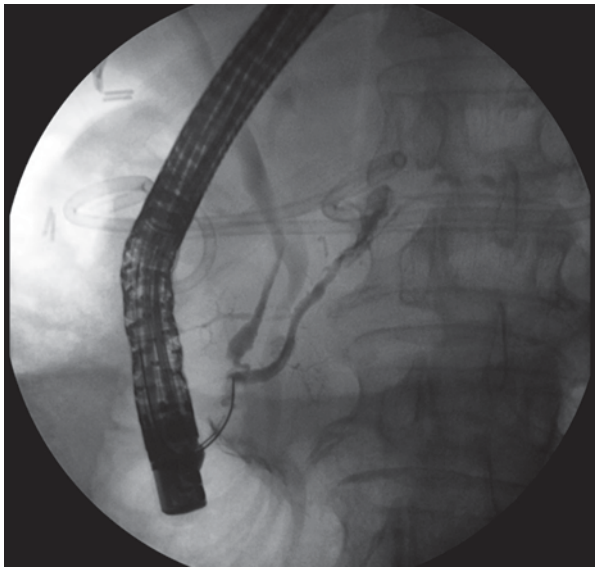
Outcomes of endoscopic management of PFCs are still evolving. There are more robust data on outcomes in pancreatic pseudocyst drainage. Data on endoscopic management of WOPN are not likely as robust due to a heterogeneous presentation of these cases, lack of uniform expertise across medical centers, and misuse of terms classifying PFCs. The updated Atlanta classification of PFCs will hopefully allow better classification and possibly better published data.

Pancreatic Pseudocysts

Overall, endoscopic drainage of liquefied PFCs (pseudocysts) is >90%.[14–16]. The major adverse event associated with the endoscopic drainage of pseudocysts is bleeding, but this is minimized with EUS-guidance [17]. Due to the success of endoscopic drainage and its low morbidity, this method is preferred to surgical management [18]. Percutaneous management of liquefied PFCs is comparable to endoscopic modalities in terms of success and adverse events. [16] Percutaneous management is an important modality for PFCs that are not adherent to the GI tract. However, it is not uncommon for percutaneous drainage to be complicated by a persistent pancreaticocutaneous fistula, if a pancreatic duct leak into the collection is present.[19] (Figs. 15 and 16)

Walled-Off Pancreatic Necrosis

With the advent of interest in natural orifice transluminal endoscopic surgery (NOTES) and associated techniques, over the last decade increasing attention has been focused on minimally invasive techniques to treat WOPN significant amounts of solid necrotic debris and are unlikely to respond adequately to the placement of small caliber stents alone. Radiologically placed percutaneous drains can successfully treat infected necrotic pancreatic tissue without a need for debridement in less than 35% of the patients [20, 21]. The traditional approach to treatment when the cyst was infected or contained copious debris was an open necrosectomy.



Figs. 15 ERCP demonstrating pancreatic duct leak with extravasation of contrast. ERCP endoscopic retrograde cholangiopancreatography

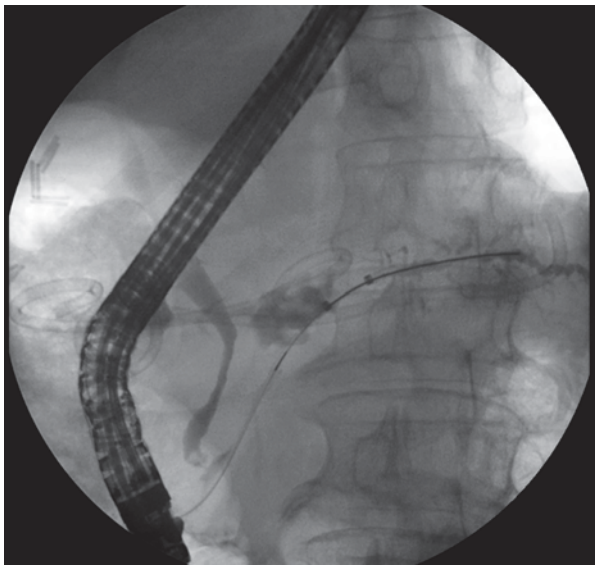


Fig. 16 ERCP demonstrating pancreatic duct leak with extravasation of contrast. ERCP endoscopic retrograde cholangiopancreatography

An open necrosectomy is associated with the complications in 34–95% of patients and death in up to 39%. Additionally, the open necrosectomy has been associated with pancreatic insufficiency. [22, 23] However, over the last decade, studies have shown that minimally invasive techniques are superior to open necrosectomy with regard to morbidity, mortality, hospital stay, and postoperative pancreatic insufficiency. The minimally invasive techniques include video assisted retroperitoneal debridement via a radiologically placed percutaneous tract as well as endoscopic necrosectomy techniques.

The Dutch pancreatitis study group presented their results of a multicenter study which randomized 88 patients with necrotizing pancreatitis and infected necrosis to primary open necrosectomy or to a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by video-assisted retroperitoneal debridement via the percutaneous tract. The primary end point was a composite of major complications (new-onset multiple-organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death. The primary end point occurred in 31 of 45 patients (69%) in the open necrosectomy group and in 17 of 43 patients (40%) following the step-up approach (risk ratio with the step-up approach, 0.57; 95% confidence interval, 0.38–0.87; $P=0.006$). Of the patients assigned to the step-up approach, 35% were treated with percutaneous drainage only. New-onset multiple-organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% versus 40%, $P=0.002$). The rate of death did not differ significantly between groups (19% versus 16%, $P=0.70$). Patients assigned to the step-up approach had a lower rate of incisional hernias (7% versus 24%, $P=0.03$) and new-onset diabetes (16% versus 38%, $P=0.02$). The authors concluded that a minimally

invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite end point of major complications or death among patients with necrotizing pancreatitis and infected necrotic tissue. [21]

A subsequent study by the same Dutch pancreatitis study group randomly allocated patients with infected necrotizing pancreatitis to either endoscopic transgastric or surgical necrosectomy. An endoscopic necrosectomy consisted of transgastric puncture, balloon dilatation, retroperitoneal drainage, and necrosectomy. A surgical necrosectomy consisted of video-assisted retroperitoneal debridement or, if not feasible, laparotomy. The primary end point was the post-procedural proinflammatory response as measured by serum interleukin 6 (IL-6) levels. The secondary clinical end points included a predefined composite end point of major complications (new-onset multiple-organ failure, intra-abdominal bleeding, enterocutaneous fistula, or pancreatic fistula) or death. In the 22 patients who were randomized, endoscopic transgastric necrosectomy reduced the post-procedural IL-6 levels compared with surgical necrosectomy ($P=0.004$). The composite clinical end point occurred less often after endoscopic necrosectomy (20% versus 80% $P=0.03$). The endoscopic necrosectomy did not cause new-onset multiple-organ failure (0% versus 50%, $P=0.03$) and reduced the number of pancreatic fistulas (10% versus 70%; RD, 0.60; 95% CI, 0.17–0.81; $P=0.02$). The authors concluded that in patients with infected necrotizing pancreatitis, endoscopic necrosectomy reduced the proinflammatory response as well as the composite clinical end point compared with surgical necrosectomy [24].

The endoscopic management of WOPN is successful in achieving resolution in a majority of patients [8, 25]. There have been a number of studies evaluating combination therapy for WOPN. A number of studies have evaluated dual modality combined endoscopic and percutaneous management [11, 26, 27].

Adverse Events

There are a number of adverse events associated with endoscopic management of PFCs (Table 2). It is recommended that the endoscopic drainage might be performed with appropriate back-up support from surgery and interventional radiology. Life-threatening adverse events are rare, but are mainly from severe hemorrhage and air-embolization. It is highly recommended that carbon dioxide (CO2) be used for insufflation to minimize the chance of air-embolization.

The most feared complications associated with endoscopic drainage of PFCs are bleeding and perforation. Bleeding that occurs during enterotomy tract creation can be managed endoscopically with a balloon tamponade within the tract, placement of a fcSEMS [28] to tamponade bleeding, epinephrine injection +/-hemoclip placement. If bleeding cannot be controlled, then the angiographic embolization or surgical management may be necessary. A perforation occurs when the site selected for transmural access is not adherent to the PFC. If a perforation occurs, this may lead to contamination of the peritoneal cavity with GI contaminates and PFC con-

Table 2 Adverse events related to endoscopic management of PFCs

Anesthesia related events
Aspiration
Air embolization
Bleeding
Infection
Perforation
Stent migration

PFC pancreatic fluid collections

taminates. Such a complication will require surgical intervention if there is a clinical worsening despite conservative measures including intravenous antibiotics and intermittent nasogastric suctioning. A perforation that leads to egress of PFC liquid between the PFC and the GI tract could potentially be addressed by the placement of an fcSEMS, or percutaneous drainage or surgical intervention depending on the clinical scenario.

Infections occur due to inadequate drainage of fluid or solid necrotic debris. This can be managed by antibiotics, stent revision, placement of percutaneous drains, and ensuring adequate outflow at the enterotomy tract. Rarely, a stent migration can occur either within the collection or into the GI lumen. If stents migrate within the collection, these can be endoscopically retrieved if the enterotomy tract is still patent and the collection has not completely collapsed.

Future Directions

The endoscopic management of PFCs has evolved over the years as endoscopic tools and techniques have evolved. While the current management of liquefied PFCs likely would not change significantly, the newer generation lumen apposing fcSEMS will likely play a larger role in the management of WOPN. The Xlumena Axios stent comes in multiple diameters 15 mm and soon 20 mm will likely be utilized in a greater frequency to manage WOPN [29, 30]. (Fig. 17) These larger diameter lumen apposing fcSEMS will allow for easier access into the collection, possibly quicker resolution of the necrotic material due to the present of gastric acid, and fewer repeat endoscopic procedures. Patients with disconnected duct syndrome after pancreatic necrosis might be managed with a “permanent” fistula tract to the stomach by leaving an Axios stent in situ. This may obviate the need for patients to undergo a distal pancreatectomy due to persistent pancreatic juice production and no outlet. Patients with WOPN may also be initially managed with a multiple gateway method [13]. One would envision the placement of two Axios stents adjacent to each other. An irrigating catheter could be advanced via a percutaneous endoscopic gastrostomy (PEG) tube through one of the Axios stents for irrigation, while the other stent would be used for the outlet. This might lead to quicker resolution,

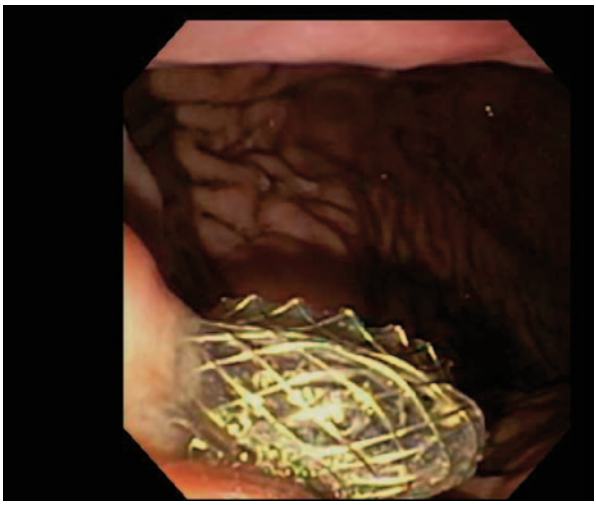


Fig. 17 Axios stent placed across gastric wall

decreased risk of adverse events (bleeding and fistula formation from a percutaneous drain). Prospective studies are required to understand the optimal use of these newer covered metal stents in the management of WOPN.

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Endoscopic Treatment of Obesity

Shelby Sullivan

Abbreviations

RYGB	Roux-en-Y gastric bypass
BMI	Body mass index
BPD	Biliopancreatic diversion
GJ	Gastrojejunostomy
EBT	Endoscopic bariatric therapy
IGB	Intragastric balloon
DJBL	Duodenal jejunal bypass liner

Introduction

Obesity increases morbidity and mortality and adversely affects every organ system [1–3]. Recent data suggest that there is a 2–3 fold increase for incremental health care costs in obese adults in the USA compared with normal weight adults [4]. The age adjusted prevalence of obesity in the USA from the 2011–2012 national health and nutrition examination survey (NHANES) was 34.9%, and overall there has been no change in prevalence since the 2003–2004 NHANES [5]. Although it is encouraging that the prevalence of obesity has plateaued in the USA, the lack of a reduction in prevalence highlights the need for additional treatment strategies. With new advances in the development of endoscopic therapy for obesity, endoscopists are poised to fill the gap in current treatment options. This chapter focuses on therapies for endoscopic revision of RYGB and primary endoscopic bariatric therapies.

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Endoscopic Revision of Bariatric Surgery

Weight regain is a significant problem following bariatric surgical procedures. Data from the Swedish obesity study found that after a maximal total weight loss of 38 ± 7 % 1 year after RYGB, only 25 ± 11 % weight loss was maintained at 10 years with 8.8 % of patients maintaining < 5 % total weight loss [6]. This was similar to the findings in LAGB (Laparoscopic Adjustable Gastric Banding) with 21 ± 10 % weight loss at 1 year, 13.2 ± 13 % weight loss at 10 years with 25 % of patients maintaining < 5 % weight loss at 10 years [6]. Christou et al. found a significant increase in body mass index (BMI) from nadir (28.6 ± 0.3 kg/m^2) to follow-up 11.4 years later (33.6 ± 1.3 kg/m^2) [7]. This was most pronounced in patients with a BMI ≥ 50 kg/m^2, with a nadir of 31.4 ± 0.7 kg/m^2 to 38.3 kg/m^2 at follow-up. Further, they used the Reinhold classification (a classification of weight-loss failure after bariatric surgery based on the start BMI) [8] to evaluate 10-year outcomes for RYGB and compared them to previously published data on biliopancreatic diversion (BPD) [7, 9]. They found equivalent rates of weight-loss failure at ≥ 10-year follow-up: patients with a presurgery BMI of < 50 kg/m^2 had follow-up failure rates of 20.2 % and 20.4 % for BPD and RYGB, respectively and patients with a presurgery BMI of > 50 kg/m^2 had follow-up failure rates of 40.9 % and 34.9 % for BPD and RYGB, respectively. Similar findings at 5-year follow-up were also seen by Magro et al. with weight regain seen in 50 % of patients, and higher rates of failure in patients with a presurgery BMI > 50 kg/m^2 [10].

The mechanisms for weight regain are likely multifactorial, but not well understood. Disordered eating behaviors [11–16] and dilated gastrojejunostomy (GJ) diameter and gastric pouch volume [17, 18] correlate with weight regain, but do not account for all weight regain. Obese patients who have undergone RYGB experience a decrease in the hedonic response (how much a stimulus is liked or disliked) to sweet or highly palatable foods [19, 20], and also make healthier food choices [21]. It was also recently shown that at 4–6 months after RYGB with 20 % weight loss, repetitive tasting of sucrose changed from pleasant to unpleasant compared to both baseline testing and to patients who had 20 % weight loss in 4–6 months after laparoscopic adjustable gastric banding [22]. In addition, the RYGB was associated with improvement in eating behaviors [22] and a remission of food addiction in 93 % of subjects with presurgery food addiction [23]. Conversely, weight regain after RYGB has been shown to correlate with the loss of aversion to sweet snacks [24], binge eating, loss of control eating, and grazing behaviors [11–16]. Unfortunately, preoperative food preferences and eating behaviors do not predict weight regain after RYGB. A meta-analysis including five studies of RYGB and five studies of laparoscopic adjustable gastric banding showed no difference in weight loss between binge eating and nonbinge eating groups as assessed prior to surgery [25]. Interestingly, cognitive restraint of eating as assessed by the three factor eating questionnaire improved after revision of the GJ with endoscopic transoral outlet reduction (TOR) procedure in patients who had regained weight after RYGB, and there was a trend toward improvement in uncontrolled eating [26]. These data

suggest that changes to gastrointestinal anatomy affect eating behaviors and food preferences. Moreover, revising the postsurgical anatomy may restore that effect in patients who have regained weight after RYGB.

Both gastric pouch size and GJ diameter have been shown to correlate with weight regain after RYGB. Roberts et al. found a small, but significant correlation between pouch size and weight loss after RYGB at 12 months (R squared = 0.188, $p = < 0.002$) [27]. Campos et al. also found pouch size to be associated with poor weight loss in univariate and multivariate analyses [28]. Heneghan et al. found a significant difference in stoma and pouch size in bariatric surgery patients with weight regain compared with a control group of bariatric surgery patients without weight regain; pouch length 5.0 ± 2.4 cm versus 5.8 ± 2.6 cm, $p = 0.005$ and stoma diameter 2.1 ± 0.8 cm versus 2.5 ± 1.0 cm, $p < 0.001$ in the control compared with weight regain group, respectively [18]. Abu Dayyeh et al. found a significant correlation between weight regain and GJ diameter, even when controlled for other factors related to weight regain ($\beta = 0.19$, $p = 0.003$)[17]. These data support dilated gastric pouch size and GJ diameter as important factors contributing to weight regain after gastric bypass.

Treatment of patients with weight regain after bariatric surgery has been a challenge. Although weight loss has been demonstrated with surgical revision of the GJ and gastric pouch, the complication rates are higher than with the initial procedure [29–32]. This has prompted the evaluation of endoscopic approaches to revise the dilated postsurgical anatomy including suturing, tissue plication, sclerotherapy, and clips.

Endoscopic Suturing

Endoscopic suturing has emerged as an effective tool for GJ and gastric pouch revision. The transoral outlet reduction (TORe) [33–36] procedure was piloted by Thompson et al. in 2006 with the endocinch suturing system (C.R. BARD Inc, Murray Hill, NJ, USA), a superficial suturing device. The technique usually includes mucosal ablation using cautery or argon plasma coagulation, then placing sutures around the dilated stoma to reduce the diameter of the stoma. In practice, additional sutures can be placed in the gastric pouch, if the gastric pouch is also dilated; however, this has not been routinely done in all cases. TORe was demonstrated to produce weight loss or weight stabilization in patients who regained weight after RYGB in a multicenter, randomized sham controlled trial in 77 subjects (active $n = 50$, sham $n = 27$, RESTORe Trial) [35]. The mean procedure time was 107 ± 183 min; and technical success, defined as reducing the GJ to 10 mm or less, was achieved in 89.6% of the subjects. The percentage weight loss in the intention to treat group with the last observation carried forward was 3.5% (95% CI,1.8–5.3%) and 0.4% (95% CI, −2.3 to 3.0%) in the TORe and Sham groups, respectively ($p = 0.021$). More importantly, weight loss or weight stabilization occurred in 96% of TORe patients, but only 78% of controls, $p = 0.019$. A recently published

retrospective analysis of 25 consecutive patients who underwent the TORe procedure with a full thickness suturing device, the overstitch endoscopic suturing system (Apollo endosurgery, Austin, Tx) found that 16 patients who were observed at 12 months lost 56% of the weight that they had regained from their lowest weight after RYGB. More importantly none of those patients continued to gain weight after the TORe procedure while two patients who were known to have a failure of the TORe sutures due to postprocedure vomiting continued to gain weight [37]. Furthermore, in a matched cohort study of superficial thickness suturing devices compared with full thickness suturing devices for TORe, the weight loss with full thickness TORe was superior to superficial thickness TORe (1 year percentage excess weight loss 18.9±5.4% and 9.1±2.3% for full thickness and superficial thickness TORe, respectively)[38]. Adverse events with TORe have included nausea and vomiting, a small gastric mucosal tear with minor bleeding, pharyngolaryngeal pain, bleeding requiring transfusion and constipation. These efficacy and safety data support TORe as a valid approach for GJ and gastric pouch revision for weight regain after RYGB.

Tissue Plication

The incisionless operating platform (IOP) (USGI Medical, San Clemente, California, USA) is a tissue plication system that allows the placement of full thickness tissue anchors, in a procedure called the revision obesity surgery endoscopic (ROSE) procedure. The operating platform, called the TransPort, contains four large working channels which allow the placement of an ultra-slim endoscope and endosurgical instruments. Tissue is grasped and pulled into a tissue approximator. Placing a needle and tissue anchor through this tented tissue creates a full thickness tissue fold. Two small pilot studies in patients with weight regain after RYGB demonstrated short-term weight loss of 7.8–8.8 kg at 3 months after placement of tissue anchors for both GJ diameter reduction and gastric poch volume reduction [39, 40]. Data from a multicenter registry of 116 patients reported 6.5±6.5 kg weight loss at 6 months with stoma diameter reduced by 50% to 11.5 mm, and pouch length reduced by 44% to 3.3 cm [41]. Twelve-month follow-up was available in 73 of those subjects, demonstrating 5.9±1.1 kg weight loss [42]. This device is currently not being offered in the USA, but may be reintroduced in the future.

The StomaphyX device (EndoGastric Solutions Inc, Redmond, Washington, USA) is also a tissue plication device that tents tissue with a suction device and deploys polypropylene H-fasteners to approximate serosal surfaces. This device was first used to treat weight regain in small studies with short follow-up [43, 44]. In one study, 12-month excess body weight loss was 19.5%, but was only reported in six of 39 subjects[43]. A subsequent study of 59 patients with a mean follow-up of 41 months demonstrated a weight loss of 1.7±9.7 kg, and endoscopy on 12 patients revealed no significant difference in pouch or stoma size at 18 months compared to the baseline [45]. Moreover, a randomized sham controlled trial was closed early

because primary efficacy endpoints of reaching ≥15% excess BMI loss on average and BMI of 35 kg/m^2 or less at 12 months were not achieved at the interim analysis. Only 22.2% of patients reached ≥15% excess BMI loss and BMI <35 kg/m^{2}at month 12. However, a significant difference in excess BMI loss was seen in the active compared with the sham group (7.8%±10.7% and 2.0%±8.5% at 12 months, respectively, $p<0.05$) [46]. Due to the failure of meeting the primary endpoints of this trial, EndoGastric Solutions has abandoned StomaphyX as a tool for endoscopic RYGB revision.

Sclerotherapy

Sclerotherapy involves injecting a sclerosant (usually sodium morrhuate) into multiple points around the GJ. The scar formation results in a decrease in the diameter of the GJ with weight loss or weight stabilization in 72–96.5% of patients at 12–18 months [47–52]. The largest study of this therapy followed 231 consecutive patients with an average of 36% weight regain from nadir who underwent 1–4 sclerotherapy sessions between September 2008 and March 2011. The baseline GJ diameter was 19±5 mm and the mean volume of sodium morrhuate used was 16±5 ml per session. The weight regain stabilized in 76% of all patients included in the analysis at 12 months, but it stabilized in 90% of patients who received two or three sclerotherapy sessions. This indicates a need for repeat sclerotherapy to optimize the effect on GJ diameter reduction. Complications of sclerotherapy included abdominal pain, bleeding, small ulcerations, and transient diastolic blood pressure increases [51].

Clips

Over-the-scope-clips (OTSC, Ovesco, Tubingen, Germany) have been primarily been used in the treatment of fistulas as a complication of bariatric surgery. However, one study reported 94 subjects whose stoma diameter was reduced from 35 to 8 mm with placement of up to two OTSCs placed on the opposite sides of the stoma [53]. The mean BMI decreased from 32.8±1.9 to 27.4±3.8 at 12 months.

Summary

Weight regain after RYGB occurs in a minority of patients after RYGB, but has a significant negative impact on those patients. The mechanisms for weight regain are not well understood. Eating behaviors and dilated gastric pouch and GJ anatomy are likely to play a role in weight regain after RYGB. They may also be related to each other and the evidence suggests that changes in the gut anatomy may cause changes

in eating behavior and food preferences. Multiple techniques for endoscopic revision of the GJ and gastric pouch have been evaluated. Randomized sham controlled trials of superficial suturing or plication devices showed similar total weight loss, although one trial was stopped early due to a failure to meet predefined efficacy endpoints. Full thickness suturing procedures and full thickness plication devices have not undergone randomized sham controlled evaluation; however, the case series and one cohort study comparing superficial thickness to full thickness suturing indicate that full thickness suturing or plication is superior to superficial suturing for maximum weight loss and long-term weight maintenance. Sclerotherapy may be an effective treatment, but frequently requires more than one endoscopic sclerotherapy session for maximum benefit. This may limit the overall effectiveness of sclerotherapy.

Further research in endoscopic therapy of weight regain after bariatric surgery is needed. Heneghan et al. demonstrated statistically different, but clinically similar stoma diameter between patients with weight regain and those maintaining their weight loss. In addition, there has been variability in the pre-endoscopic revision stoma and pouch diameter seen in the RYGB revision studies with one third of patients in the RESTORe trial excluded for a GJ diameter < 20 mm. Although most of the endoscopic RYGB revision cases have resulted in cessation of further weight gain, there was significant variability in weight loss. Additional tools to identify patients who would mostly benefit from endoscopic revision of the post RYGB surgical anatomy and when to intervene would allow clinicians to better allocate resources to those patients.

Primary Endoscopic Bariatric Therapy

Bariatric surgery is currently the most effective treatment for obesity and has been shown to be superior to lifestyle therapy (consisting of diet, exercise, and behavior therapy) [54–56] and pharmacotherapy [57] for weight loss, weight maintenance, and treatment of obesity related diseases [56, 58]. Although there has been some recent controversy over the cost-effectiveness of bariatric surgery [59], the majority of cost–benefit analyses demonstrate a long-term cost-effectiveness of bariatric surgery [60–62]. Minor postoperative complications occur frequently, but serious complications or reoperation occur in 7% or less of postbariatric surgery patients and the mortality rate is low [58, 63]. Despite this, < 1% of people who qualify for bariatric surgery actually get surgery [63]. Multiple factors are likely involved in the percentage of patients opting for bariatric surgery including: fear of surgical risks or unacceptable surgical risk due to comorbidities, unacceptable recovery times, limited access, lack of primary care physician referral, and, unacceptable out-of-pocket expense.

Primary endoscopic bariatric therapy (EBT) overcomes many of the barriers preventing patients from undergoing traditional bariatric surgery. First, primary EBT procedures and devices that are currently in practice or are being evaluated in

trials are associated with lower complication rates and shorter recovery times than the bariatric surgery. Some primary EBTs may only require conscious sedation, so sicker patients who may not be good candidates for surgery may still qualify for endoscopic placement of a device. Primary EBT will also likely be more accessible to patients, because the number of primary EBTs that could be performed per year dwarfs the number of bariatric surgeries that are performed per year due to both the higher number of endoscopists (either gastroenterologists or surgeons) that could perform the procedures and the short procedure time allowing for more procedures per day. Further, most gastroenterologists have a strong referral base, potentially lowering the threshold for primary care referrals, and increasing the number of patients that are referred for primary EBT. Lastly, although primary EBT will likely not be covered by third party payers in the short-term, the cost of the procedures will be low enough to appeal to a large number of self-paying patients. Moreover, as the acceptability of these therapies and the improvements in obesity related comorbidities becomes evident, third party payers may cover these procedures in their policies further reducing the barrier to effective obesity treatment. Multiple devices have been or are currently in the development and testing stages for primary EBT.

Intragastric Balloon

The intragastric balloon (IGB) is a space occupying EBT designed to increase satiation with a meal and thereby decrease food intake resulting in weight loss. Currently, no IGBs are approved for use in the USA, however several balloons have been approved for use around the world. The Garren-Edwards gastric bubble was the first IGB that was approved for use by the FDA in 1985. In 1992, it was taken off of the market due to both safety concerns and lack of efficacy. The device had a cylindrical shape with edges which damaged the mucosa and was made from polyurethane that was too easily deflated. This led to the mucosal breaks and ulcerations in the stomach as well as deflations which caused small bowel obstruction after the deflated device migrated into the small bowel. Also, there was no difference in weight loss between the device and sham groups in randomized sham-controlled trials [64–71]. The volume of the Garren-Edwards gastric bubble was only 220 ml when fully distended, and evidence suggests that a volume of $\geq$400 ml is needed for a reduction of food intake [72]. Several new designs have been developed which address the issues surrounding the failure of the Garren-Edwards gastric bubble (Table 1). All of the new generation of balloons have spherical shapes and minimize edges that could cause mucosal damage. These devices differ significantly in their designs to mitigate balloon deflation, migration, and small bowel obstruction and to allow fill volumes great enough for weight loss (Table 1). Some of the balloons have features that prevent migration of the device in the event of a deflation including the Reshape Duo balloon (Fig. 1) and the Spatz adjustable balloon. Although all of the balloons listed are designed to be removed endoscopically, some of the balloons may be small enough when deflated to pass through the gastrointestinal tract without causing obstruction.

Table 1 Characteristics of intragastric balloons evaluated in humans

Name	Company	Design	Fill	Placement/ retrieval
ORBERA (formerly Bioenterics Intragastric Balloon)	Apollo endosurgery, Austin, TX	500 ml silicon balloon	500 ml saline with methylene blue	Endoscopic/ endoscopic 6-month duration
ReShape Duo balloon	ReShape Medical, San Clemente, CA	Two 450 ml silicon balloons tethered to a flexible silicone shaft	375–450 ml saline with methylene blue	Endoscopic/ endoscopic 6-month duration
Heliosphere bag	Helioscopie medical implants, Vienne, France	550 cm^3 polyurethane and silicone sphere	550 ml air	Endoscopic/ endoscopic 6-month duration
Spatz adjustable agstric balloon	Spatz FGIA, Jericho, NY	800 ml silicon balloon mounted on a catheter, adjustable after initial placement	500–800 ml saline	Endoscopic/ endoscopic 12-month duration
MedSil balloon	MedSil, Moscow, Russia	700 ml silicon balloon	400–700 ml saline	Endoscopic/ endoscopic 6 months
Silimed gastric balloon	Silimed Industria de Implantes, Rio De Janeiro, Brazil	650 ml silicone balloon	632 ml saline, 20 ml Iopamiron contrast, 10 ml 2% methylene blue	Endoscopic/ endoscopic 6 months
Obalon	Obalon therapeutics, Carlsbad, CA	250 ml balloon, up to 3 placed sequentially	Nitrogen gas	Swallowed pill/ endoscopic 3 months

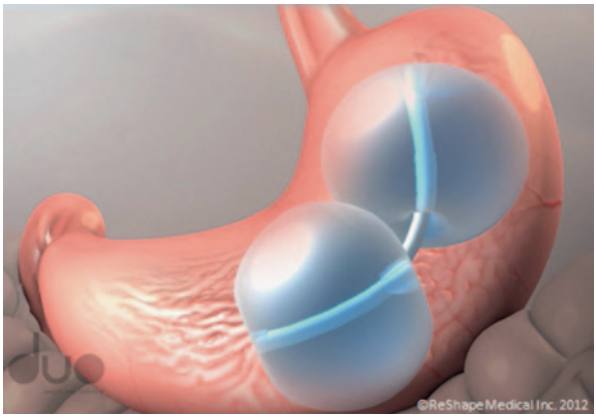

Fig. 1 The ReShape Medical ReShape Duo Balloon inflated in the stomach

IGBs have been shown to be effective at inducing weight loss greater than lifestyle therapy alone or pharmacotherapy alone. A meta-analysis with 3608 subjects demonstrated an estimated mean total body weight loss of 12.2% (14.7 kg) with at least 12 weeks of therapy with the ORBERA balloon [73]. A randomized controlled cross-over trial demonstrated superiority of IGB's to pharmacotherapy. At balloon retrieval (6 months) total weight loss with IGB was 14.5 ± 1.2% compared to 9.1 ± 1.5% in the sibutramine group, $p < 0.05$ [74]. Moreover, at 1 year 50% of patients who received an IGB plus lifestyle therapy maintained ≥ 10% total body weight loss compared to 35% of patients in the sibutraine group.

Long-term weight loss data after one balloon placement is sparse. One studyevaluated patients 60 months after balloon removal; however, only 195/474 patients returned for 60-month evaluation [75]. Total weight loss was 27.3 ± 9.6 kg and 7.26 ± 5.4 kg at the time of the balloon removal and at 60 months, respectively, with 23% maintaining percent excess weight loss > 20%. Although, the maintenance of some weight loss long-term is encouraging, investigators have evaluated the repeated use of IGB for long-term weight loss therapy. Genco et al. reported 100 obese patients who were randomized to receive an IGB for 6 months followed by lifestyle therapy alone or IGB followed by another IGB placement 1 month later for 6 months [76]. Thirteen-month percentage excess weight loss was 51.9 ± 24.6% in the two consecutive IGB group and 25.1 ± 26.2% in the IGB then lifestyle therapy alone group. A subsequent study by Genco et al. followed 83 patients for 6 years, and replaced the IGB after the patients regained ≥ 50% of the weight lost from the previous IGB placement [77]. All patients required a second balloon placement after an average of 12 months (range 1–55 months). Eighteen patients required a third balloon and one patient required a fourth balloon. Initial BMI prior to the first balloon placement was 43.7 kg/m^2, and 37.6 kg/m^2 at 76-month follow-up. However, 18 patients underwent bariatric surgery instead of continuing balloon placement between 12 and 72 months after the first balloon was removed.

The rate of serious complications in a large case series of 2515 patients was < 3% and including gastric perforation, gastric or small bowel obstruction, esophagitis, and gastric ulceration [78]. Two deaths related to gastric perforations occurred. Common mild to moderate adverse reactions in the first few days after balloon placement include nausea, vomiting, and abdominal pain which occur in most patients for the first few days after device placement. This was treated with oral medication and hydration in an outpatient setting in most patients, and typically resolved in a few days.

Taken together, these data suggest that the current generation of IGB has lower complication rates and better efficacy than the first generation of IGB. Although acute postplacement nausea, vomiting, and abdominal discomfort occurs, it is controlled with oral medications and dietary changes in most patients. IGB placement is an effective tool for short-term weight loss, and is superior to both lifestyle therapy alone and pharmacotherapy. Long-term weight loss does occur in some patients after IGB removal, but repeated balloon placement based on weight regain may be a better strategy for long-term weight control. Additional research is needed to address these long-term management questions.

Fig. 2 The GI Dynamics EndoBarrier, a duodenal jejunal bypass liner

Duodenal Jejunal Bypass Liner

The duodenal jejunal bypass liner (DJBL; EndoBarrier, GI Dynamics, Boston, MA; Fig. 2) is an impermeable flouropolymer duodenal jejunal liner that extends 60 cm into the small bowel. The device is placed endoscopically and anchors in the duodenal bulb via a nitinol anchor with barbs that allow for reversible fixation. Ingested nutrients flow into the liner, which prevents contact with the intestinal mucosa or biliary secretions until the liner ends in the mid-jejunum, creating a functional bypass of the duodenum and proximal jejunum which mimics the biliopancreatic limb of a RYGB.

Multiple studies have demonstrated the efficacy of bariatric surgery in treating type 2 diabetes, including two recent randomized control trials of bariatric surgery compared with the intensive medical and lifestyle therapy for the treatment of type 2 diabetes [56, 79]. The RYGB was superior to medical/lifestyle intervention [56, 79] and laparoscopic adjustable gastric banding [56] at inducing partial or complete remission of type 2 diabetes. Animal models suggest that jejunal nutrient sensing after duodenal exclusion plays a role in the early improvement in glycemic control after duodenal jejunal bypass surgery [80], and support the hypothesis that exclusion of the biliopancreatic limb has weight loss independent effects on multiorgan insulin sensitivity and glucose metabolism. However, the human studies are less clear and confounded by the effect of calorie restriction and altered metabolic responses to a meal which occurs immediately after surgery [81–84].

Initial experience with the DJBL demonstrated the device to be superior to lifestyle therapy in multiple short (12–24 weeks) single arm and randomized controlled trials for weight loss [85–87]. Subjects in the DJBL group achieved 19.0–23.6% excess weight loss (EWL) compared to 5.3–6.9% EWL in the control groups. A longer therapy has subsequently been shown to produce more weight loss, and a single arm trial with 52 weeks of therapy in 39 subjects demonstrated 22.1 ± 2.1 kg weight loss (19.9 ± 1.8% total body weight loss) [88]. A sham controlled trial for preoperative weight loss demonstrated lower weight loss 11.9 ± 1.4% compared with 2.7 ± 2% excess weight loss in the DJBL ($n = 13$) and control groups ($n = 24$), respectively ($p < 0.05$) [89]; however, another 24 week randomized sham-controlled trial demonstrated superiority of the DJBL over sham control for decreasing HbA1c in patients with type 2 diabetes (−2.4 ± 0.7% and −0.8 ± 0.4% in the DJBL and control groups, respectively, $p < 0.05$) [90]. Similar decreases in HbA1c were also seen in a single

arm 24-weeks trial (HgbA1c 8.4±0.2% to 7.0±0.2% from baseline to end study, $p<0.01$)[91], but more importantly, glycemic control after a liquid mixed meal test improved 1 week after implantation before any significant weight loss occurred, suggesting that the effect on glucose control may be weight loss independent. Subsequently, longer studies have been performed out to 52 weeks including a study in obese diabetic subjects with a 52-week HbA1c reduction of −2.3±0.3% in 13 subjects [92]; and in subjects with lower BMI (30.0±3.6 kg/m^2) with a week 52 HbA1c reduction from 8.7±0.9% to 7.5±1.6% (baseline to end study, respectively, $p=0.004$) with only 6.5±4.1 kg weight loss [93].

A few serious adverse events have been reported and no deaths have occurred in relation to the DJBL. One duodenal perforation requiring laparoscopic closure has been reported [94]. Of note, 17–40% of subjects enrolled in the studies mentioned above had early device removal predominantly due to complications including: gastrointestinal bleeding, abdominal pain, nausea and vomiting, anchor migration, or obstruction. However, in most of these cases, the issues resolved with the removal of the device.

The efficacy data and relative safety of this device are promising as an effective treatment for obese subjects and potentially even overweight subjects with diabetes. A large multicenter randomized sham controlled trial of this device in diabetic subjects is currently underway in the USA. This will provide crucial information on efficacy and safety end points as well as further information on any persistent effects of the DJBL on glucose control after the device has been removed.

Intragastric Suturing to Alter Gastric Anatomy

A number of different approaches have been studied for per-oral gastric volume reduction. Transoral gastric volume reduction in the TRIM (transoral gastric volume reduction as intervention for weight management) trial utilizing the RESTORe suturing system (Bard/Davol, Warwick, RI) to plicate the anterior and posterior walls of the stomach was first reported in humans in 2010 [95]. This procedure reduces gastric volume by using a plication device to approximate the anterior and posterior gastric walls, and is thought to be a restrictive procedure. A total of 18 patients received an average of six plications; however, only 14 subjects completed 12 months of follow-up demonstrating a weight loss of 11.0±10.0 kg (excess weight loss 27.7±21.9%). No serious adverse events occurred, but plication was only successful in 16 patients and at the 12-month endoscopy, all sutures had spontaneously released in five subjects [95].

Transoral gastric volume reduction has also been reported with the overstitch endoscopic suturing system (Apollo Endosurgery, Austin, Tx; Fig. 3) in a single center pilot study. The full thickness endoscopic suturing device was used to create an endoscopic sleeve gastroplasty in four subjects [96]. The weight loss data are not available; however, a repeat endoscopy at 3 months in two patients revealed intact endoscopic gastric sleeves with only a small portion of the sleeve open in the

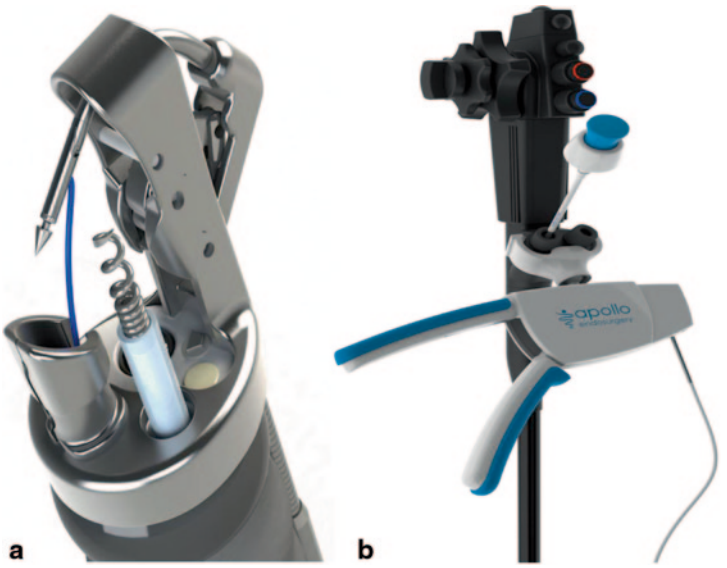

Fig. 3 The Apollo Endosurgery Overstitch tip with suturing arm and tissue helix on the end of an endoscope (panel A) and Apollo Overstitch handle attached to dual lumen endoscope (panel B)

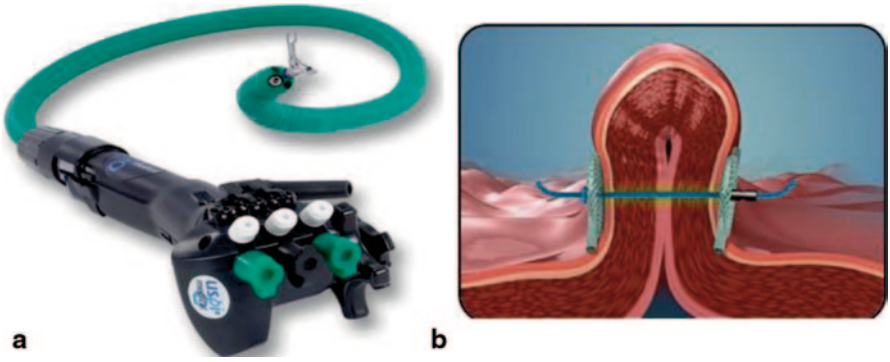

Fig. 4 The USGI Medical IOP Transport (panel A) and tissue plication with suture anchors (panel B)

gastric fundus of one subject. No serious adverse events occurred, but nausea and abdominal pain occurred in three patients, with one patient admitted for conservative therapy. All symptoms resolved by 72 h post-procedure. Since the overstitch endoscopic suturing system has been approved for intragastric suturing by the Food and Drug Administration (FDA), select centers in the USA and abroad have now started offering this therapy.

The IOP (USGI Medical, San Clemente, California, USA, Fig. 4) has also been used to create gastric tissue plications as a primary weight-loss procedure (primary obesity surgery endoluminal, POSE). This procedure involves creating tissue pli-

cations in the fundus and in the distal gastric body, which is thought to impair both gastric accommodation with a meal and delay gastric empyting. This increases satiation with a meal and satiety between meals, reducing food intake to produce weight loss. Results of a single arm, single center study of 45 patients was published in 2013. The 6 month data were only available for 27 of the subjects and demonstrated 16.3 ± 7.1kg (15.5 ± 6.1 %) total weight loss [79]. No serious adverse events occurred. Minor post-operative adverse effects included sore throat, abdominal pain, nausea, and chest pain; however, these typically resolved within 24 h and did not require additional hospital stay. A multicenter randomized sham-control trial is currently underway in the USA to further investigate the effectiveness of this procedure.

Transoral mucosal excision with sutured gastroplasty, which employs the use of both a tissue excision device and suturing device to create a gastric pouch similar to the pouch created with laparoscopic adjustable banding, has been demonstrated to be feasible in four patients [97]. The BMI ranged from 39–61 kg/m2, and percentage excess weight loss ranged from 0–68 % at 24 months. One subject had evidence of perforation on chest x-ray on post-operative day 1; however, no perforation was detected on a combined laparoscopic/endoscopic procedure performed that day. The patient did recover, but an endoscopy performed at 6 months demonstrated a loose gastroplasty with no food restriction.

Although gastric volume reduction is still in its infancy, the initial data is promising as a means to alter gastric anatomy without the need for external incisions. Further studies are necessary to evaluate the efficacy and long-term durability of these procedures.

Aspiration Therapy

Aspiration therapy involves the use AspireAsisst™ system (Aspire Bariatrics, King of Prussia, PA, Fig. 5) to remove up to 30 % of the calories consumed in a meal for weight loss. This is done through a gastrostomy tube called an A-Tube, which is placed with the pull technique commonly used for placement of percutaneous endoscopic gastrostomy tubes. This is capped with a skin port that allows for connection to the companion, which is a hand held device that allows for bidirectional flow of fluid either into the stomach or out of the stomach controlled by an external lever. Patients infuse tap water to aid with aspiration of gastric contents, and then switch the direction of the flow to allow gastric contents to drain out into the toilet. Data from one randomized control pilot study demonstrated superior weight loss in the aspiration therapy group ($n = 10$) compared to the lifestyle therapy only group ($n = 4$) at 1 year (18.6 % ± 2.3 % and 5.9 % ± 5.0 % total body weight loss, respectively; $p = 0.021$). Lifestyle therapy consisted of 15 individual therapy sessions plus quarterly group sessions. 7 out of 10 subjects in the aspiration therapy group completed 2 years of therapy and were successful in maintaining their weight loss; 21.2 % ± 2.8 % total body weight loss at 1 year and 20.1 % ± 3.5 % total body weight

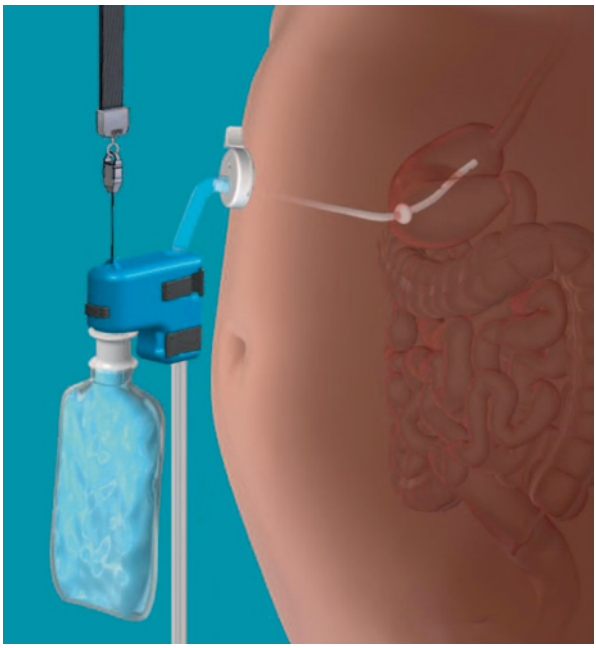

Fig. 5 The components of the Aspire Bariatrics Aspire-Assist™ System assembled for aspiration

loss at year 2, respectively; $p = 0.547$[98]. Multiple psychological evaluations were performed in these subjects, which demonstrated no adverse effects of this therapy on eating behaviors. Indirect measurements of food consumption also suggest that subjects did not eat more to compensate for calories that were aspirate. No serious adverse events occurred; however, abdominal pain in the first 4 weeks after device placement and peristomal skin irritation were common. Pain after the first 4 weeks of device placement was common with the initial A-Tube design used in the study. The A-Tube was modified during the trial to an all-silicone tube. The sustained weight loss and safety profile of the aspiration therapy support further evaluation of this therapy. More recently, preliminary results of a pilot trial conducted in the Czech Republic on six super obese patients (BMI 59.5–71.9 kg/m^2) were presented as an abstract [99]. Weight loss at 3 months was 15.5 kg. Only two subjects had reached the 12-month time point at the time of the abstract, with an average weight loss of 42 kg. Only three minor adverse events occurred, procedure success rate was 100 %, and all subjects were still using the therapy at the time of the abstract presentation. These early results suggest that the aspiration therapy may be a good long-term treatment for obesity even in the super obese population. Further studies are currently underway in Europe for obese and super obese subjects, and in the USA, a multicenter trial is also being conducted in obese subjects.

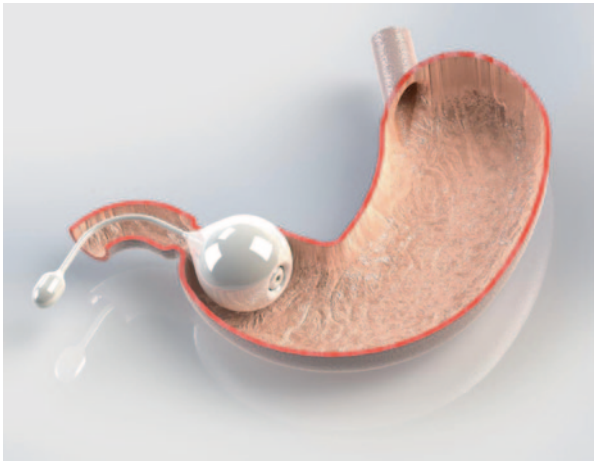

Fig. 6 The BAROnova TransPlyoric Shuttle in the pyloric position

TransPyloric Shuttle

The transpyloric shuttle (TPS, BAROnova Inc., Goleta, CA; Fig. 6) is a spherical bulb that is connected to a smaller spherical bulb by a flexible tether. The larger spherical bulb intermittently obstructs the pylorus, which is thought to delay gastric emptying and promote satiation resulting in early termination of a meal. One pilot trial has been reported in 20 subjects (BMI 36.0 ± 5.4 kg/m^2) [100]. The subjects were divided into two groups; a 3-month cohort ($n = 10$) with the TPS removed at after 3 months and a 6-month cohort ($n = 10$) with the TPS removed after 6 months. Subjects in the 3-months cohort achieved 8.9 ± 5.0 % total body weight loss while the 6 month cohort achieved 14.5 ± 5.8 % total body weight loss. No serious adverse events occurred and the TPS was generally well-tolerated without nausea or abdominal pain even immediately after device placement. However, ten subjects developed gastric ulcerations, and two of those subjects required early device removal (one in the 3-month cohort and one in the 6-month cohort).

Smart Self-Assembling Magnets for Endoscopy

Creation of gastroenteric anastomoses with smart self-assembling magnets for endoscopy has been shown to be technically feasible in an animal model [101]. The procedure described required advancing the gastroscope into the peritoneal space to secure the small bowel for placement of one set of the magnets. It is possible that this technique may be modified to be used in a human model. This presents a potential new mechanism for permanently bypassing the duodenum and proximal jejunum for weight loss and treatment of diabetes without the need for external incisions.

Summary

Primary EBT fills an important gap in the treatment of obesity. Multiple devices currently being studied are poised to meet FDA requirements for approval. While these new technologies provide an important step forward for obesity treatment, they do present new challenges for gastroenterologists. First, these devices and procedures were studied in conjunction with the lifestyle therapy. Endoscopists who wish to use these therapies for their patients will be required to develop an aftercare program that includes weight management program or partner with a reputable bariatric program. Secondly, the EBTs presented in this chapter have different mechanism of actions, and each one likely benefits a subpopulation of obese patients. The endoscopists will need to develop a skill set that allows them to determine which therapy best suits each individual patient based on a variety of patient characteristics. Third, these devices and procedures will likely not be covered by third party payers when they are initially introduced into the market. This will force the endoscopists to explore new financial models currently in place for other self-pay medical services.

Conclusions

Bariatric endoscopy for both weight regain after RYGB and for primary therapy is rapidly progressing into an important part of obesity therapy. A few therapies are already available for endoscopists, and multiple therapies will likely be commercially available in the next few years. While this opens the door to the endoscopists providing important therapies for obesity, it also presents new challenges that endoscopists must face in order to use these therapies successfully.

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Evaluation of the Small Bowel and Colon

Patricia Sanchez-Fermin, Jason Dundulis, Rajiv Chhabra and Wendell K. Clarkston

Introduction

Currently available endoscopic technologies for small bowel and colon evaluation include traditional endoscopic techniques, deep enteroscopy techniques, and wireless video capsule endoscopy. Wireless video endoscopy can roughly be defined as the use of means other than directly controlled, applied, or introduced electrical devices to obtain imaging data from the gastrointestinal tract to provide a diagnostic and/or treatment modality for a disease. In the world of science fiction, we imagine the ability to diagnose disease via a noninvasive "tricorder" like device (Star Trek, circa 1960s), and then perhaps employ nanotechnology targeted to the abnormality to treat it (Star Trek, circa 1990s). An analogy to this is the development of wireless video surveillance and weapons systems, some of which can be remotely guided, for use by law enforcement and the military. A tremendous amount of resources for research and development is required to develop this type of remote wireless technology, which is also still highly dependent on operator training and experience to be effective. In this chapter, we review existing wireless video technologies currently in use in diagnosing and treating gastrointestinal diseases of the small bowel and colon, and those modifications that are currently in the development and planning stages. We also review the means of wireless physiologic assessment of the small bowel (SmartPill) and current and potential future applications of more traditional "wired" endoscopic technologies, including single balloon enteroscopy, double balloon enteroscopy, spiral enteroscopy, and NaviAid.

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Wireless Video Capsule Endoscopy

The first publication describing the technological advance of wireless video capsule endoscopy was in *Nature* in the year 2000 [1]. Since that time, multiple peer-reviewed journal publications have ensued, coupled with significant advances in the quality of images, software, and algorithmic use of this new technology. In general, this initial capsule and subsequent capsules consist of an enclosed imaging component, power supply, and wireless communications hardware, a series of cutaneous electrodes to collect the transmitted images which are connected to a portable computer, and a computer terminal containing software used to view and interpret the images. The primary advantage of this technology over traditional endoscopic technology, such as push enteroscopy, single balloon enteroscopy, or double balloon enteroscopy has been its ability to easily reach otherwise difficult to access areas of the gastrointestinal (GI) tract to allow imaging of specific abnormalities. In addition, due to its relatively noninvasive nature, it has been proposed as a means to provide imaging of the GI tract in patients deemed high risk for traditional endoscopic procedures or sedation.

Available video capsule endoscopy devices, their year of introduction, technical specifications, and status of Food and Drug Administration (FDA) approval are included in Table 1. Four small bowel capsules are currently commercially available in different countries [1–4]. These include the the PillCam SB 2 (Given Imaging, Yokneam Israel), EndoCapsule (Olympus, Tokyo Japan), Mirocam (Intromedic, Seoul, South Korea), and OMOM (Jinshan S and T Co., Chongqing, China). PillCam SB 2, EndoCapsule, and MiroCam are FDA approved in the USA. MiroCam has incorporated a unique method of image transfer: electric field propagation that uses the body to conduct images and reduce the energy required to achieve transmission. OMOM was introduced as a lower cost alternative to Pillcam. OMOM, introduced in 2005, is not FDA approved in the USA. PillCam ESO (Given Imaging, Yokneam Israel), FDA approved in 2004, allows closer evaluation of the esophagus for detection of Barrett's esophagus and esophageal varices. Recently, Given Imaging has received FDA approval of PillCam Colon 2 (Given Imaging, Yokneam Israel), for screening for colorectal polyps and neoplasms in patients who have experienced an incomplete traditional optical colonoscopy.

Indications for Small Bowel Video Capsule Endoscopy (VCE)

There are several well-established indications for small bowel video capsule endoscopy (VCE), including obscure GI bleeding, investigation of Crohn's disease, and evaluation of small bowel tumors and hereditary polyposis syndromes. The use of VCE in the evaluation of celiac disease remains under investigation.

Table 1 Video capsule endoscopy devices

	VCE device	Manufacturer	Year introduced	FDA approved	Dimensions	Angle of view	Max images per second	Single/dual optical dome	Battery life
Small bowel	Pillcam SB I (M2A)	Given Imaging LTD, Yokneam, Israel	2001	Yes	11 × 26 mm	140	2	Single	8 h
	Pillcam SB 2	Given Imaging LTD, Yokneam, Israel	2007	Yes	11 × 26 mm	156	2	Single	8 h
	EndoCapsule	Olympus, Tokyo, Japan	2007	Yes	11 × 26 mm	145	2	Single	8 h
	OMOM	Jinshan S and T Co., Chongqing, China	2004	No	13 × 27.9 mm	140	2	Single	8–16 h
	MiroCAM	IntroMedic, Seoul, Korea	2005	Yes	11 × 24 mm	140	3	Single	11 h
Esophagus	Pillcam ESO	Given Imaging LTD, Yokneam, Israel	2004	Yes	11 × 26 mm	140	14	Dual	20 min
	Pillcam ESO 2	Given Imaging LTD, Yokneam, Israel	2007	Yes	11 × 26 mm	169	18	Dual	30 min
	Pillcam ESO 3	Given Imaging LTD, Yokneam, Israel	2011	Yes	11 × 26 mm	169	35	Dual	30 min
Colon	Pillcam Colon	Given Imaging LTD, Yokneam, Israel	2006	No	31 × 11 mm	156 × 2		Dual	Unspecified
	Pillcam Colon 2	Given Imaging LTD, Yokneam, Israel	2009	Yes	31.5 × 11.6 mm	172 × 2	35	Dual	Unspecified

Obscure GI Bleeding

Obscure GI bleeding (OGIB) is defined as recurrent episodes of clinically evident GI bleeding (i.e., melena, hematochezia, or hematemesis), positive fecal occult blood testing, or chronic iron deficiency anemia (IDA) despite negative upper and lower endoscopies. Obscure GI bleeding may include either overt or occult obscure GI bleeding. Overt GI bleeding indicates the visible presence of blood in the vomitus or stool, as opposed to occult bleeding, which presents as normal appearing stools with either positive fecal occult blood testing or unexplained iron deficiency anemia. OGIB is by far the most common indication for VCE. Numerous studies have demonstrated the superiority of VCE in identifying a source of OGIB compared to the other methods of small bowel evaluation, with the exception of double balloon enteroscopy (DBE), which has a similar diagnostic yield [5–8]. Based on a multicenter meta-analysis published by Kamalaporn et al., agreement between VCE and DBE was 74% for angioectasias and approximately 95% for all other lesions such as polyps, tumors, and ulcerations [9] (Figs. 1, 2). Given the invasive and time-intensive nature of double balloon enteroscopy (DBE), VCE is a more reasonable first-line study for the evaluation of OGIB.

A retrospective review of 260 OGIB cases revealed diagnostic yields of 60% in cases of overt obscure bleeding versus 46% in patients with occult obscure bleeding [10]. In cases of overt obscure bleeding, capsule endoscopy has the highest diagnostic yield within the first 48 h following hospitalization [11]. Negative VCE studies are also clinically important as these have been associated with rebleeding rates of

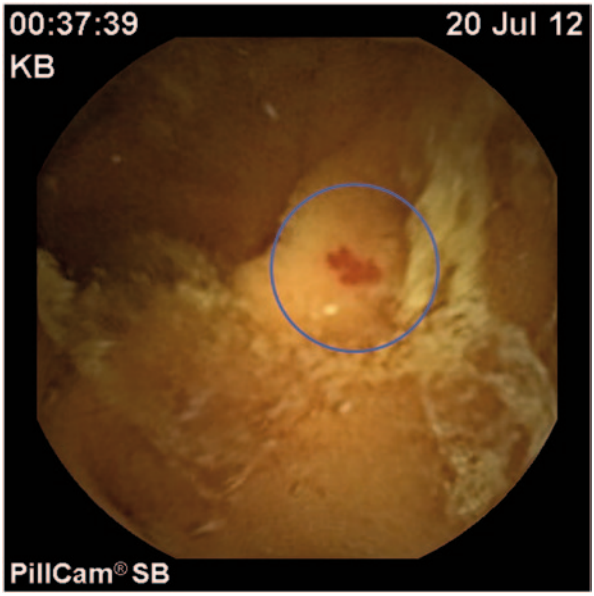

Fig 1 Nonbleeding small bowel angioectasia, jejunum

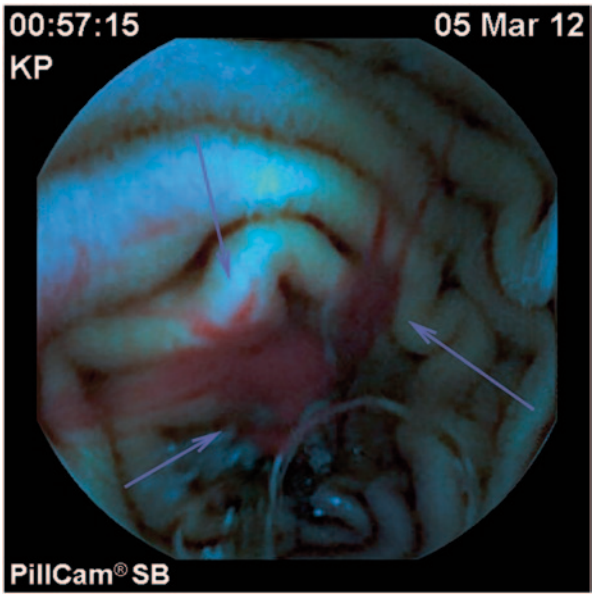

Fig 2 Active bleeding, small bowel angioectasia

less than 5% compared to patients with a positive study, in whom rebleeding rates approach 50% [12]. In a study by Apostolopoulos et al., 57% of 51 ambulatory patients with IDA referred for VCE were found to have likely sources of bleeding [13]. Since VCE is purely diagnostic, further evaluation or definitive therapy usually requires single or double balloon enteroscopy, surgery, or angiography.

Crohn's Disease

In the setting of known or suspected Crohn's disease, VCE may be helpful in establishing or confirming the diagnosis, assessing the extent and severity of small bowel involvement, determining mucosal response to therapy, and evaluating recurrent disease following surgery (Fig. 3). The use of VCE may also be considered in patients diagnosed with ulcerative colitis with atypical clinical features and in cases of indeterminate colitis [14]. Studies have yet to show significant difference in diagnostic yield of VCE compared to the current imaging modalities [15]. VCE's ability to directly visualize small bowel mucosa potentially may represent a novel means of monitoring disease activity and response to treatment. It is unclear whether VCE is superior to traditional imaging when evaluating recurrent disease [16] although this was suggested in a study published by Pons Beltron et al., which showed higher rates of recurrence in postsurgical patients monitored with VCE compared to endoscopic evaluation of the colon and neoileum [17]. Several scoring systems have been developed to aid the physician in quantifying disease severity although none

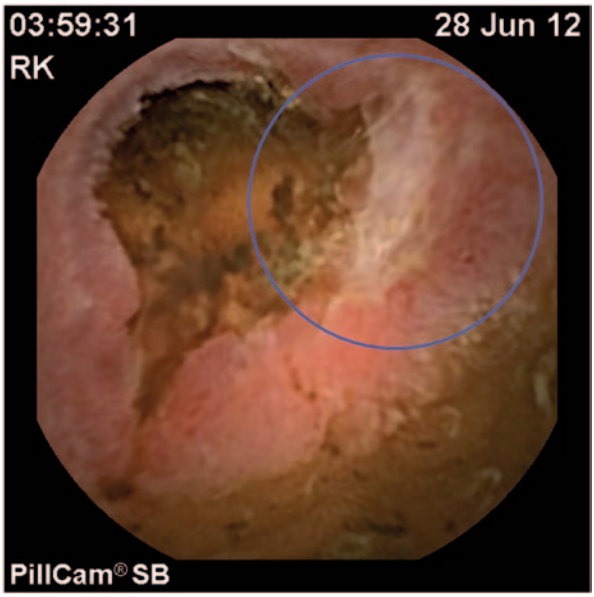

Fig 3 Ulceration of distal ileum consistent with recurrent Crohn's disease

have yet been adopted for widespread use. Recent studies have failed to show a significant correlation with mucosal healing and clinical symptom improvement, and as such, the importance of mucosal healing in the treatment of Crohn's disease remains under investigation [18].

VCE has significant limitations in assessing Crohn's disease. Although very good at visualizing small bowel ulcerations, VCE cannot readily distinguish between ulcers associated with Crohn's disease or due to other etiologies such as nonsteroidal anti-inflammatory drug (NSAID) use. For this reason, it has been suggested that patients undergoing VCE for evaluation of Crohn's disease should avoid NSAIDs for at least 1–2 months prior to the exam [19]. VCE is also unable to evaluate extraluminal manifestations of Crohn's disease such as abscess or fistulas. Due to the concerns of capsule retention in Crohn's disease patients, the evaluation of small bowel patency with Small Bowel Follow Through Radiologic Examination (SBFT) Computerized Tomography (CT), or a patency capsule is generally performed prior to capsule endoscopy [20, 21]. Several scoring systems have been developed over the years in an attempt to standardize the evaluation of small bowel Crohn's disease. The first such scoring system was developed by Kornbluth et al. in 2004 which examined five parameters: erythema, edema, nodularity, ulcers, and stenosis [22]. The scoring index introduced by Gralnek et al. in 2005, divided the small bowel into thirds and evaluated each segment for villous edema, ulcers, and stenosis [23]. Finally, the capsule endoscopy Crohn's disease activity index (CECDAI) is the most recent scoring system which was introduced by Gal et al. in 2008 [24]. The CECDAI divides the small bowel into two sections (proximal and distal) and scores each section depending on the most severe disease present, the extent of

Table 2 Capsule endoscopy-related Crohn's disease activity index (CECDAI

Segment	A: Inflammation (0–5)	B: Extent (0–3)	C: Stricturing (0–3)	CECDAI score
Proximal	0 = None	0 = None	0 = None	A1 × B1 + C1
(section 1)	1 = Mild/moderate	1 = Focal	1 = Single	
	2 = Severe	2 = Patchy	2 = Multiple	
	3 = Ulcer < 5 mm	3 = Diffuse	3 = Obstructing	
	4 = Ulcer 5–20 mm			
	5 = Ulcer > 20 mm			
Distal	0 = None	0 = None	0 = None	A2 × B2 + C2
(section 2)	1 = Mild/moderate	1 = Focal	1 = Single	
	2 = Severe	2 = Patchy	2 = Multiple	
	3 = Ulcer < 5 mm	3 = Diffuse	3 = Obstructing	
	4 = Ulcer 5–20 mm			
	5 = Ulcer > 20 mm			
			Section 1 + section 2 = Total	

disease, and the presence of strictures (Table 2). A multicenter, double-blind, prospective study published by Niv et al. in 2012 validated CECDAI and advocated its use in future studies [25].

At present, VCE has a complementary role in the diagnosis of Crohn's disease and is typically used to identify patients with possible inflammatory disease of the small bowel when the traditional imaging and endoscopic modalities have failed to make a definite diagnosis. On the other hand, VCE in the evaluation of recurrent disease and grading of disease severity does not have a clearly defined role currently and further studies are needed.

Hereditary Polyposis Syndromes and Small Bowel Tumors

Although there are only a few published studies regarding VCE and polyposis syndromes, VCE would appear to be an excellent tool in the detection of small bowel polyps. VCE is superior to barium contrast studies and magnetic resonance imaging (MRI) for polyps less than 15 mm. Advantages of MRI include more accurately determining polyp location and, in cases of large polyps, better estimation of polyp size when compared to VCE [21, 26].Patients with familial adenomatous polyposis (FAP) should undergo complete GI tract evaluation at the time of diagnosis, although the presence of upper GI adenomas prior to colonic disease is rare. Lifetime development of duodenal adenomas is high (60–90 %) and the risk of duodenal or periampullary malignancy is estimated at 5–12 %. Due to limited visualization of the ampulla on VCE, esophagogastroduodenoscopy (EGD) with a side-viewing instrument in addition to forward-viewing scope is mandatory. The

endoscopic surveillance intervals and the treatment approaches are determined by the Spigelman staging (a classification system based on the number, size, histology, and grade of dysplasia of duodenal polyps). The role for more distal small bowel screening is still unclear. Jejunal and ileal adenomas develop in approximately 40 and 20% of FAP patients, respectively, with very rare transformation to adenocarcinoma. Hence, there are no consensus guidelines for small-bowel surveillance past the duodenum, and no guidelines as to what lesions would warrant DBE with biopsy or polypectomy. One suggested approach is to perform VCE in patients with stage III-IV duodenal polyposis with subsequent small bowel enteroscopy for biopsy and/or removal of high-risk polyps [27–29].

Patients with Peutz-Jeghers syndrome (PJS) are at increased risk for a variety of cancers, including the small bowel (13% of all cancers in PJS patients). A routine screening of the small bowel with VCE is recommended every 2–3 years, with subsequent DBE and polypectomy if polyps are detected. No routine screening of the small bowel is currently recommended in other polyposis syndromes [27, 28].

Small bowel tumors in the absence of polyposis syndrome were thought to be fairly uncommon, but increased use of VCE has led to an increment in their detection: between 2.4 and 9.6% of patients undergoing VCE for OGIB have been found to have a small bowel tumor. Of these, the majority are gastrointestinal stromal tumors (GIST), followed by adenocarcinomas, carcinoids, lymphomas, and sarcomas [30–36].

Celiac Disease

Although celiac disease can be suspected on clinical grounds or by serologic assays, the gold standard for diagnosis remains small bowel biopsy with histological changes of villous atrophy and increased intraepithelial lymphocytes. Two studies examining patients with suspected celiac disease based on positive serological tests compared conventional EGD with duodenal biopsies to VCE. One found sensitivities for VCE of 85–87.5% and specificities between 90–100% [35, 37]. The second study examined the diagnostic yield of VCE in patients with biopsy proven celiac disease and reported a sensitivity and specificity of 92 and 100%, respectively. The obvious limitation of VCE in diagnosing celiac disease is the inability to detect microscopic changes of celiac disease, which can be present without evident macroscopic mucosal changes. Moreover, typical macroscopic changes of celiac disease such as scalloping can also be seen in a variety of other conditions such as amyloidosis, eosinophilic enteritis, giardiasis, and human immunodeficiency virus (HIV) enteropathy. For these reasons, VCE is not routinely used in the diagnosis of celiac disease [37–39].

One instance where VCE may provide additional diagnostic benefit is in patients with suspected or refractory celiac disease. Although celiac disease usually involves the proximal duodenum, there have been cases where the fourth portion of the duodenum and proximal jejunum are the only affected areas. These more distal changes can be observed on VCE and may help determine if this subset of patients

would benefit from a push enteroscopy and histologic confirmation. In refractory celiac disease, VCE may help exclude the presence of ulcerative jejunoileitis and enteropathy associated T-cell lymphoma (EATL) [40, 41].

Esophageal Capsule Endoscopy

The role of video capsule endoscopy in assessing the esophagus remains an issue under ongoing investigation. EGD remains the gold standard for evaluation of the esophagus due to the ability to perform endoscopic interventions, carefully inspect and interrogate areas of interest, and insufflate to permit optimal visualization. EGD is also relatively quick, well-tolerated, widely available, low cost, and is associated with minimal complication rates. Despite the advantages of EGD, VCE is an attractive option for the examination of the esophagus in those at high risk for anesthesia-related complications and those who prefer noninvasive means of diagnostic evaluation. The most studied indications for VCE include screening and surveillance of varices, screening for Barrett's esophagus, and evaluation of reflux esophagitis.

In 2004, Given Imaging Ltd. developed the PillCam ESO®, which was the first wireless video capsule specifically designed for noninvasive evaluation of the esophagus. This capsule was similar in size to the intestinal capsule (11 × 26 mm) but equipped with two optical domes instead of one, which captured 14 images per second (7 from each optical dome) and had an operational time of 20 min. In 2007, the PillCam ESO 2® was released, which increased the angle of view from 140° to 169°, increased the frame rate to 18, improved image quality, and added the ability to adjust illumination in real time. The PillCam ESO 3®, which boasts an increased frame rate of 35 images per second, received FDA approval in 2011. Ingestion protocol for these devices involve the patient lying on their right side and taking sips of water every 15 s for 3 min following ingestion of the capsule [42, 43].

Studies comparing VCE to EGD have focused primarily on the difference in detection rates of Barrett's esophagus and esophageal varices. There has been significant heterogeneity among studies; when compared to EGD as the gold standard, VCE detection rates of Barrett's esophagus and erosive esophagitis have ranged from 60–100% and 50–90%, respectively [44–47]. There appears to be similar heterogeneity in VCE rates of variceal detection, ranging from 68 to 100%, depending on the study [48–53]. A meta-analysis conducted by Lu et al. examined over 440 patients and reported sensitivity and specificity rates of 86 and 81% when comparing VCE to EGD, with sub-group analysis showing markedly lower specificity of 55% in the screening-only population [54]. One study compared EGD to the use of a video capsule attached to a string, allowing for longer evaluation of the esophagus and reported >95% agreement in detecting varices [55]. At present, there is insufficient data to recommend the use of VCE as an alternative to EGD for evaluation of the esophagus. Although VCE is largely preferred by patients involved in comparison studies, the wide variability in specificity seen across numerous studies raises questions about whether it can be adopted as standard practice. Much of the variability

likely resides in the novelty of such wireless VCE evaluations and relative lack of expertise in interpreting the studies. As the functionality of these devices continues to improve and their use becomes more widespread, further studies will determine whether wireless VCE can find a niche in everyday practice.

Colon Capsule Endoscopy

Colon capsule endoscopy (CCE), approved by the US FDA in 2014 for screening for colorectal cancer in patients with incomplete traditional colonoscopy, represents the newest modality in offering a minimally invasive means of screening for colorectal cancer and its precursor lesions.

The first PillCam Colon® (Given Imaging Ltd.) was introduced in 2006. It was a 31 × 11 mm video capsule with two optical domes allowing for an angle of view of 156°. It acquired images at the rate of four images per second (two from each dome) and had an operational time of 10 h. At the start of an exam, the capsule would transmit images for 3 min, after which it would enter a "sleep mode" for 105 min to save battery life. A second generation model, the PillCam Colon 2® (See Figure), is slightly larger at 31.5 × 11.6 mm but has an increased angle of view to 172° (344° total viewing). Rather than having a "sleep mode," the newer PillCam Colon will obtain 14 images per minute until small bowel is detected, after which the capsule records images using an adaptable frame rate to preserve battery life; while motionless, the capsule takes four images per second, but once motion is detected, the number of images per second automatically increases to 35. Additionally, the liquid crystal display (LCD) on the external recording device can prompt the patient to continue the preparation protocol, once the capsule has moved into the small intestine. The viewing software includes tools such as a polyp size estimator [56].

In the USA, Pillcam Colon 2 has been approved for detection of colon polyps in patients after an incomplete optical colonoscopy. Potential future applications may be similar to those for diagnostic colonoscopy, such as colorectal cancer screening in average risk individuals, surveillance in patients with prior colorectal adenomas or cancer, as well as diagnostic evaluation of colorectal symptoms (in patients at high risk for cardiopulmonary complications due to sedation or in subjects with significant comorbidities). Colon capsule endoscopy provides an advantage over CT colography in that it does not involve exposure to radiation and may be used in patients who have had an incomplete colonoscopy [57]. Since it is a minimally invasive, diagnostic-only examination, anticoagulants need not be stopped. There are, however, several limitations of colon capsule endoscopy, including the inability to perform interventions such as biopsy or snare, inability to insufflate, wash, or suck, which limits the quality of the inspection, and incomplete examinations resulting from extended examination duration and insufficient battery life.

As there is no means to clean the colon wall during a capsule endoscopy, an exceptionally well-prepped colon is required for adequate visualization. Numerous colon cleansing protocols combined with prokinetics have, therefore, been suggested,

since traditional colon preparations achieve complete examinations in only 20% of patients—an unacceptably low rate. The first modified colon preparation used by Schoofs et al. [58] involved a clear liquid diet the day prior to the exam, followed by 3 L of polyethylene glycol solution. Patients then had to drink an additional liter of Polyethlene Glycol (lavage solution) (PEG) over an hour to be finished 1 h prior to capsule ingestion. Patients were given domperidone (not FDA approved in the USA) 15 min prior to capsule ingestion, and then were made to ingest sodium phosphate with a liter of water both 2 and 4 h post ingestion. After 8.5 h, the patient administers a bisacodyl suppository. Several studies showed sodium phosphate was integral for capsule transit and expulsion within the 10-h exam time [59, 60].A newer protocol developed by Eliakim et al. [61] included a more balanced split dose PEG preparation (2 L the evening before and the morning of the exam), lower dose of sodium phosphate boosters, and domperidone only if the capsule failed to pass from the stomach after 1 h. Under the protocol described by Schoofs (often referred to as the "Belgium Regimen"), capsule excretion rates within 10 h were reported to be between 83 and 100%, with a median of 92% (fairly close to the >95% benchmark recommended for complete screening colonoscopies). In the Eliakim et al. study, the excretion rate at 8 h was 81%, at which time a colonoscopy was performed as part of the study design. Even with strict adherence to the vigorous colon preparations used for CCE, approximately 20% of exams are deemed inadequate due to insufficient visualization.

A more recent regimen was suggested in 2011 following a pilot study consisting of 60 prospectively enrolled patients. These patients followed a split regimen of PEG administration (2 L the night prior to the test and 2 L on the morning of the procedure) and a 45 mL dose of sodium phosphate. Four senna tablets and a low-residue diet 2–5 days before capsule ingestion were also proposed. CCE excretion rate, colon cleansing, and accuracy were assessed [62]. At CCE, bowel preparation was rated as good in 78% of patients, fair in 20%, and poor in 2%. CCE excretion rate occurred in 83% of patients.

A large meta-analysis published by Rokkas et al. [63] examined polyp detection rates between the PillCam Colon® and traditional colonoscopy. Compared to colonoscopy, CCE detection of polyps greater than 5 mm had sensitivity and specificity of 68 and 82%, respectively. Two studies comparing the PillCam Colon 2® to conventional colonoscopy reported much higher sensitivity in detecting polyps greater than 5 mm at 84–89% with a specificity of 64–76%. For polyps larger than 1 cm, sensitivity of 88% and specificity of 89–95% were reported [64]. Both studies examined populations of patients with known colon disease. Given the lower prevalence of polyps in an average risk individual, sensitivity is likely to be lower in a screening population. Further studies examining polyp detection rates with new generation colon VCE devices are needed. In another multicenter study that included 320 patients, out of 19 cancers detected by colonoscopy, CCE identified 14 (sensitivity 74%, specificity 74%) [65]. In patients with unremarkable findings on CCE, a repeat screening test is recommended in 5 years, unless the quality of the prep was inadequate [66].

Similarly, studies examining the use of capsule endoscopy to assess disease severity in ulcerative colitis compared to colonoscopy have had mixed results and further studies are needed [67].

Is CCE cost-effective for use in the general population? This has not yet been determined. However, its safety profile does appear to be excellent, with no major complications reported in any study so far. Only minor limitations have been reported—in the study by Eliakim et al., 2 of 126 patients (1.6%) were unable to swallow the capsule. In cases such as these, the capsule could be introduced into the stomach or duodenum via a capsule delivery system.

Potential future areas for research include the assessment of efficacy and limitations in colorectal screening, its use to investigate signs and symptoms, assessment of risks (e.g., capsule retention due to the large capsule size), cost analysis compared to traditional colonoscopy, and determination of optimal bowel preparation methods for the procedure [68].

Future of Wireless Video Capsule Endoscopy

Despite tremendous technological advances in wireless video capsule endoscopy, there will be continued opportunities for further refinement and improvement in the future.

Examples of these improvements could include development of smaller, less expensive, cost-effective, easier to swallow capsules, with less risk of capsule retention. Further improvement in the field of vision and use of dual-ended video capsule imaging devices may further reduce the risk of missed lesions. Enhancements in software to more reliably and rapidly detect actively bleeding or vascular lesions, enhanced software to reduce video length that identify "sameness," as well as software enhancements to better identify significant non-bleeding lesions, such as small bowel tumors should be forthcoming. Use of flexible spectrum imaging color enhancement (FICE) or other imaging enhancement technology or other "electronic chromoendoscopic" techniques are on the horizon [69]. Better localization of lesions detected within the GI tract is desirable, and the ability to control the capsule to alter or regulate its speed of passage through the GI tract, perhaps with use of directional magnets, is technologically feasible [70, 71].

Further research and development into the indications for video capsule endoscopy as well as clinical algorithms to guide its use in specific diseases is desirable.

Further therapeutic applications, such as release of specific chemical agents, coagulation of lesions, etc., are theoretically possible but less likely advancements. It is likely that enhanced "wired" technologies, such as double balloon or spiral enteroscopy and enhanced colonoscopic techniques will continue to serve as the main therapeutic modalities to treat small bowel and colonic diseases, once a specific abnormality or cause of symptoms has been identified by wireless video capsule endoscopy.

Wireless Motility Capsule (SmartPill)

The SmartPill is an ingestible 26.8 × 11.7 mm capsule that measures intraluminal pressure (0–350 mmHg), pH (0.05–9.0), and temperature (25–49 °C) throughout the entire gastrointestinal tract. Introduced in 2006, the SmartPill is FDA approved for the evaluation of gastroparesis and chronic constipation. Patients follow an overnight fast and consume a standardized meal or snack prior to ingestion of the capsule. An external recording device collects data for 3–5 days, after which time, the patient returns the recording device. A software program determines gastric emptying time, small bowel transit time, colonic transit time, combined small/large bowel transit time, and whole gut transit time [72]. Studies comparing SmartPill gastric emptying time (GET) and 4 h gastric emptying scintigraphy (GES) have shown a positive correlation of 0.73, with GET sensitivity and specificity of 65 and 87% in the diagnosis of gastroparesis [73]. A similar study compared the SmartPill to radio opaque markers (ROMs) in the assessment of colonic transit time (CTT). Correlation of CTT between the two modalities at days 2 and 5 was 0.74 and 0.69, respectively. The sensitivity and specificity of the SmartPill to detect slow transit constipation was reported as 46 and 95%, comparable to day 5 ROM [74–78].

The clinical utility of the SmartPill's capability to measure intraluminal pressure remains an area of investigation. While antroduodenal manometry (ADM) can evaluate peristaltic waves using multiple sensors along a probe, the SmartPill inherently lacks this ability. For this reason, it is also limited in its ability to distinguish between myopathic and neurologic small bowel disorders. The SmartPill, however, has the advantage of being less invasive and may find future indications in the initial evaluation of contractile disorders due to better patient tolerance, ease of administration, and greater availability. The ability to measure the frequency and force of contractions and calculate a standardized "motility index" for each segment of the GI tract also has potential clinical implications. Studies comparing normal patients to those with gastroparesis have shown significant differences in the pressure profiles recorded by the SmartPill [77, 79].

Advantages of the SmartPill include absence of radiation exposure and the ability to evaluate the motility of all segments of the GI tract in one study. Procedure risks include capsule retention and aspiration. Significant obesity (BMI > 40) may result in impaired signaling between the capsule and the external recorder. Contraindications include dysphagia, Crohn's disease, recent gastrointestinal surgery, known or suspected history of strictures, fistulas, or obstruction, and implantation of a cardiac pacemaker or other electric medical device. As with other wireless capsules, the passage of the device should be confirmed prior to attempting an MRI.

Deep Small Bowel Enteroscopy

Endoscopic evaluation of small bowel has long been a challenge due to its length and free intra-peritoneal location and has long been considered the final frontier of the gastrointestinal tract. Push enteroscopy became established in the 1980s but is

limited in its ability to intubate deep into the small bowel. The advent of capsule endoscopy and, subsequently, device-assisted deep enteroscopy has allowed diagnostic and therapeutic capabilities for management of small bowel disorders. Deep enteroscopy has several advantages over VCE, including the use of air insufflation to optimize visualization of the mucosa, the ability to obtain tissue sampling, and the capability to perform various therapeutic modalities (such as hemostasis, polypectomy, mucosectomy, foreign-body extraction, and dilation). The image-enhancing techniques can also be used with these devices, such as confocal laser endomicroscopy, chromoendoscopy, and magnification endoscopy, which can improve the quality of these studies. Flexible spectrum imaging color enhancement (FICE), a technique that heightens the presence of vascular malformations, flat lesions, and dysplastic changes throughout the intestinal mucosa, is available for use with these endoscopes. Currently four device-assisted enteroscopy modalities are approved in the USA (in the order of introduction): double balloon enteroscopy (DBE), single balloon enteroscopy (SBE), spiral enteroscopy (SE), and NaviAid (Table 2).

Double Balloon Enteroscopy (DBE)

Double balloon enteroscopy was the first device-assisted enteroscope developed in 2001 in Japan by Dr. Hironi Yamamoto [80]. The system is made commercially by Fujinon Inc. (Japan) and consists of a balloon at the tip of an enteroscope and an overtube with a second balloon (Fig. 4). Inflation of two balloons in a series of steps employing push and pull technique allows gripping of the intestinal wall and prevents loop formation, and thus, allowing deeper intubation of small bowel [81]. The therapeutic double balloon enteroscope has a working length of 200 cm, an

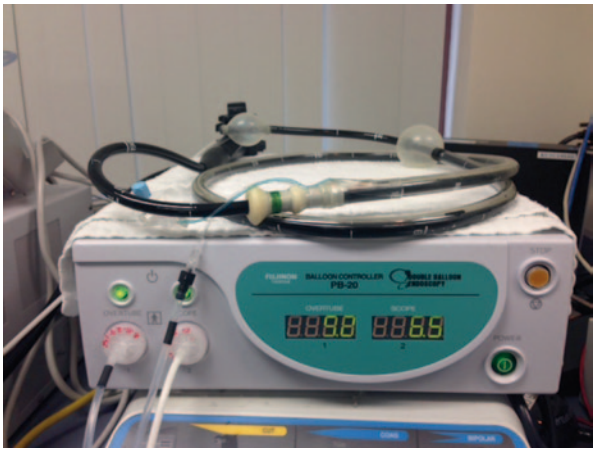

Fig 4 Double Balloon Enteroscopy

endoscope diameter of 9.4 mm and an accessory channel of 2.8 mm. The overtube is 13.3 mm wide, with a length of 140 cm. The maximum balloon inflation pressure is capped at 45 mm Hg to prevent patient discomfort or perforation, while allowing sufficient force to anchor the intestinal tract. Its additional diagnostic and therapeutic advantages over capsule endoscopy include the ability to biopsy a lesion, achieve hemostasis, foreign body retrieval, polypectomy, stricture dilation, and stenting [82, 99]. The main complications of double balloon enteroscopy include perforation, pancreatitis, and ileus. The incidence of complications ranges from 0.8 to 4% [83, 84]. The depth of insertion ranges from 240 to 360 cm with the antegrade approach, and from 102 to 140 cm with the retrograde approach [85, 101]. Difficulty in pleating the small bowel in double balloon enteroscopy may be caused by adhesions from prior surgeries or by fat in the mesentery in obese patients.

Total enteroscopy with the double balloon enteroscope is defined as a complete evaluation of the small bowel, with either a single approach or a combined antegrade and retrograde approach and is achieved in 16–86% of patients [86, 98]. The initial route of insertion is based on the location of suspected pathology: the antegrade approach is recommended for lesions in the proximal 75% of the small bowel, whereas, the retrograde approach is recommended for lesions in the distal 25% [87]. Patient comfort and depth of insertion can be enhanced by the use of CO2 instead of air for insufflation [88].

The overall diagnostic yield of double balloon enteroscopy has ranged from 43 to 80% with the most common indication being obscure GI bleeding [87, 89]. The diagnostic yield of capsule endoscope and double balloon enteroscopy are comparable when the entire small bowel is examined [90, 91] (Fig. 5, GIST tumor detected by DBE).

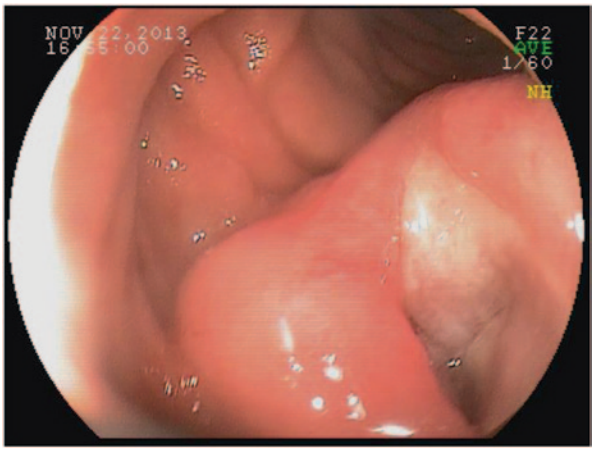

Fig 5 Ulcerated mass: GIST tumor of the small bowel detected by DBE

The DBE is a complex procedure and requires a trained and experienced endoscopist and assistant. These factors in addition to the long duration of the procedure are limitations which have precluded widespread adoption of this technique.

The relative contraindications for double balloon enteroscopy are latex allergy, altered surgical anatomy, coagulopathy, recurrent or active pancreatitis, and high–grade bowel obstruction [92].

Single Balloon Enteroscopy (SBE)

The single balloon enteroscopy was introduced in 2007 and the commercially available enteroscope is produced by Olympus Optical Co. (Japan). It has a working length of 200 cm and outer diameter of 9.2 mm and is equipped with a working channel of 2.8 mm. The overtube is about 140 cm long and is made of silicon, as is the balloon. In contrast to the DBE system, there is only one balloon at the distal end of the overtube and the tip of the scope is used to anchor the small bowel by angling behind the fold and by using a "power suction maneuver" to stabilize, while advancing the overtube [93, 94]. The depth of insertion ranges from 133 to 256 cm with the antegrade approach and from 73–163 cm with the retrograde approach [95, 96]. Though the depth of insertion for the SBE is slightly less than the DBE, the diagnostic yield is quite comparable with ranges from 47 to 60 % [95, 96, 97]. Total enteroscopy can be successfully achieved in 15–25 % of cases.[93, 96] The complication rates are quite similar to DBE at 1 % and include perforation and pancreatitis, though some studies have suggested a lower risk of acute pancreatitis with the SBE than DBE [98].

Spiral Enteroscopy (SE)

The spiral enteroscopy system consists of a special overtube called "Discover Small Bowel" (Spirus Medical Inc., Stoughton, MA, USA). This overtube has a length of 118 cm, an outer diameter of 16 mm, and an internal diameter of 9.8 mm, and is made of polyvinyl chloride (PVC). The tip of the overtube has a raised hollow spiral that is 5.5 mm high over a length of 21 cm. This overtube is compatible to use with push enteroscopes and Pediatric colonoscopes made by both Fujinon and Olympus. The enteroscope with overtube system is advanced beyond the ligament of Treitz and then the device is rotated using clockwise movements to pleat the small bowel onto the overtube. Once the furthest extent possible is reached, the enteroscope is unlocked and advanced beyond the overtube. Subsequently, opposite counterclockwise rotations are used while withdrawing the enteroscope [99]. The depth of intubation of the small bowel ranges between 176 to 250 cm and is comparable to the SBE system [100, 101]. The SE is usually done by peroral route, although a retrograde approach has been reported in one study [102]. One prospective

randomized study comparing the DBE with SE showed significant shorter procedure time for SE but much greater rate of achieving complete enteroscopy with DBE as compared to SE (92% versus 8%, respectively). Also, much greater mean depth of insertion was achieved with DBE as compared to SE (346.15 cm versus 268.46 cm, respectively for peroral route) [103].

A self-propelled version of SE with an integrated motorized remote spiral has been developed and is currently being tested for its safety profile. It has the inherent advantages of being able to be used with a 160 cm enteroscope without an overtube; thus, the rapid advancement through the small bowel significantly reduces the procedure time [104].

NaviAid

NaviAid AB device (SMART medical systems Ltd., Ra'anan, Israel) is an on-demand balloon catheter system that is inserted through the instrument channel of a standard colonoscope and enables deep retrograde intubation into the small bowel with significantly shorter procedure time. It consists of a balloon inflation/deflation system and a single-use pressure sensitive balloon catheter, designed for anchoring in the small bowel. The balloon catheter is advanced as far as possible into the small bowel after intubation of the terminal ileum, and the balloon is inflated to serve as an anchor in the intestine. A repetitive push–pull technique is used to advance the endoscope over the catheter to the balloon inflated in the distal small bowel. The catheter may be removed to allow for therapeutic intervention. The average depth of insertion is 156 cm for antegrade examinations and 89 cm for the retrograde approach [105]. This device is particularly useful for assessment of the distal ileum in patients with suspected Crohn's disease [106].

Table 3 Deep endoscopy specifications

	DBE	SBE	SE	NaviAid
Diagnostic yield (mean +/− 2 SD)	64.4 +/− 5.9 (43–80%)	53.9 +/− 5.6 (47–60%)	47.0 +/− 9.3 (10–65%)	45%
Complete enteroscopy rate	16–86%	15–25%	8%	
Depth of insertion (cm)	240–346 (oral) 102–140 (anal)	133–256 (oral) 73–163 (anal)	176–250 (oral) 78 (anal)	50–350 (mean 156) (oral) 20–150 (mean 89) (anal)
Procedure time in min (mean +/− 2 SD)	71.6 +/− 5.9 (oral) 84.5 +/− 7.6 (anal)	59.8 +/− 10.0 (oral) 68.8 +/− 10.3 (anal)	41.0 +/− 4.5 (oral) 46.0 +/− 0 (anal)	15.5 (oral)
Therapeutic yield (mean +/− 2 SD)	40.1 +/− 9.0 (9–72%)	26.8 +/− 8.3 (5–48%)	29.7 +/− 10.5	

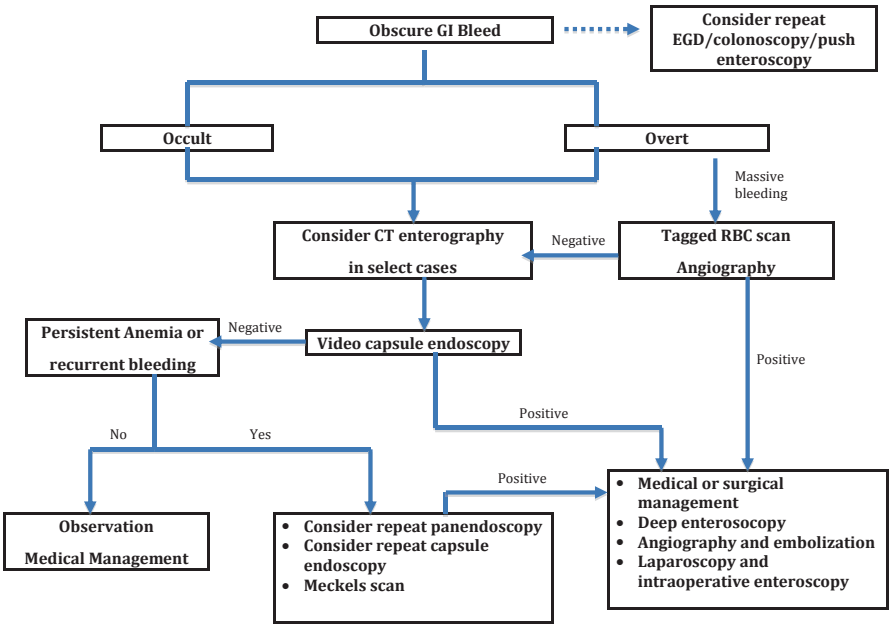

Fig 6 Evaluation of Obscure GI Bleeding

Summary, Deep Endoscopy Techniques

In the past, when radiologic studies revealed small intestinal abnormalities beyond the reach of push enteroscopy, intraoperative endoscopy by laparotomy was the only available option for confirmation and treatment. With the availability and achievement of technology allowing deeper endoscopy insertion (Table 3), the algorithmic approach to diagnosing small bowel lesions has changed dramatically (Fig. 6).

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High-Resolution Manometry and Assessment of Esophageal Reflux

Mary K. Rude and C. Prakash Gyawali

Introduction

The esophageal body and its associated sphincters participate in the esophageal phase of deglutition. The esophagus and its sphincters also serve as a barrier to reflux of gastric contents into the proximal foregut, airway, and pharynx. While most aspects of esophageal transit are facilitated by gravity in the upright position, esophageal peristalsis strips and propels bolus remnants eventually leading to the completion of bolus transit from the pharynx to the stomach by a series of coordinated events. The tubular esophagus, or esophageal body, is composed of three contraction segments—a proximal striated muscle segment under direct central nervous system control via the lower cranial nerves, and two smooth muscle segments, controlled by plexuses within the enteric nervous system with input from the autonomic and central nervous systems. Several techniques exist to assess the neuromuscular, peristaltic, and barrier functions of the esophagus, including endoscopy, barium X-ray, radionuclide transit study, pH- and pH-impedance monitoring and esophageal manometry. Advances in acquisition and display of pressure data have resulted in more intuitive manometry systems that are more convenient for the patient and less cumbersome for the operator, termed high-resolution manometry (HRM).

The anorectal sphincter serves to maintain bowel continence, while facilitating expulsion of fecal material when socially appropriate. The anorectal sphincter too has a striated volitional component, the external anal sphincter and the puborectalis muscle, and a smooth muscle involuntary component, the internal anal sphincter which is controlled by the enteric nervous system and local reflexes. The principles of esophageal manometry can be applied to the pressure measurement within the anorectal sphincter, termed anorectal manometry. High-resolution techniques are similarly applied to anorectal manometry.

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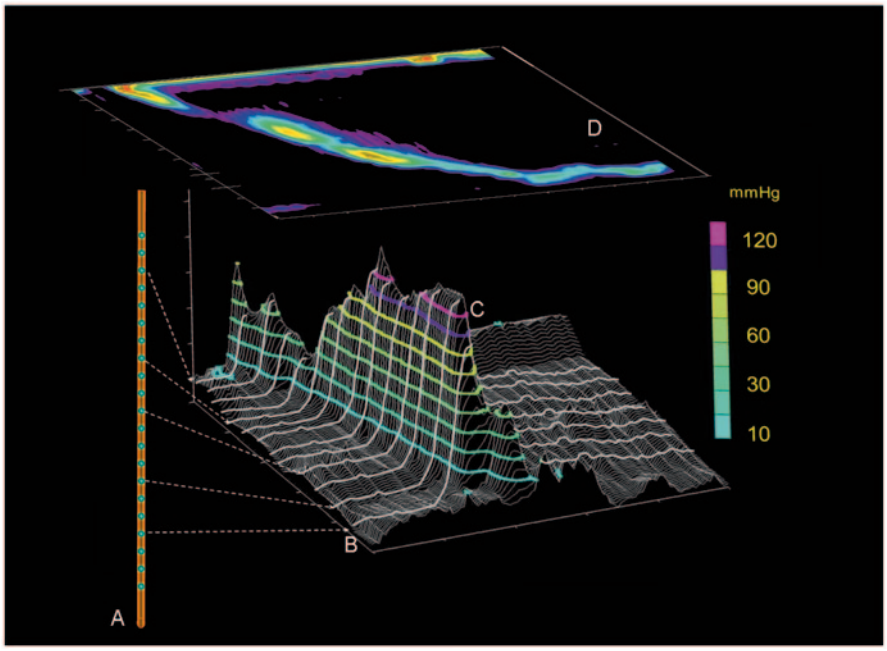

Fig. 1 The concept of esophageal high-resolution manometry (HRM). In contrast to conventional manometry, HRM requires multiple sensors 1 cm apart on an esophageal motility catheter (**a**) that generate multiple recordings of pressure phenomena from each individual sensor throughout the esophagus (**b**). The space between recording sensors is filled with the best-fit data using dedicated computer software, which also color codes amplitude levels (**c**). Finally, the image is smoothed out electronically, and displayed as a topographic contour plot representing the peristaltic sequence when viewed from above (**d**). The contour plots are termed Clouse plots in honor of Ray Clouse, who conceived and developed HRM. (Reproduced with permission from [8])

Esophageal Manometry

Manometry is a technique of measuring pressure phenomena at the esophageal sphincters and along the tubular esophagus. Adequate esophageal peristalsis is implied when aboral movement of the esophageal pressure wave is identified concurrent with relaxation of the sphincters on esophageal manometry. All manometry systems consist of two components: (a) a thin flexible catheter inserted through the nostril that traverses the esophagus and extends into the stomach. Older systems have water-perfused side holes along the catheter that transmit pressure to the sensors, which convert intraluminal pressure measurements to electrical signals. New systems have solid-state pressure sensors of varying density along the catheter (Fig. 1), (b) a recording device that amplifies and displays these electrical signals in the form of pressure graphs [1, 2]. With modern high-resolution manometry systems, the pressure recordings are displayed as contour plots, simplifying interpretation as described below [3].

Conventional Esophageal Manometry

In 1977, Dodds and Arndorfer created the first high-fidelity manometry system. This system consisted of a bundle of thin flexible tubes, each with a single small "side-hole" perpendicular to the esophageal lumen, spaced 3–5 cm apart along the catheter. A pneumo-hydraulic pump connected to the catheter pumped gas-free water into each tube and out each side-hole. This column of water transmitted esophageal luminal pressure to a transducer, which converted the measured pressure into an electrical signal displayed as a wave form [4]. This low-compliance water-perfused catheter system increased accuracy of pressure measurements while relatively durable and inexpensive.

An ideal manometry system should collect pressure measurements continuously and concentrically, accounting for all esophageal motor activity and pressure fluctuations along the asymmetrical esophageal lumen and sphincters. In the earliest conventional manometry system, however, the pressure sensors were spaced several centimeters apart and were unidirectional, leading to inaccuracies in recorded pressure data [1, 2, 4]. For instance, the radial asymmetry of the sphincters led to inaccurate pressure measurements from the unidirectional pressure sensors. Further, the tubular esophagus shortens relative to the catheter during swallowing, and the sensor designated to record the lower esophageal sphincter (LES) pressure may no longer remain within this sphincter. To better assess LES pressure measurements, a 6 cm perfused sleeve sensor (known as the "Dent sleeve") was devised, positioned at the distal end of the catheter to provide continuous pressure within the LES [5]. Finally, the localization of the sphincters, especially the LES, required a "stationary pull through maneuver," which consisted of pulling the catheter back 1 cm at a time, observing typical sphincteric pressure profiles, and localizing the LES relative to the nostril so that the catheter could be maneuvered into place for the actual manometry study. This process was cumbersome for the operator and unpleasant for the patient.

Since water-perfused manometry was labor intensive, fraught with artifacts, and required technical expertise for data acquisition and interpretation, water-perfused sensors were subsequently replaced with solid-state pressure transducers [1, 2, 6]. Solid-state manometry used strain gauge transducers placed along the catheter at regular intervals and measured pressure in a unidirectional fashion or averaged pressure around the circumference of the transducer. The development of a solid-state manometry system improved the accuracy of assessment of esophageal peristalsis and sphincter function, but the systems were fragile and expensive [1]. Further, the sensors remained widely spaced, and the problems with incomplete assessment of the pressure continuum persisted.

Esophageal High-Resolution Manometry (HRM)

In the early 1990s, Ray Clouse and colleagues began investigating how best to circumvent the limitations of conventional manometry. Clouse believed that pressure

events between the widely spaced conventional manometry sensors could provide additional clues to esophageal motor function in health and disease. Innovative and pioneering research addressing these limitations led to the concept and development of HRM and esophageal pressure topography (EPT) [3, 7]. Clouse first performed pull-through maneuvers 1 cm at a time with water-perfused catheters, charting pressure events along the esophagus. He then digitized the pressure recordings, filled space between the 1 cm recordings with best-fit data, and assigned colors to different pressure levels. This allowed 3-D display of the peristaltic sequence, colors indicating pressure amplitudes, and the x- and y-axes indicating distance along the esophagus and time, respectively—images generated are now termed Clouse plots [8]. Using these concepts, Clouse initially created a system with 21 water-perfused pressure sensors located every centimeter along the catheter [7]. Using data collected from these sensors, the EPT plots were created with dedicated computer software. This representation of continuous esophageal peristalsis, sphincter location, and pressure is similar to that of geographic topographic maps. Today, the HRM can be performed using water-perfused or solid-state systems. The commercially available systems utilize 32–36 circumferential solid-state sensors spaced at 1 cm intervals (Fig. 1).

The HRM using EPT has considerable theoretical and practical advantages over conventional manometry, allowing for more consistent and accurate assessment of esophageal function and dysfunction [2, 9]. In practice, compared to conventional manometry, the HRM is relatively simple and fast for both the operator and the patient [10, 11]. The stationary pull-through maneuver is obsolete as the pressure profile of the esophagus can be visualized in real time immediately upon catheter placement; this ensures that the catheter is placed correctly and that it traverses both the upper esophageal sphincter (UES) and the LES. The close spacing between pressure sensors ensures that the HRM generates dynamic and detailed depiction of pressure phenomena along the tubular esophagus and sphincters [2]. Many esophageal motor abnormalities and disorders create distinct and recognizable HRM and EPT patterns, easily identified even by novice and trainee esophagologists in many instances [12]. Pattern recognition with HRM and EPT plots has allowed for improved inter-observer agreement amongst interpreters, providing a user-friendly interface for teaching trainees with better diagnostic accuracy compared to the conventional line tracings [12−14].

The advent and use of HRM and EPT plots has contributed to better understanding of the esophageal phase of deglutition. The accuracy of assessment of abnormal LES function has been impacted the most, as the LES can now be followed proximally with esophageal shortening during swallows—with conventional manometry, this could have created an appearance of “pseudo-relaxation” of the LES as the sphincter shortened proximal to the LES sensor [15]. Prior to HRM, the concept of two smooth muscle contraction segments in the esophageal body was not established [7]. The behavior of the smooth muscle contraction segments on EPT defines motor abnormalities at both ends of the motor disorders spectrum; hypermotility and hypomotility. Finally, HRM has allowed uniformity in data reporting and interpretation, as software tools can be utilized to assess and report motor phenomenon [16].

Indications for Esophageal HRM

Esophageal manometry has multiple indications in the evaluation of esophageal motor function. While some of the same indications as for conventional manometry apply for HRM, additional detail can be obtained with this technique, providing for gains in diagnostic accuracy. The traditional indications for manometry include diagnosis of obstructive motor disorders (e.g., achalasia) in the setting of dysphagia without a structural etiology on endoscopy or barium esophagogram, localizing the proximal margin of the LES for placement of pH probes, and assessing the adequacy of esophageal body peristalsis [1, 2, 16]. While HRM fulfills these indications efficiently, additional detail is obtained regarding the structure, integrity, and function of the esophageal sphincter. Further, esophageal body motor patterns can be better defined, and motor patterns hitherto unknown have been described (e.g., jackhammer esophagus, premature contraction sequences, fragmented contraction sequences) that may explain both obstructive transit symptoms as well as perceptive symptoms from esophageal hypervigilance associated with certain motor patterns [17–20]. Evaluation of unexplained noncardiac chest pain and post-fundoplication dysphagia has been further refined with HRM. While evaluation of the UES was suboptimal with conventional manometry, HRM has shown potential in identifying the UES dysfunction. The superimposition of impedance with HRM (high-resolution impedance manometry, HRIM) allows assessment of bolus transit with liquid, viscous, and solid boluses—while this has potential for additive benefit, outcome studies are unavailable to date and research continues [21]. Finally, a newer HRM system with a short segment of even closer sensor distribution (3-D manometry) may provide further sphincteric detail [22].

Abnormal or dysfunctional esophageal motility can cause esophageal dysphagia. Therefore, HRM is indicated in the diagnostic workup of esophageal dysphagia after endoscopy or barium esophagography has excluded more common structural defects (such as a stricture, ring, mucosal inflammation, eosinophilic esophagitis), or when a motor disorder is suspected after initial testing. Clinical utility of HRM is better when the pretest probability of a motor disorder is high, as nonspecific abnormalities on manometry studies may not correlate well with symptoms [23, 24]. Achalasia and advanced spastic disorders (such as diffuse esophageal spasm), on the other hand, correlate with symptoms such as dysphagia and regurgitation from abnormal bolus transit and are easily recognized on HRM [25]. HRM may also have the utility in situations where multisystemic disease processes affecting the smooth muscle or the enteric nervous system, such as scleroderma where striated muscle function is normal in the proximal esophagus, but peristalsis is diminished or absent in the smooth muscle esophagus with decreased or absent LES pressure [26, 27]. Finally, there is evidence that HRM findings may help stratify patients being considered for antireflux surgery (i.e., fundoplication) [28]. In this setting, important outcomes from HRM are the identification of esophageal outflow obstruction, which contraindicates fundoplication and esophageal aperistalsis without outflow obstruction, which necessitates a partial rather than a standard fundoplication [28, 29]. Provocative maneuvers such as multiple rapid swallows (MRS) may help assess esophageal peristaltic reserve in settings where peristalsis is hypomotile [29].

Acquisition and Interpretation of HRM

Patients scheduled for HRM should be fasting for at least 6 h prior to the procedure, and medications that affect gut motility are typically withheld [1, 2]. Once the HRM catheter is disinfected and calibrated, it is inserted transnasally with the operator directly visualizing pressure patterns to ensure proper catheter placement. Two bands of pressure generated by the UES and LES respectively anchor the HRM Clouse plot at either extent, and the operator learns to recognize these to confirm that the catheter tip is in the stomach [2]. The point of pressure inversion with respiration can ascertain that the diaphragmatic crura have been traversed in most instances—this is distal to the LES high-pressure zone when a hiatus hernia is present. Once catheter placement is appropriate, the patient undergoes a standard manometry protocol in the supine position, consisting of a 30 s baseline recording period without swallowing, followed by a series of ten 5 ml water swallows (delivered by a syringe into the patient's mouth) every 20–30 s. The interval between swallows allows for the esophageal motor function to return to the baseline [2]. Viscous and solid boluses can be administered if desired. Finally, provocative maneuvers can be performed. The simplest of these consists of administering five small (2 mL) water boluses in rapid succession 2–4 s apart, termed multiple rapid swallows (MRS) [2]. This provocative maneuver tests esophageal neural connections responsible for both deglutitive inhibition (absence of esophageal smooth muscle peristalsis and profound relaxation of LES during MRS), and esophageal contractile reserve (robust esophageal body contraction and reestablishment of LES tone following deglutitive inhibition) [29, 30]. Deglutitive inhibition is often impaired in disorders with inhibitory nerve dysfunction such as achalasia and esophageal spasm [31, 32], while post-MRS contraction is impaired in hypomotility disorders [29].

Interpretation of EPT plots starts with identification of esophageal sphincters. The UES and LES are easily identified on EPT plots as bands of abrupt pressure increase at proximal and distal extents of the esophagus (Fig. 2) . The esophagogastric junction (EGJ) is superimposed on the LES high-pressure zone under normal circumstances [2, 16]. The location of diaphragmatic crura can be further ascertained by asking the patient to take a deep breath when inspiratory contraction of the crural diaphragm can be visualized. However, separation of the LES from the crural diaphragm defines an axial hiatus hernia.

Integrity of esophageal peristalsis is then assessed. During a normal wet swallow, the EPT plot will display pharyngeal contraction and UES relaxation, followed by the progressive and sequential esophageal body contraction in the three esophageal segments (Fig. 2). Software tools such as the isobaric pressure contour can be used to assess peristaltic integrity, typically with the tool set at a threshold of 20 mmHg [2, 16]. A distinct pressure trough between the first and the second segments, the transition zone, identifies transition of peristalsis from striated to smooth muscle, and consequently, from central nervous system control to the enteric nervous system [33, 34]. The LES relaxes promptly upon initiation of the swallow as visualized by UES relaxation, and demonstrates after-contraction while regaining resting tone as the peristaltic wave terminates in the distal esophagus.

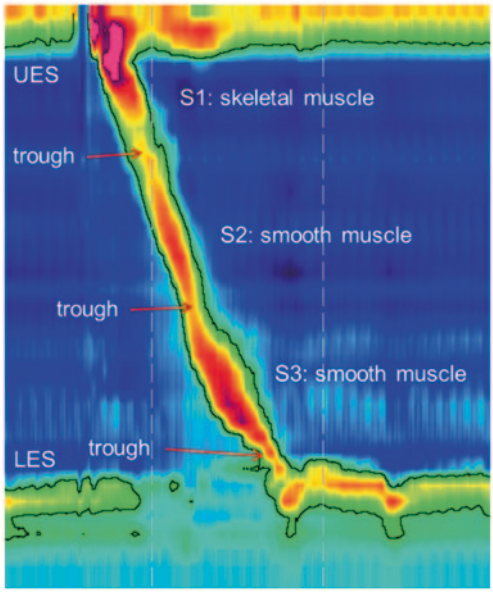

Fig. 2 Normal high-resolution manometry Clouse plot. The plot is anchored by two pressure bands, the upper esophageal sphincter (*UES*) and the lower esophageal sphincter (*LES*). The pressure in the sphincters dissipates to designate relaxation in conjunction with a peristaltic sequence. Smooth muscle contraction segments consist of a proximal striated muscle segment (*S1*), followed by two smooth muscle segments (*S2, S3*). Sphincter relaxations and contractions of the three peristaltic segments occur in smooth continuity with normal esophageal peristalsis

The most important aspect of interpretation of HRM Clouse plots is the determination of adequate LES relaxation with swallows. Integrated relaxation pressure (IRP) is the universally accepted metric for assessing this, and represents four continuous or discontinuous seconds of nadir pressure during LES relaxation [2, 16]. The IRP, therefore, interprets resistance to bolus flow through the EGJ and is determined by both hydrostatic pressure generated from the esophageal peristalsis and outflow resistance at the EGJ. The threshold of normal has been determined to be 15 mmHg. The classic condition with an elevated IRP, typically in the face of absent or nonpropulsive esophageal peristalsis, is achalasia (Fig. 3). The IRP may also be elevated by any process that increases outflow resistance (such as infiltration or inflammation of the EGJ, or an anatomic process such as a stricture). Determination of the presence or absence of esophageal outflow obstruction using the IRP is the first interpretative element of HRM analysis, since outflow obstruction is the most treatable of esophageal motor disorders [2, 16].

The HRM Clouse plots allow better characterization of esophageal body motor function. Characteristics evaluated include the proportion of wet swallows that result in peristaltic sequences, the velocity of transmission, and certain characteristics of the contraction sequence. Bolus transport is abnormal when a wet swallow does not result in a peristaltic sequence, either with partial or complete failure of esophageal contraction, or with simultaneous nonpropulsive contraction [35]. The velocity of the peristaltic transmission varies throughout the esophagus. Pressure waves travel about 3 cm/s in the upper-esophageal body, 5 cm/s in the mid-esophageal body, and 2.5 cm/s in the distal-esophageal body [36]. In general, a velocity greater than 6 cm/s is abnormal and may cause ineffective bolus transit [37]. The amplitude of the pressure wave is defined as the difference between the baseline

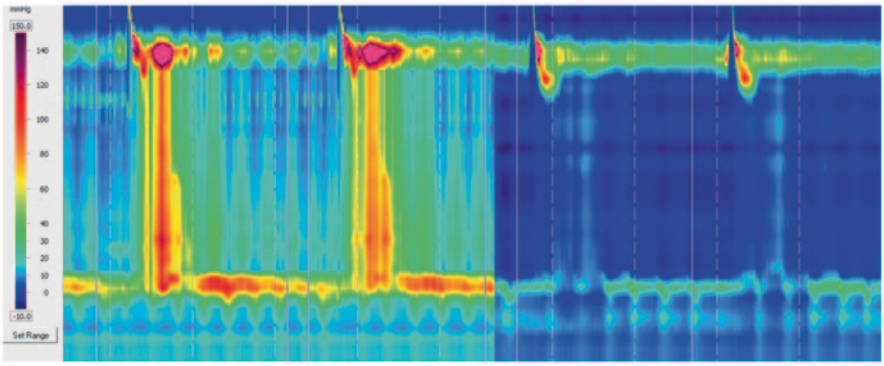

Fig. 3 Examples of HRM Clouse plots in achalasia and scleroderma esophagus. The *left panel* demonstrates aperistalsis and panesophageal compartmentalization of intrabolus pressure between the UES and the nonrelaxing LES with each swallow, features characteristic of achalasia. Because of the panesophageal compartmentalization of pressure, this pattern designates the achalasia as type II. The *right panel* also demonstrates aperistalsis, but in this instance, the skeletal muscle contraction segment is intact, the LES is hypotensive, and relaxes with each swallow. This pattern, if consistent throughout the study, suggests esophageal smooth muscle dysfunction. The combination of aperistalsis and a hypotensive but relaxing LES is termed scleroderma esophagus, despite the fact that scleroderma may not be the etiology in the majority of instances. These examples demonstrate the intuitive and visually descriptive nature of HRM. *HRM* high-resolution manometry, *UES* upper esophageal sphincter, *LES* lower esophageal sphincter

resting pressure and the highest pressure during peristalsis [1]. Normal pressure wave amplitude ranges between 30 and 180 mmHg. Pressure waves with amplitudes < 20 mmHg are not classified as being produced by a contraction; amplitudes consistently < 30 mmHg are generally described as hypotensive; while averaged amplitudes > 180 mmHg are generally described as hypertensive [35, 38, 39].

Software tools are also available for interrogation of esophageal body peristalsis. The vigor of peristalsis in the smooth muscle esophagus is addressed by the distal contractile integral (DCI), which takes into account the length, amplitude, and duration of smooth muscle contraction, expressed as mmHg/cm/sec [2]. Single-swallow DCI values above 8000 mmHg/cm/sec, and averaged values above 5000 mmHg/cm/sec are almost never encountered in asymptomatic adults; these thresholds define hypercontractile disorders. However, the DCI provides a broad assessment of smooth muscle contraction rather than specific details, and further inspection of contraction segments may provide additional contraction detail that may explain esophageal symptoms [2, 16]. For instance, contraction wave abnormalities (such as multiple peaked waves, elevated distal contraction amplitudes > 180 mmHg, and intermittently prolonged wave duration) may not necessarily result in an abnormal DCI [40]. Distal latency (DL) is another HRM metric that defines timing of esophageal peristalsis, measured as the time from UES relaxation to the transition point between fast proximal and slower distal peristaltic propagation speeds (termed contractile deceleration point or CDP). Values < 4.5 s define the premature arrival of esophageal peristalsis in the distal esophagus, segregating sequences that may not

propel boluses [2, 16]. The speed of esophageal body peristalsis is further assessed as contraction front velocity, and values >9 cm/s identify simultaneous esophageal peristalsis, and diffuse esophageal spasm.

For establishing uniformity in interpretation of HRM and EPT plots for non-obstructive dysphagia, the Chicago Classification scheme was created [16]. This employs a 3-step approach to classify HRM and EPT findings that consist of: (1) assessing the EGJ anatomy and function by examining the EGJ morphology and basal pressure, and calculating the IRP; (2) assessing esophageal body function by evaluating the DCI and peristaltic integrity; and (3) assessing pressurization patterns. This diagnostic algorithm classifies HRM and EPT findings into four groups: (1) achalasia (further subdivided into subgroups as described below), (2) EGJ outflow obstruction, (3) abnormal motility disorders not observed in normal subjects (i.e., distal esophageal spasm, hypercontractile esophagus, and absent peristalsis), and (4) borderline motility with abnormalities not within the range of normal values (i.e., weak peristalsis, frequently failed peristalsis, rapid contractions with normal latency, and hypertensive peristalsis) [16].

Achalasia, defined as aperistalsis and incomplete LES relaxation, creates a distinct pattern that is easily identified on EPT plots (Fig. 3). Achalasia results from death or significant dysfunction of the inhibitory nerves, typically from idiopathic inflammation of inhibitory neurons in susceptible individuals. The Chicago Classification categorizes achalasia into three subgroups, types I–III, with each type representing a distinct phenotype and response to the treatment [41]. In this scheme, the threshold for the diagnosis includes esophageal outflow obstruction with IRP >15 mmHg. Achalasia subtypes are defined as follows: Type I achalasia (i.e., "classic achalasia") with 100% failed peristalsis; type II achalasia (i.e., "achalasia with esophageal compression") has no normal peristalsis and panesophageal pressurization with at least 20% of swallows; and type III achalasia has no normal peristalsis with preserved spastic fragments of distal peristalsis or premature contractions with at least 20% of swallows [16]. Available first-line treatments for achalasia include pneumatic dilation or surgical myotomy, which disrupt the nonrelaxing LES and thereby resolve esophageal outflow obstruction [42]. Type I achalasia patients are reported to respond better to Heller myotomy compared to pneumatic dilation, type II patients respond fairly well to all acceptable treatments, and type III patients respond incompletely to therapy mainly from a persistent perceptive element related to partially retained spastic contraction [11, 43, 41]. Peroral endoscopy myotomy (POEM) is a relatively new minimally invasive option that is reported to adequately resolve esophageal outflow obstruction in achalasia [44].

Esophageal body motor dysfunction generally falls along the lines of hypomotility (poor contraction, breaks in peristaltic integrity, fragmentation of peristalsis, absent peristalsis) and hypermotility (exaggerated contraction, simultaneous peristalsis) based on pathophysiological mechanisms that correspond with easily recognizable EPT patterns [18, 45]. Hypomotility processes can affect the LES and/or the esophageal body, and can result from either poor excitatory mechanisms or failure of the smooth muscle to respond to excitatory stimuli. Hypomotility patterns are frequently associated with poor esophageal clearance and suboptimal barrier function

at the EGJ, associated mainly with gastroesophageal reflux disease (GERD) patterns. Hypermotility patterns manifest aberrant inhibitory nerve function, exaggerated excitatory function, or combinations thereof, and can be associated with esophageal hypervigilance and perceptive "hypersensitivity" symptoms [19].

pH- and pH-Impedance Monitoring

A trial of empiric proton-pump inhibitor (PPI) therapy is considered the standard of care for initial evaluation and management of patients with suspected GERD symptoms, reserving endoscopic evaluation for alarm situations or lack of response to this empiric approach. However, certain situations necessitate further diagnostic evaluation for either establishing the presence of abnormal esophageal acid exposure in explaining esophageal symptoms, or for ruling out a reflux mechanism for symptoms [46, 47]. Evaluation is typically performed using ambulatory pH monitoring, with or without concurrent impedance monitoring. Indications for pH testing include symptomatic states that could be consistent with GERD, but refractory to seemingly adequate PPI therapy, and when aggressive treatment options such as antireflux surgery are being considered. Currently, the ambulatory pH monitoring options include conventional catheter-based pH monitoring with two pH sensors 15 cm apart, and wireless pH monitoring using a single sensor pH probe that can be attached to the esophageal mucosa [46, 47]. Multichannel intraluminal impedance monitoring can assess bolus movement along the tubular esophagus and can complement pH monitoring. This consists of the measurement of resistance (impedance) to flow of a tiny electrical current, generated by esophageal tissues or intraluminal bolus within the esophagus. Resistance (impedance) decreases below the resting baseline with liquid content adjacent electrode pairs along the impedance catheter, and increases with air in the lumen. The multiple electrode pairs placed along the catheter allow assessment of directionality of impedance change, and hence direction of bolus movement along the esophagus. This technology can be combined with ambulatory pH monitoring to better characterize reflux events (Fig. 4), or with stationary HRM to define the relationship between esophageal peristaltic patterns and bolus clearance [46–48].

Data Acquisition and Analysis

Ambulatory pH monitoring documents the exposure to acid mainly in the distal esophagus. This can be performed using a transnasal catheter-based system consisting of two recording sensors 15 cm apart or a wireless system with a single sensor; both systems require a data recorder worn by the patient. With the catheter-based systems, the reflux events are monitored over a 24 h period while the patient keeps a diary of activities and meals. By convention, the distal pH recording sensor on

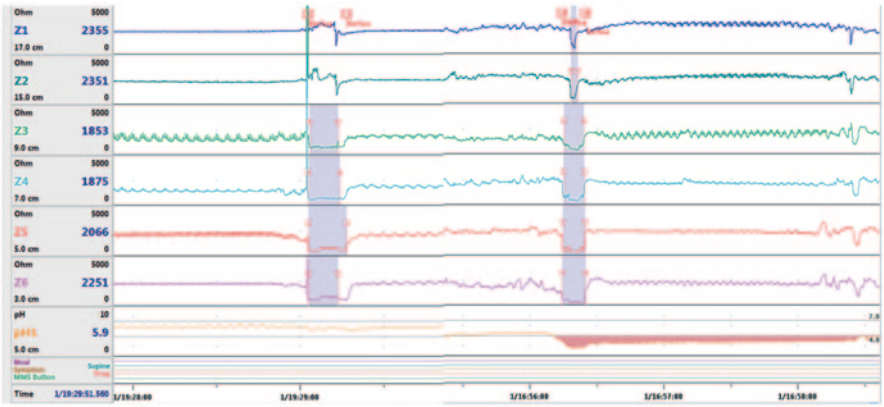

Fig. 4 Esophageal pH and impedance tracing showing a reflux event. The first event does not demonstrate a drop in pH, and therefore, represents a weakly acidic or nonacidic reflux event. The drop in pH associated with the second event indicates that the reflux event is acidic. Decrease in esophageal impedance is seen moving retrograde up the esophagus, indicating that these episodes represent reflux and not swallowed boluses

catheter-based devices is placed 5 cm above the proximal LES margin defined by manometry [46–48]. Wireless pH probes record acid exposure for 48–96 h, and are placed 6 cm above the measured squamocolumnar junction, which corresponds to the location of the distal pH sensor on catheter-based systems [49]. pH drops below a threshold of 4.0 define reflux events. The duration for which pH is <4.0 can be quantified, typically reported as the percentage of time this threshold is crossed over a day (acid exposure time, AET). Normal thresholds are typically 4% for total AET, 6% while upright, and 2% while supine. Correlation of symptom episodes to reflux events can be assessed. Patients record symptoms electronically using buttons on their recording device; symptoms occurring within 2 min of reflux events are extracted and considered correlated to reflux events [46]. A simple proportion of correlated symptoms to all symptoms define the symptom index (SI). A more sophisticated measure is the symptom association probability (SAP), which statistically assesses the probability of chance association between symptoms and reflux events—chance association <5% defines strong confidence in symptom reflux association, which corresponds to a p value of <0.05 on this test, or SAP >95% [50]. Increasing ambulatory pH monitoring from 24 to 48 h has been shown to increase the diagnostic yield of the study, especially in bringing out day to day variation in acid exposure times, and assessing symptom reflux association for infrequent symptoms, particularly atypical symptoms [51–54]. Limited data exist on even longer pH monitoring, up to 96 h, with further augmentation of diagnostic yield. The 96 h study can sometimes be used to assess response to acid suppression, when the first half of the study is performed off antisecretory therapy and the second half on therapy [55].

While the wireless pH system may be tolerated better by patients, disadvantages include a single pH-sensing site (which is unable to differentiate refluxed acid from

swallowed acidic content), placement at endoscopy (in most instances, although manometric measurements of distance to LES can be utilized for transoral placement using a correction factor), potential for detachment, and higher cost [46–48]. Despite this, the wireless system is a validated alternative to catheter-based pH monitoring, especially if a higher AET threshold is utilized to allow for swallowed acidic material [49].

pH systems lack the ability to detect weakly acidic or nonacidic reflux events, especially in patients remaining on antisecretory therapy during the study. Combined impedance and pH monitoring may overcome this disadvantage, as bolus movement can be identified regardless of the pH of esophageal content [46, 56]. Impedance pH monitoring may be the most helpful when evaluating patients with confirmed GERD having persistent symptoms despite the PPI therapy. In this situation, performing an impedance pH test while on PPI therapy may document ongoing acid reflux consistent with PPI failure, or reflux with weakly acidic or nonacidic content correlating with symptoms (Fig. 4). Multicenter studies have suggested that nonacid or weakly acid reflux could explain persisting reflux symptoms in 30–40 % of patients on seemingly adequate PPI therapy [57, 58]; this patient population could potentially be offered antireflux therapy. However, the outcome studies documenting successful management directed by impedance parameters alone are limited in the literature, and the clinical utility of esophageal impedance monitoring continues to be evaluated.

The impedance monitoring can also be combined with conventional or the HRM to assess bolus transport in the esophagus. Effective peristalsis (as determined by manometry) does not always correlate well with successful bolus transport [59]. While impedance manometry is a reliable and accurate method of assessing bolus transit [60, 61], the clinical role of impedance manometry remains unclear. The value of impedance manometry is particularly limited in patients with advanced motor disorders (achalasia and scleroderma); it also does not seem to provide additional information in patients with normal manometry and dysphagia [62, 63]. Further studies are ongoing to further determine the clinical utility of impedance manometry, and how this technology can contribute to patient management.

Anorectal HRM

Coordinated function of the anorectum and pelvic floor allows for proper defecation and maintenance of fecal continence through voluntary and involuntary control mechanisms. The rectum consists of a 12–15 cm muscular tube that terminates at the anus, where the internal anal sphincter and external anal sphincter work in concert to maintain continence at rest. The puborectalis muscle, or “anal sling,” anchors the rectum anteriorly and reinforces the anorectal angle; this functions as a mechanical barrier during the voluntary contraction of this muscle [64, 65]. During normal defecation, the presence of stool in the rectum leads to the rectal disten-

sion and the sensory urge to defecate. The rectoanal inhibitory reflex (RAIR) is triggered by rectal distension, which relaxes the internal anal sphincter. The anal canal is a highly developed sensory organ that is able to differentiate solid, liquid, and gaseous content, triggering appropriate responses on the part of the patient. Under socially acceptable circumstances, the patient is then able to volitionally relax the external anal sphincter and the puborectalis muscles, and simultaneously contract the diaphragm and abdominal muscles to expel rectal content.

Disorders of the pelvic floor occur when this orchestration of sensory perception and relaxation, and contraction of involuntary and voluntary muscles fail to coordinate properly [66]. While dyssynergic defecation typically results from poor coordination of volitional relaxation of the pelvic floor during defecation, fecal incontinence can be a consequence of structural and/or motor failure of the sphincteric apparatus. Anorectal manometry has emerged as a useful technique of quantifying and evaluating the relationships between the internal and external anal sphincters, reflexes (RAIR), rectal compliance, and rectal perception; these facilitate proper diagnosis of disorders of pelvic floor dysfunction and guide treatment. Similar to esophageal manometry, high-resolution anorectal manometry has demonstrated gains over conventional anorectal manometry in assessing defecatory disorders.

Data Acquisition and Analysis

Similar to the progression of esophageal manometry, anorectal manometry initially consisted of a water-perfused system which was eventually replaced with a solid-state system. Despite the type of probe used (solid-state or water-perfused), conventional anorectal manometry consists of a probe with circumferentially arranged side-holes or transducers spaced approximately every 2 cm, and a small balloon attached to the distal end of the probe. With the probe in place inside the anorectum, baseline sphincter pressures are first measured. The patient is then asked to perform certain maneuvers such as volitional squeeze and attempted defecation. To assess RAIR, the change in anal sphincter pressure is measured after the intrarectal balloon is rapidly inflated with 50 mL of air, and anal sphincter pressure decline is evaluated. Rectal sensation testing is performed by inflating the rectal balloon in 10 mL increments until the patient reports a sensation, pain, and/or urge to defecate [67]. External sphincter contraction with cough and Valsalva maneuver can also be assessed. Finally, the ability of the patient to expel a rectal expulsion balloon is assessed, which is filled with 50 mL of ambient temperature water to simulate stool. When first introduced, conventional manometry allowed for a novel approach to assessing the physiology and pathophysiology of the anorectum that proved helpful in diagnosing and directing therapy for patients with pelvic floor disorders. However, the clinical information gained from anorectal conventional manometry was still hindered by the lack of continuous pressure measurements along the anorectum and the conventional line tracing display technique.

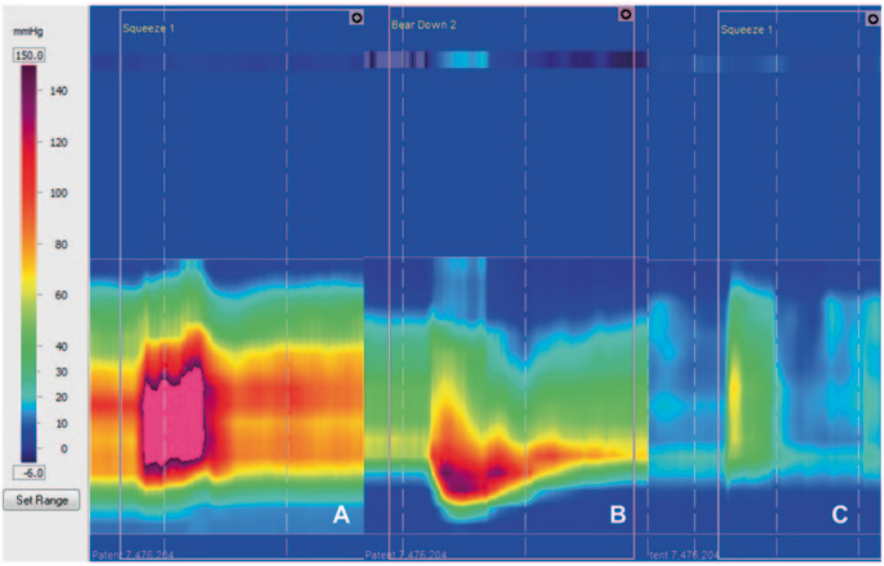

Fig. 5 High-resolution anorectal manometry images. **a** High resting sphincter tone, with exaggerated augmentation during the squeeze maneuver indicative of a spastic sphincter, **b** paradoxical contraction of the sphincter during the bear down maneuver in dyssynergic defecation, **c** weak sphincter with low-resting pressures and suboptimal-squeeze pressures

After proving to be user-friendly and descriptive in identification of esophageal motor disorders, the concept of HRM was naturally applied to the anorectum. High-resolution anorectal manometry employs 36 solid-state circumferential pressure sensors placed at 1 cm intervals that display pressure measurements by employing a 3-D topographical plot of intraluminal pressure relative to time and location (Fig. 5). This interface allows for better interpretation of normal physiology and also pathophysiology in patients with pelvic floor dysfunction. Also, as disorders of pelvic floor dysfunction commonly respond to biofeedback therapy, this intuitive interface allows for easier interpretation by the patient during biofeedback therapy. An initial comparison between conventional and high-resolution anorectal manometry showed that the two techniques provide comparable pressure measurements and that HRM provides greater resolution of anorectal intraluminal pressure that may improve assessment of anorectal disorders [68].

A further advance of high-resolution anorectal manometry consists of the incorporation of tactile sensors that are spaced close together within the anorectal manometry probe resulting in a true 3-D depiction of the sphincteric apparatus. Preliminary assessment of this new technology suggests that function of individual components of the sphincter mechanism (external and internal anal sphincters, puborectalis) can be individually assessed. A 3-D wireframe image of the sphincter

can be generated, which can provide intuitive and descriptive sphincter function at baseline and with maneuvers. However, the outcome studies using high-resolution anorectal manometry and 3-D anorectal manometry are lacking, and further research is needed to document the added yield of these new techniques in clinical practice.

Indications for Anorectal HRM

Fecal incontinence is an extremely common complaint among patients presenting to gastroenterologists, especially in middle-aged women and elderly patients. Risk factors for fecal incontinence include increasing age, multiparity, vaginal obstetrical injuries, and diarrhea [69, 70]. Fecal incontinence has several contributing factors, including low resting or squeeze sphincter pressures, puborectalis weakness, altered rectal or anal sensation, diarrhea, and diminished rectal capacity [66]. Anorectal manometry is an established part of the diagnostic evaluation of fecal incontinence, documenting sphincter anatomy, endurance, and motor function. Anorectal manometry can also be employed to objectively measure changes in these parameters following intervention aimed at addressing fecal incontinence, such as biofeedback, drug therapy, or surgical intervention [64].

Anorectal manometry is also indicated in the evaluation of dyssynergic defecation, which can present as outlet constipation and straining with attempted defecation (Fig. 5). Dyssynergic defecation is the inability to appropriately defecate due to discoordination of abdominal and pelvic floor muscles, and a paradoxical increase in sphincter pressure with attempted defecation, paradoxical anal contraction, or inadequate anal relaxation [71]. Pressure changes with attempted defecation can complement abnormal balloon expulsion in the diagnosis of dyssynergic defecation. Using anorectal manometry, four types of dyssynergic defecation have been described: paradoxical anal contraction with normal push effort (type I), paradoxical anal contraction with insufficient push effort (type II), impaired anal relaxation with adequate push effort but no paradoxical contraction (type III), and impaired anal relaxation and abnormal push effort but with no paradoxical contraction (type IV) [71]. Recognition of dyssynergic defecation allows for appropriate and specific therapeutic interventions, especially biofeedback therapy, which is extremely effective in dyssynergic defecation. Randomized controlled trials have demonstrated that biofeedback is superior to placebo, laxatives, and standard medical management in dyssynergic defecation [72, 73]. Not only does anorectal manometry aid in identifying patients who would benefit from biofeedback therapy, but it also can be used as the patient interface for biofeedback therapy (Table 1, 2, 3, and 4).

Table 1 Indications for high-resolution esophageal manometry

Diagnosis of esophageal outflow obstruction
Esophageal type dysphagia and no structural lesion on endoscopy and/or barium esophagography
Esophageal type dysphagia and high suspicion of motor disorder on other testing
Post-fundoplication dysphagia
Diagnosis of esophageal body motor disorders
Esophageal type dysphagia and no structural lesion on endoscopy and/or barium esophagography
Chest pain and no alternate explanation
Other esophageal symptoms and no alternate explanation
Placement of pH-probes and pH-impedance probes
Localization of the proximal margin of the lower esophageal sphincter
Assessment of esophageal body peristaltic function
Prior to antireflux surgery, for exclusion of esophageal motor disorders contraindicating fundoplication and identification of severe hypomotility necessitating partial fundoplication
Assessment of upper esophageal sphincter function
Patients with oropharyngeal dysphagia and globus symptoms
Diagnosis of cricopharyngeal bar or cricopharyngeal achalasia

Table 2 Steps in diagnosis of motor disorders with the Chicago classification scheme

Step 1: Identification of esophageal outflow obstruction: IRP > 15 mmHg
Achalasia: Type I: no esophageal body peristalsis
Achalasia: Type II: panesophageal compartmentalization of pressure in ≥2 sequences
Achalasia: Type III: spastic pattern within esophageal body in ≥2 sequences
Other outflow obstruction: with retained esophageal body peristalsis
Step 2: Identification of hypermotility disorders
Hypercontractile esophagus: DCI > 8000 mmHg/cm/s in any one swallow
Hypertensive esophageal peristalsis: DCI ≥ 5000 mmHg/cm/s
Premature peristalsis: DL > 4.5 s in ≥2 s
Step 3: Identification of hypomotility disorders
Proportion of failed sequences
Breaks in the peristaltic contour
If none of these characteristics are fulfilled, the motor pattern is designated to be normal

IRP integrated relaxation pressure, *DCI* distal contractile integral, *DL* distal latency

Table 3 Indications for esophageal pH and pH-impedance monitoring

Quantitation of esophageal acid exposure prior to antireflux surgery (preferably performed off PPI therapy)
Correlation of symptoms with reflux events (preferably performed off PPI therapy)
Exclusion of abnormal esophageal acid exposure with atypical on unexplained symptoms (performed off PPI therapy)
Determination of mechanism of continued esophageal symptoms in patients with confirmed reflux disease (pH-impedance testing on maximal PPI therapy may be preferred)
Determination of abnormal reflux in patients with hypochorhydria or achlorhydria (pH-impedance testing)
Determination of mechanism of post fundoplication esophageal symptoms (performed off PPI therapy)

PPI proton-pump inhibitor

Table 4 Indications for anorectal manometry

Diagnosis of obstructed defecation from a motor mechanism
Diagnosis of pelvic floor dyssynergia
Exclusion of pelvic floor dyssynergia in patients undergoing total colectomy for colonic inertia
Diagnosis of Hirschsprung disease
Assessment of mechanism of fecal incontinence
Determination of sphincter pressure and sphincter function

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Endoluminal Fistula and Perforation Closure

Daniel Davila-Bradley and Lee L. Swanstrom

Overview

Because it is uniformly a contaminated environment and because it generates positive intraluminal pressure through peristalsis, perforations of the gastrointestinal tract are one of the most drastic complications after gastrointestinal (GI) surgery or as spontaneous occurences. Acute perforations frequently lead to violent septic consequences while chronic perforations can result in recurrent abscesses, inability to take enteral nutrition and often heal with refractory strictures. Prompt control of a perforation or leak is ideal as it tends to avoid serious consequences like sepsis or extra-luminal infectious fluid collections. Delayed leaks are more difficult to deal with and frequently require a multimodal, multidisciplinary approach. Finally, chronic fistulas can either have mild symptoms or devastating ones, but are always the most difficult to treat due to chronic tissue changes and often an underlying pathology or malnutrition. Recent advances in endoscopic technologies have made endoluminal treatment the "front line" modality for treating most forms of perforations and fistulas although surgery and interventional radiologic approaches play important roles as well. American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend that, in the setting of inflammatory or neoplastic fistulas, dehiscence of surgical anastomoses, and spontaneous or iatrogenic perforations, nonsurgical closure may be desired [1].

In the past, there have been few options for secure endoscopic closure. Standard endoscopic hemostasis clips ("endoclips"), while not designed for closure, were the main tools the endoscopist had. More recently, covered self-expandable stents have shown the utility to bypass or exclude leaks and permit healing [2]. However, a new technology that resulted from the concept of natural orifice

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transluminal endoscopic surgery (NOTES®), allows advanced full thickness closure of the gastrointestinal wall. These devices and techniques include over-the-scope clips, endoscopic suturing devices, fistula plugs, tissue anchors, fibrin sealants, endoloops and even prototype flexible endoluminal linear staplers [1]. Although some of this technology is still experimental, many of these devices are available in the market and have been widely used for these purposes, albeit as an "off-label" indication in many cases.

Treatment Technologies and Procedures

As mentioned, the endoscopist today has a wide variety of endoscopic tools and methods, some borrowing from other disciplines, to treat holes in the GI tract. Here, we will discuss the endoscopic "toolbox" available for leak and fistula treatment, and subsequently will present algorithms for using these in a variety of clinical presentations. As previously mentioned, many of these technologies are not Food and Drug Administration (FDA) approved for GI tract closure, and therefore, are considered "off-label" uses.

Tissue Apposition

Endoscopic Hemostasis Clips ("Endoclips")

Through-the-scope endoclips have been available and used for GI tract closure for many years (Fig. 1). Many companies make them and they come in a variety of sizes and configurations. It seems that each has its own strengths and weaknesses: some able to open and close before firing and some not, some able to be spun within the endoscope and some not, some with a slightly bigger or wider

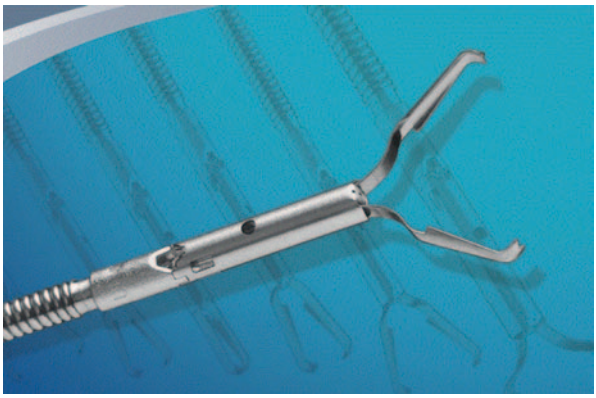

Fig. 1 Through the scope endoclips come in a variety or configuartions. They can be usefull for very acute closures

opening, etc. Their biggest drawback is their very small size which confines their use to fairly non-diseased tissues and closure of the mucosa only in most cases. They are, however, sometimes used as an adjunct to other closure techniques such as endoloops.

Several brands of clips are commercially available. These include the Quickclip (Olympus Corporation, Japan), the Resolution Clip (Boston Scientific, USA) and the Instinct and Triclip (Cook Medical Inc, USA). The first two have two prongs and the Triclip, as it name states, has three prongs and is the one that opens the widest (12 mm). All clips are currently made of stainless steel. Newer versions not commercially available yet (still in development) are titanium clips and even concepts for multi-firing devices [3].

Over-the-Scope Clips

The NOTES experience highlighted the need for secure, full-thickness closure of the GI tract [4]. One response from industry was the development of large clips that are attached to the end of the endoscope ("over the scope") and are designed for robust, full-thickness closures and apposition of even relatively diseased tissues. There are currently two of this type of clips in the market that function very similarly. The over-the-scope clip (OTSC) (Ovesco, Tübingen, Germany) is a nickel–titanium alloy (Nitinol) clip that is highly elastic and has shape memory [5] (Fig. 2). It is designed to cover lesions from 9–11 mm (depending on the size of the clip). The clips are designed with different forms (atraumatic, sharp, or blunt edges) in order to be used in a range of scenarios from iatrogenic perforations to chronic fistulas. The OTSC has an ability to grasp more tissue than standard endoclips creating full thickness closure of a gastrointestinal wall defect, even in the presence of inflammation or induration.

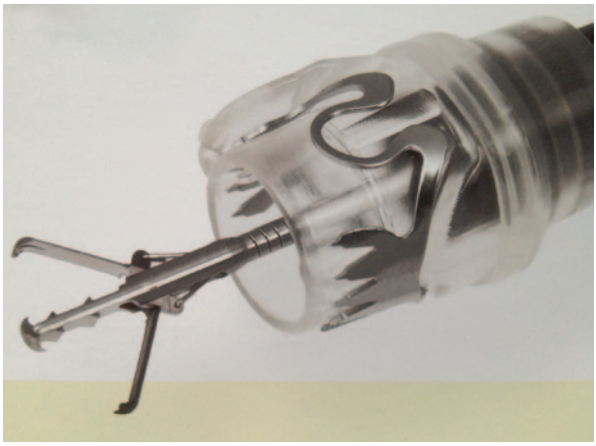

Fig. 2 Over the scope clips allow a more robust, full-thickness closure

Fig. 3 Ovesco makes a clever double grasper to permit traction on both sides of a defect.

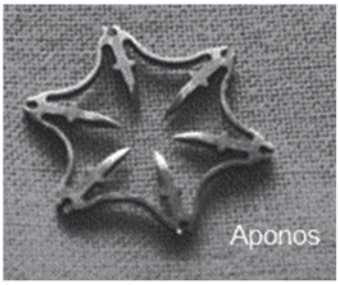

Fig. 4 The Padlock clip from Aponos, is another over the scope clip with full-thickness closure capabilities

The OTSC clip is delivered with an applicator cap mounted on the tip of the scope. A thread is attached to the clip and it is released by tightening the thread with a hand wheel. The caps come in different sizes (11, 12, and 14) to fit different endoscopes and in two different depths (3 and 6 mm) for grasping more or less tissue. Tissue capture is achieved by both robust tissue retraction and by sucking tissue into the cap. Ovesco has also produced two types of tissue retraction devices as standard endoscopic graspers are seldom robust enough to adequately pull tissue like this into the cap. These include an "anchor catheter" and a novel twin grasper (Fig. 3). The "anchor" is a long flexible catheter with three retractable pins that pierce the tissue in order to retract it into the cap and assist in the placement of the clip. The twin grasper is similar to a traditional grasper, but has the ability to open the two jaws of the grasper independently. This feature allows the endoscopist to grasp one side of the defect, hold it without releasing, and then grasp the opposite edge and approximate the tissue before releasing the clip. The OTSC received 'Conformite European' (CE) certification in Europe in 2009 and 510(k) clearance by the FDA in 2010 [1].

The Padlock clip (Aponos Medical, Kingston, NH), is a similar design, but the firing mechanism is adjacent to the scope, and therefore, preserves use of the biopsy channel for instrumentation or suction/irrigation. It also comes in a variety of sizes and has a universal cap that fits on most types of endoscopes (Fig. 4). It too relies both on grasping the tissue and retracting and suction into the cap to achieve full-thickness closure. The Padlock received the FDA clearance in 2012, but is not currently cleared by a CE for sale in Europe.

There have been multiple case reports and several small series that have documented the ability of the OTSC to close acute perforations, leaks, and fistulas [2, 5–12]. Animal studies have shown the superiority of the OTSC versus regular endoscopic clips in closing iatrogenic perforations [13]. The success is higher in GI perforation than for fistulas [1], but the preliminary results are promising. In order to facilitate the endoscopic closure of chronic perforations and fistulas, cauterization, debridement, and curettage of the margins should be performed. These techniques might improve healing around the edges of the perforation. Of note, is that once these clips are deployed, their characteristics make it extremely difficult to remove them without damaging the tissue between their jaws. The endoscopist must be certain that the clip is being placed in the right position before deployment. It has been suggested that exposure to cold water might aid in the removal of a misplaced nitinol OTSC; however, in our experience, we have found this to be unreliable. The development of a retrieval mechanism or technique would be a desirable feature in these types of clips. Risks reported with the use of the OTSC are perforation, bleeding, early detachment, mucosal lacerations, and although it has not been reported, luminal obstruction is a hypothetical complication.

Suturing Technologies

One of the strongest requests to industry from clinicians interested in NOTES was the ability to suture endoluminally. The result was a flurry of concepts designed that ranged from simple (T-tags [TAS, Ethicon, Blue Ash, OH]) (Figure 5) to more complex adaptations of laparoscopic suturing devices such as the Endostitch (Covidien, Norwalk, CN) Figure 6. There were even very complex flexible surgical platforms developed capable of bimanual suturing with standard surgical suture and techniques Fig. 7). Due to the costs of many of these technologies and the fact that they arrived during the onset of the global economic crises, only a few have succeeded in reaching the market.

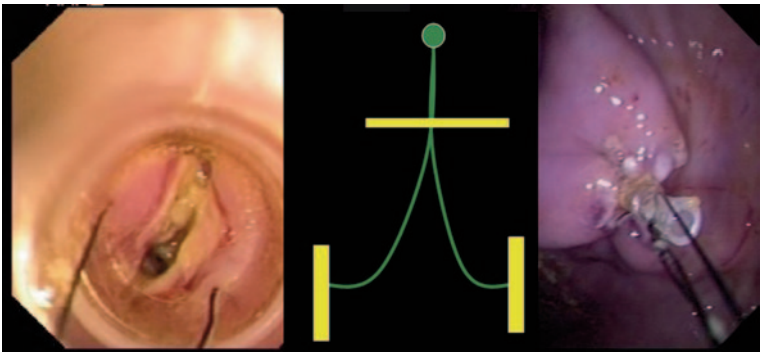

Fig. 5 T-tags were amoung the first endoscopic suturing devices

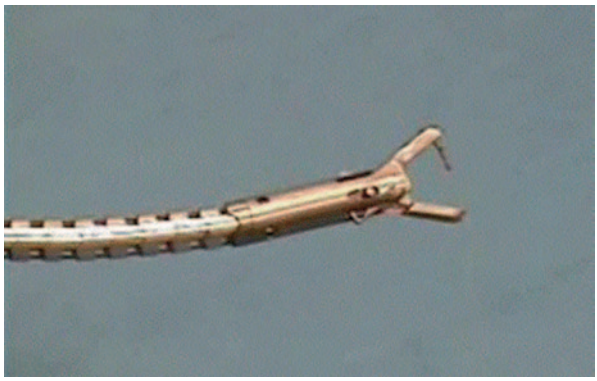

Fig. 6 Several devices were adaptations of existing laparoscopic devices like the Endostitch (Covidien, Ireland)

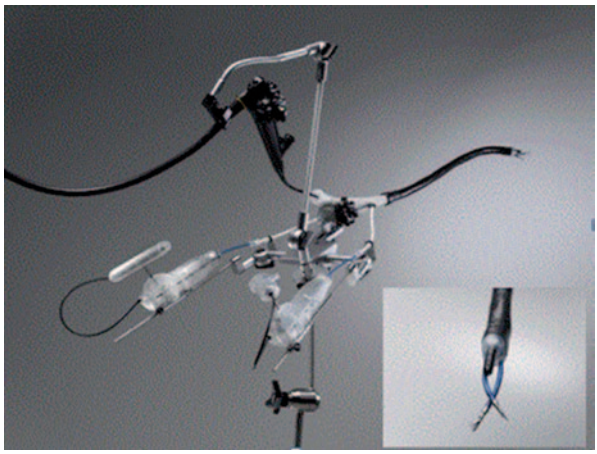

Fig. 7 An example of an endoscopic platform permitting laparoscopic like tissue interations - The DDES from Boston Scientific

G-Prox® (USGI, San Clemente, CA) The G-prox is a suturing system that delivers a full-thickness pledgeted suture with a one-way cinch to tighten it after the placement (Fig. 8). The tissue retraction is best done using a helical tissue screw to allow robust closure. It has a unique way to insure safety when passing the needle full thickness through the GI wall (always an issue with full-thickness closures performed from inside the lumen). It does this by imbricating the wall of the GI tract into the lumen, so that the needle passes through the wall and back into the lumen, where the suture can be deployed under direct vision. The biggest downside to the G-Prox is that it is a 5 mm device, and therefore, cannot be used with standard endoscopes. USGI has a special multichannel 18 mm diameter flexible scope (transport) specially designed for the G-Prox (Fig. 9). The G-Prox has been used in several thousand cases to date, including fistula closures and closures of the gastric and colon wall after perforations or NOTES procedures. [14–19]

The Overstitch® Endoscopic Suturing System (Apollo Endosurgery, Austin, TX) The Overstitch is a suturing device that is mounted onto a double-channel therapeutic

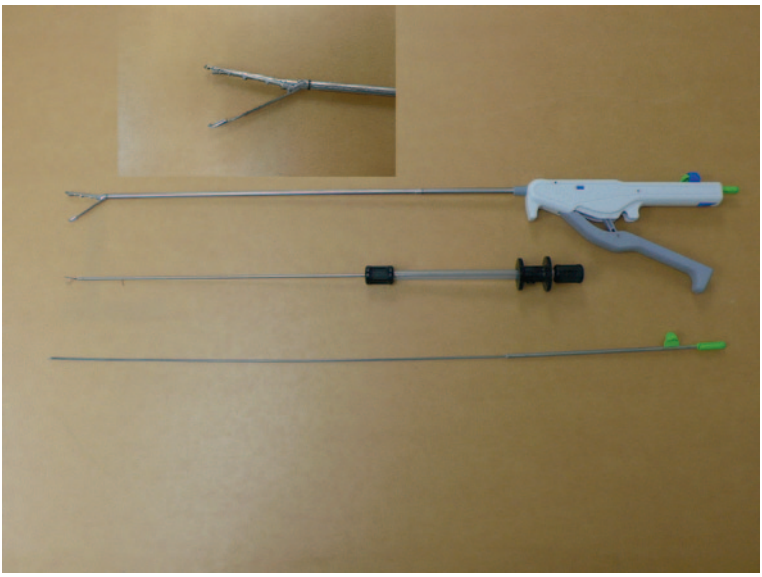

Fig. 8 The G-prox device from USGI medical

Fig. 9 The one drawback of the G-prox was the need to insert it via the Transport access device...

endoscope and allows the placement of full thickness suture. It is compatible with the Olympus 2T160. To date, there is no compatibility with other brands of endoscopes. The device obtained FDA 510(k) clearance in 2008 [1]. The main part of the suturing device is a metallic cap placed on the tip of the endoscope. A needle driver placed within the cap holds and releases the actual needle attached to the suture.

Fig. 10 The Overstitch suturing machine by Apollo Medical

The needle serves as a T-tag when it is released. Available sutures include 2-0 and 3-0 polydioxanone (absorbable) and 2-0 and 3-0 polypropylene (nonabsorbable). The needle driver passes the needle from the mobile arm to the fixed arm piercing the tissue. The needle needs to return to the mobile arm of the needle driver before attempting to take another bite of tissue. After the suturing is finished, the needle is released and a cinching device consisting of a secondary tag slides through the suture and releases a cinch to hold the suture in place. The whole mechanism is maneuvered by a handle placed on the working channel of the endoscope (Fig. 10). The cinching device has its own release mechanism. A helix device can be used for an aggressive retraction. It consists of a helical tip that is screwed into the tissue and allows pulling it into the position for suturing. The overstitch is able to place running or interrupted sutures.

A few reports exist to date showing the feasibility, safety, and durability of closures performed with the Overstitch. The first report in humans [20] presents a successful closure of a gastrocutaneous fistula after a percutaneous endoscopic gastrostomy (PEG) removal. The most common procedure the Overstitch is used for is bariatric revision surgery [21–26]. Thompson et al. reported on 25 patients who had weight regain after roux-en-Y gastric bypass due to pouch dilation or a patulous gastrojejunostomy [27]. At 1 year, patients lost an average of 11 kg with no adverse sequelae.

Flexible Endoscopic Platforms Of the complex flexible endoscopic platforms designed for NOTES surgery and complex endoluminal procedures, only the Anubis scope (Storz, Tutlingen, Germany) is commercially available, and then, only on a limited release basis and only in Europe (Fig. 11). It is however, CE-marked and approved for human use and has been used in small case series for a variety of procedures. [28, 29]. The EndoSamurai (Olympus, Tokyo) and Direct Drive Endoscopic System (DDES, Boston Scientific, Natick, MA) are development projects that have been shelved by their respective companies due to the depressed economy and lack of a clearer picture of the clinical needs that they solve. These platforms

Fig. 11 The only commercially available advanced endoscopic platform - the Anubiscope by Storz

offer the ability for two-handed tissue manipulation along with triangulation, so that it would seem perfect to replicate the ability to suture laparoscopically.

Covered Stents

Covered self expanding stents represent an important tool for dealing with all forms of breaches in the GI tract. Stents available in the market are self-expandable metal and plastic stents. Metal stents are composed of various materials like stainless steel, nitinol (nickel-titanium) with or without a silicon membrane, and elgiloy (cobalt, nickel and chromium). Nitinol stents are very flexible and elgiloy stents are corrosion resistant and capable of generating high radial force [30]. These metallic stents may be partially or fully covered by a plastic membrane [30]. Depending on the brand, they may have a distal and/or proximal flare to prevent migration [30] (Fig. 12). Plastic stents are approved for benign or malignant esophageal strictures. They have a woven polyester skeleton that is fully covered with a silicone mem-

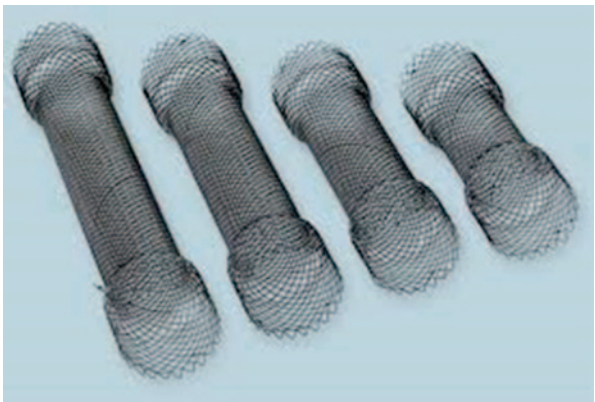

Fig. 12 stents come in many sizes and shapes

brane [30]. Although metallic stents are designed for malignant obstruction, they are widely used "off label" in the treatment of GI tract perforations. Noncovered metallic stents are equivalent to covered metallic stents in terms of technical success, clinical success, long-term patency, and survival rates for the palliative treatment of malignant obstruction in the digestive tract [31]. While stent migration or slippage is uncommon when they are used for tumor palliation, it is a major problem when covered stents are used to treat perforations as they often have no narrowing to hold the stent in position. Stent migration is also more common in covered stents, but noncovered stents are more prone to tissue ingrowths and obviously would be unsuitable for perforation treatment [31]. Stainless steel stents might also migrate more often than nitinol ones [31]. A variety of techniques to prevent migration have been described, but none is totally perfect. On a systematic review on benign esophageal rupture or anastomotic leaks, van Boeckel et al. [32] reported no difference in clinical success between fully covered, partially covered metallic, and plastic stents. Stent migration (25 % of patients) was more common in fully covered stents (plastic or metallic) than in partially covered stents. Tissue ingrowth was not significantly different. They recommended leaving the stents in place for approximately 7 weeks to achieve healing.

Miscellaneous Tools (Fibrin Glues, Atrial Septal Plugs, Acellular Matrix Fistula Plugs)

Sealants The use of fibrin glue has been described as a fistula treatment for more than 20 years [33]. The theory behind its use is that the fibrinogen and thrombin in the fibrin glue combine in the presence of factor XIII and calcium chloride to form a fibrin clot. This fibrin plug acts as a physical barrier until healing begins [34]. Theoretically, it might also promote adhesions on the peritoneal side with migration of fibroblasts and subsequent collagen production. Small series report successful closing of gastrointestinal leaks after gastric bypass, sleeve gastrectomy,

Fig. 13 An example of a cellular matrix fistula plug

and biliopancreatic diversion with duodenal switch [35–37]. Although initially proposed for patients who are unfit to undergo a surgical procedure, it has been suggested that fibrin glue might be used alone or in combination with closure and/or stents for perforations in stable patients with no sepsis and who do not need immediate surgical treatment.

Acellular Matrix Fistula Plugs SurgiSIS®, an acellular fibrogenic matrix biomaterial, is commonly used for hernia repair in the setting of intraperitoneal infection or where nonabsorbable synthetic materials are not desired (hiatal hernias). It is available in different sizes as tapered fistula plugs for treatment of fistula in ano and these have been used for the treatment of a variety of endoluminal fistulas as well (Fig. 13). Its use has been reported in gastrocutaneous fistula after Roux-en-Y gastric bypass [38, 39] with a success rate of 30% after one application, 55% after two applications, and 15% after a third application for a total success rate of 80%. A recent product introduced in the market is MatriStem® (Acell Incorporated, Columbia, Maryland). It is a porcine cellular structure that induces tissue growth. It is available as powder or as a sheet which can serve as a plug. The literature reports its use in the treatment of skin wounds [40]; however, initial experimental research is ongoing in the treatment of gastrointestinal perforations.

Cardiac Septal Occlusion Devices Off label use of the different cardiac septal plugs (Amplatzer Septal Occluder [AGA Medical Group, Plymouth, Minn] and the Cardio-SEAL septal repair implant [NMT Medical, Boston, Mass]) have been used for the closure of gastrointestinal fistulas and deliberate gastrostomies in NOTES [41]. These catheter-based devices consist of two self-expandable disks connected by a short waist **(**Fig. 14). The materials of the disks are woven nitinol with polyester inserts that are placed within the device to facilitate thrombosis and occlusion. When placed in the gastrointestinal wall, it allows healing of the mucosa over the disks. The real closure is achieved with the waist of the device. It functions by stenting the defect with its conjoint waist. The device achieves fixation and stability by stenting the defect and extra-stability is provided by the two atrial discs [42]. The

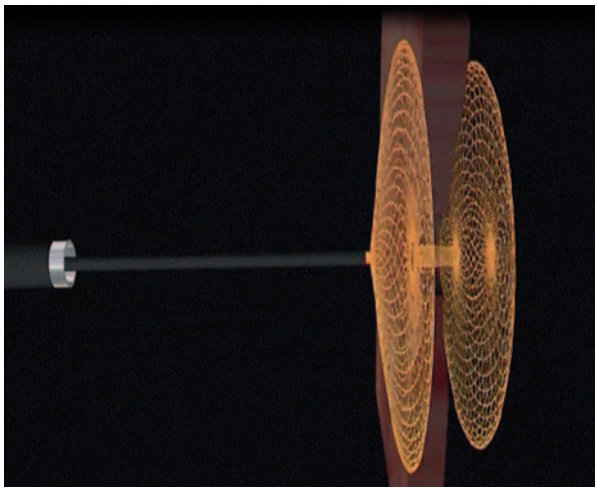

Fig. 14 a cardiac septal occluder device which has also been used to close GI tract defects

device has the advantage of being easily repositioned or removed until it is completely released from the delivery wire, thereby allowing the removal in the event of malpositioning [42]. However, the disadvantage is that it can only be placed in a defect between two hollow cavities to allow placement of the discs in each cavity. A fistula defect with a long tract would not work for this device. Another problem is that it is a permanent foreign body that can fracture or migrate with time. Even more significant is the fact that these devices are expensive (several thousand dollars each).

A case report of a gastrointestinal-related fistula include a gastrocolonic fistula that recurred 4 months after placing an Amplatzer device which was finally closed with a Cardio-seal implant with no evidence of recurrence for 18 months [41]. Other clinical experiences include the use of these devices for closure of tracheoesophageal fistulas [43–46]. The experience has not been completely satisfactory. Coppola [43] reported the enlargement of a tracheoesophageal fistula and migration of the device into the broncial tree 2 months after placing it with subsequent occlusion success after using partially covered stents and Kadlec [44] reported a dislodgment of the disc 12 days after placement with enlargement of the fistula finally requiring operative repair. Lee obtained better results although the follow-up was short (1 month) and Repici [45] obtained the best results closing a gastro-tracheal fistula after a gastric pull-up for esophageal cancer. Several attempts were made to close the fistula, including surgery, and the final attempt with the septal occlusion device was successful showing no recurrence in 8 months of follow-up.

Presentations and Indications for Treatment Presenting symptoms vary according to the location of the leak, timing of the presentation for treatment, degree of body cavity contamination, and underlying patient disease. For acute perforations or leaks, there is usually a brief "golden hour," where the patient is relatively stable, and where the immediate repair of the opening will affect a rapid cure. Acutely presenting leaks, if untreated, usually rapidly decompensate and can often progress to sepsis and car-

diovascular collapse. For patients presenting in full septic shock, a trip to the operating room (OR) and emergent surgery is usually the best course, though endoscopic treatment that can often augment surgical exploration. An example would be a laparoscopic abscess drainage and debridement with concomitant placement of a covered stent. Imaging studies are usually not needed and can delay definitive treatment.

More chronic leaks can present with a wide spectrum of symptoms: once again, full-blown sepsis is a possibility, but also a more indolent presentation is possible. Sometimes, particularly with fistulous connections to other parts of the GI tract, the patient can be asymptomatic or have hard-to-diagnose conditions like low grade fevers, diarrhea, or weight regain after a bypass surgery. These patients require a high index of suspicion and a thorough workup. Contrast x-rays and/or computed tomography (CT) scans are usually the best mode of treatment though sometimes a diagnostic endoscopy is required for a definitive diagnosis. These patients are good candidates for a try at an endoscopic repair as surgery can be quite difficult and prone to complications.

Treatment Algorithms Acute Perforation: A perforation occurring at the time of endoscopy should be repaired at the time of the occurrence or as soon as it is possible. This is best done by primary closure and it is one time that standard endoscopic clips often work well. If clip closure is not possible, a more robust closure technology can be used such as an OTSC or endoscopic suturing. If good closure can be achieved, no further adjuncts are needed though the patient should be kept nil per os (nothing by mouth, NPO) for a few days to allow healing. If doing well clinically, the patient can be started on a diet after 24–48 h.

Anastomotic Leak or Delayed Presentation Leak: Intermediate leaks, either ones that occur remote from surgery (from ischemic complications, ulcerations, etc.) or ones that were missed and presented later, require a more complex and multimodal approach for treatment. Primary closure is seldom possible or often requires adjunct treatments for success. A CT scan should usually be performed to document the extent of peritoneal, retroperitoneal, or thoracic contamination. Percutaneous drain placement should be established if indicated and possible. Endoscopy is the next step, with assessment of the breach. If the hole is found to have relatively fresh and pliable edges, primary closure can be considered. Standard clips are usually not feasible and either an OTSC or a suturing device is the better option.

It should be noted that CO_2 insufflation should be used during all perforation/leak treatments as gas extravasation is, of course, typical, and air can result in hemodynamic problems and at best, persistent subcutaneous emphysema. If large enough a defect, it is often useful to exit it with the scope and explore the abscess area. Drains should be inspected to make sure that they are not in contact with the hole as it may actually prevent healing and closure. We like to irrigate and debride abscess cavities with the scope using sterile saline.

If primary closure is not possible due to tissue characteristics, a covered stent should be placed to exclude the area (Fig. 14). The stent should be placed with a 3–5 cm overlap, and if it is necessary to place it in an area at risk for stent migration, a partially covered stent or other methods for migration prevention (stacking stents,

clips, suturing, etc.) can be used [47, 48]. Plugs and glues are not typically used in this infected setting. Stents can be left in place for 2–6 weeks depending on the size and position of the leak.

Chronic Fistula Chronic enteric fistulas are characterized by a general lack of severe infection and often either granulation tissue or mucosal lining to the tract. As with any of these lesions, size can vary from very small to massive and length from millimeters to many centimeters. Best healing is achieved with muscle to muscle or serosa to serosa closure. This necessitates destroying the mucosal lining of the opening and the tract. This can be done with energy (argon beam, electrocautery), or by mechanical means (cytology brushes, biopsy forceps, etc.). Small fistulas (<1 cm) are most successfully closed with an OTSC. Suture closure can also be performed and is sometimes needed if the defect cannot be accessed with a clip. If simple closure fails or the closure is questionable, covering with a stent may allow it time to heal.

For long, narrow fistula tracts, injecting the tract with fibrin glue and clipping the orifice can be effective. This does not work for short-length fistula. Acellular matrix fistula plugs, designed for fistula in ano, have been described for fistulas in the rest of the GI tract. They can be difficult to place and need to be secured, so that they require a degree of ingenuity tailored to each occurrence.

Results

Success in closure is directly related to the size of the defect and the timing of the intervention. Acute perforations noted at the time of an endoscopy (iatrogenic perforations, perforations during Endoscopic Submucosal Resection (ESD), etc) are typically quite successfully clipped/closed. [49, 50] At the other end of the spectrum, a large, long standing, short entero-enteric fistula is seldom permanently closed.

Stents have the best literature support for leaks and perforations (Table 1) with success rates between 40 and 100 %. Other treatments such as including the OTSCs are mostly anecdotal reports or very small series. [2, 5–13].

Chronic fistulas have the poorest overall success. Thompson reported one of the largest series (95 patients) using a variety of closure methods and showed an overall success of 35 %. Failure was progressively higher with the increasing size of defect and the best predictor of success was fistulas <1 cm [52].

Future Developments There are continual improvements in devices like clips and suturing that will continue to make the job of treating fistulas and leaks easier. The development of endoscopic staplers, which already exist in prototype forms, will be a truly disruptive advent with regard to endoluminal closure of the GI tract. Such staplers in fact currently exist in prototype formats (Fig. 15). Flexible surgical platforms such as the Anubis scope may or may not have a major role in the treatment of fistulas and leaks due their size and complexity, but will certainly be good for

Table 1 Results of stent treatment of early and late GI leaks. [51]

Table 2. Results of endoscopic stenting—early and late leaks

Study	Year	Number of patients	Indication	Time to stent	Success (%)	Migration (%)	Complications[a]	Time for healing
Iqbal	2011	17	All	<1 week	41	37	4 migrations, erosions, or perforations	49 days
Aretxabala	2011	4	Failed non-op	<1 week	75	50		6 weeks
Jurowich	2011	3	1 primary 2 failed non-op	<1 week	100	0		
Tan	2010	8	Failed non-op	<1 week	50	50	1 Gl bleed	6 weeks
Blackmon	2010	5	Failed non-op	<1 week	100	40	1 bleeding; 1 erosion	30 days
Eubanks	2008	11	Failed non-op	<1 week	91	58	3 migrations	35 days
Edwards	2008	5	Failed non-op	<1 week	100	50		44 days
Fukumoto	2007	4	Failed non-op	<1 week	75	50		6 weeks
Beqe	2011	22	Failed non-op	> 4 weeks	41	59		86 days
Spyropouls	2011	8	Failed non-op	>1 week	100	0	1 Gl bleed	43.2 days
Blackmon	2010	5	Failed non-op	>1 week	100	40	1 bleeding; 1 erosion	30 days
Casella	2009	3	Failed non-op	>1 week	100	33		55 days
Toussaint	2009	3	"Large" leak	>2 weeks	33	0		
Eukbank	2008	2	Failed non-op	>1 week	50	58		35 days
Serra	2007	5	Failed non-op	>1 week	80	20		12 weeks
Salinas	2006	17	Failed non-op	>1 week	94	6	2 mucosal tears	12 weeks

GI gastrointestinal

[a] Requiring surgery

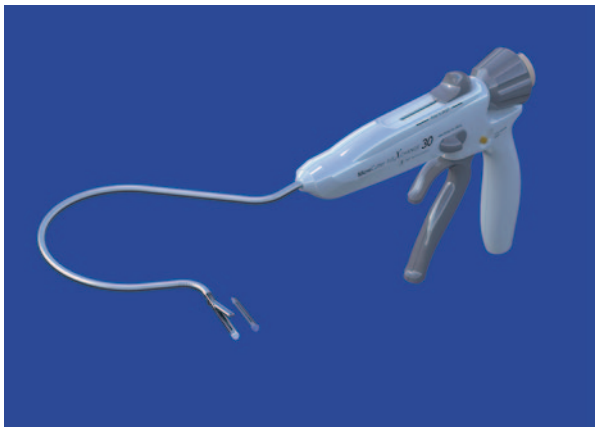

Fig. 15 A prototype through the scope stapling device (Cardica Medical)

some. Finally, alteration of the disrupted wound environment through cell therapy is being looked at and may be a future therapy for the currently hard-to-treat chronic fistulas. [53].

Conclusions

Endoscopic tools and approaches derived from NOTES have dramatically influenced how we consider and approach defects in the GI tract. New technologies such as suturing devices and full-thickness clips have increased the treatment options endoscopists have. Using a multidisciplinary approach, and often a combination of endoscopic therapies, has converted what was once a mandatory surgical procedure into a truly minimally invasive endoscopic procedure. Future developments such as staplers and stem cell therapy may further increase the success rates of endoscopic treatments.

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Advances in EUS

Masayuki Kitano and Ken Kamata

Introduction

Endoscopic ultrasonography (EUS) is an ultrasound system that employs a high-frequency transducer [1, 2]. It facilitates the close observation of organs inside and outside the digestive tract wall and can yield high-resolution images. In particular, because the ultrasonic transducer at the tip of the echoendoscope can be placed into the esophagus, duodenum and stomach, the EUS can generate high-resolution images of the pancreatobiliary system and upper gastrointestinal tract. Consequently, EUS is more accurate than transabdominal ultrasound, computed tomography (CT), and magnetic resonance imaging in terms of detecting and staging of upper gastrointestinal tract and pancreatobiliary diseases [3–5]; however, the ability of conventional EUS to characterize the lesions in digestive organs is limited. This problem has recently been addressed by the development of several new EUS-imaging technologies, namely, tissue elastography [7–9] and contrast enhancement [9–10], which greatly enhance the diagnostic ability of EUS, because they provide detailed information on the tissue structure.

In 1992, EUS-guided fine needle aspiration (EUS-FNA) with a curved linear array probe was introduced for the diagnosis of the pancreatic masses [11]. Since then, EUS-guided puncture has been used to diagnose various diseases. It is also used for two kinds of treatment, namely, drainage and injection. The targets of EUS-guided drainage include pancreatic cyst, bile duct, gallbladder, and pancreatic duct. In particular, EUS-guided biliary drainage has recently been used to treat patients with obstructive jaundice when endoscopic retrograde cholangiopancreatography (ERCP) was unsuccessful [12, 13]. The most common EUS-guided injection is ethanol injection into the celiac plexus and ganglia for cancer-related pain [14–16]. This chapter focuses on such new techniques of imaging and therapy in the field of EUS.

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EUS Elastography

Principle of EUS Elastography

The technique of tissue elastography is based on low-frequency compression of the tissue, which is applied manually via gentle compression with ultrasound transducer, or using physiological body movement such as respiration or pulsation [17, 18]. The main principle of tissue elastography is that a compressive force is applied to tissue causing axial tissue deformation (strain), which is then calculated by comparing the echo sets before and after the compression [19–21]. The degree of deformation is used as an indicator of the stiffness of the tissue, which is smaller in hard tissue than in soft tissue. The method relatively characterizes differences of strain between tissues [19–21].

EUS elastography is an adjunctive imaging technique that allows the tissue elasticity of a solid mass to be assessed during a conventional EUS examination [6–8]. This technique allows direct visualization of the strain information superimposed on the fundamental B-mode image as a strain distribution map ("the elastogram"), which, for visualization purposes, is color-coded, and displayed next to the fundamental B-mode image on the screen [6–8]. Red is used for encoding soft tissues, blue for hard tissues and yellow/green for tissue of intermediate stiffness [6–8]. The elasticity information derived by this method is qualitative or semi-quantitative. The strain of each area is compared with the remaining tissue within the elastogram, which is a relative image available for visual comparison only.

Several different variables have been used in EUS elastography as a measure of tissue elasticity, namely, (1) color patterns [8, 22–26], (2) strain ratio [27], (3) hue-histogram analysis [28, 29], and (4) artificial neural networks [30, 31]. The first variable, which is qualitative, may be limited by its subjectivity, which could lead to differences in interpretation between endosonographers. This problem is less likely for the remaining three quantitative variables, which is supplementary to the qualitative variable.

EUS Elastography for Evaluating Pancreatic Masses

1. Qualitative color patterns
   There are several studies on the EUS elastography, particularly on its ability to differentiate benign from malignant pancreatic masses. Tissues that are depicted in blue are hard and are interpreted as being malignant; by contrast, red represents soft tissue and is interpreted as being normal (Fig. 1). A typical EUS color pattern elastographic image of a pancreatic carcinoma is shown in (Fig. 2). A systemic review and meta-analysis showed that this method differentiates benign from malignant pancreatic masses with a pooled sensitivity and specificity of 99 and 74%, respectively [32]. Giovannini et al. reported that this EUS elas-

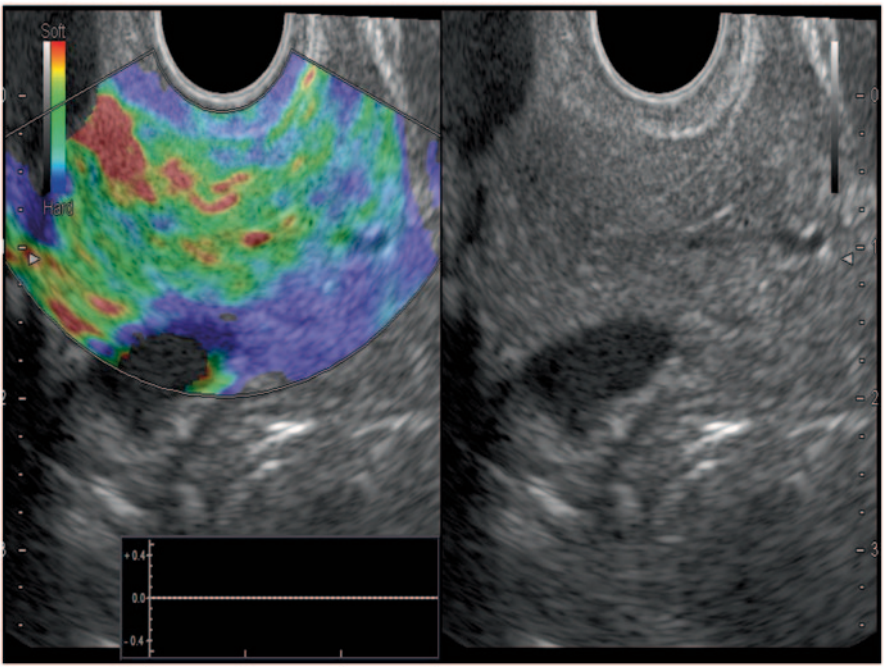

Fig. 1 Typical conventional EUS (*right*) and EUS elastography (*left*) images of the normal pancreatic parenchyma. EUS elastgraphy (*right)* shows red and green area in the entire pancreatic parenchyma which indicate soft tissue. *EUS* endoscopic ultrasonography

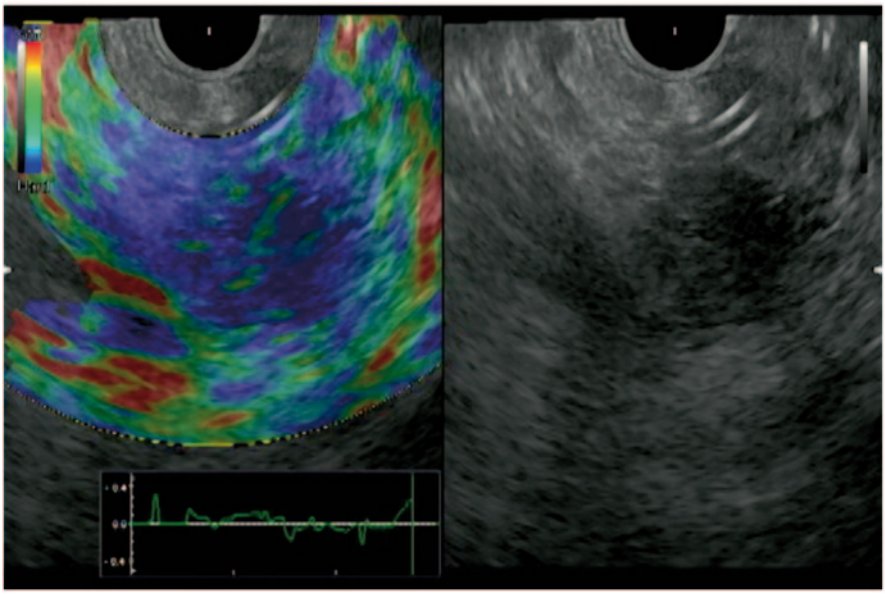

Fig. 2 Typical conventional EUS (*right*) and EUS elastography (*left*) images of the pancreatic carcinoma. Conventional EUS (*right)* shows a hypo-echoic lesion at the head of the pancreas. EUS elastography (*left)* reveals blue area in the entire lesion which indicates hard tissue. *EUS* endoscopic ultrasonography

tography method diagnoses pancreatic masses more accurately than fundamental B-mode imaging [12, 23]. Iglesias-Garcia et al. extended the field further by using four patterns, as follows: homogeneous green, heterogeneous green-predominant, homogeneous blue, and heterogeneous blue-predominant patterns [24]. They found that this method diagnosed pancreatic malignancy with a sensitivity, specificity, and overall accuracy of 100, 85.5, and 94 %, respectively.

2. The strain ratio
   The strain ratio is the ratio of the elasticity of a reference region in the adjacent tissue to the elasticity of the suspicious mass, thus in each procedure, the elasticity of the mass lesion (A) and the soft-tissue reference area (B) is measured and the corresponding mean strain ratios (i.e., B/A) are calculated [27]. Two studies have assessed the accuracy of strain ratio-based EUS elastography for diagnosing pancreatic malignancies with the sensitivity ranging from 93 to 100 % and the specificity ranging from 17 to 95 % [28, 29]. Therefore, the strain ratio-based EUS elastography results are variable, especially in terms of specificity.

3. Hue histogram analysis
   Hue histogram analysis involves a quantitative scale of elasticity that ranges from 0 (softest) to 255 (hardest) and is applied by analyzing the traditional color distribution of hardness by post-processing software [29, 30]. Several studies have shown that, when the average hue histogram value of >175 is used to indicate malignancy, the hue histogram-based EUS elastography differentiates benign from malignant pancreatic masses with a sensitivity and specificity of 85–93 % and 64–76 %, respectively [29, 30].

4. Artificial neural networks
   Recently, a study on neural networks that used artificial intelligence methodology was reported. In that study, the post-processing software analysis was used to compute the individual elastography frames into a numeric matrix [31, 32]. These data were then subjected to extended neural network analysis that automatically differentiates benign from malignant patterns. This method differentiated benign from malignant pancreatic masses with a sensitivity of 88 % and a specificity of 83 % (33 %). Moreover, the corresponding area under the receiver operating characteristic curve was 0.94, which was significantly higher than the values obtained by simple mean hue histogram analysis (33 %).

EUS Elastography for Evaluating Pancreatic Parenchyma

The EUS elastography is also used for diagnosis of chronic pancreatitis. The color map of chronic pancreatitis is more heterogeneous than that of normal pancreatic parenchyma (Fig. 3). A significant linear correlation is obtained between the strain ratio and the number of EUS criteria of chronic pancreatitis ($r = 0.813$; $P < 0.0001$)

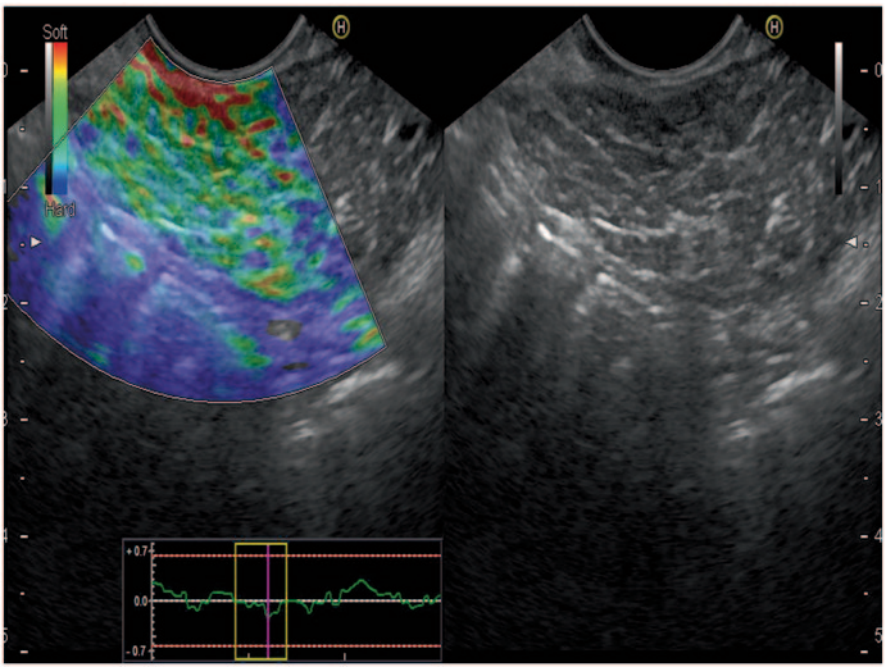

Fig. 3 Typical conventional EUS (*right*) and EUS elastography (*left*) images of the chronic pancreatitis. The color map of chronic pancreatitis is more heterogeneous than that of normal pancreatic parenchyma which is shown in Fig. 1. *EUS* endoscopic ultrasonography

[34]. The area under the receiver operating characteristic (ROC) was 0.949 and the accuracy with which EUS elastography diagnosed chronic pancreatitis was 91%, when the cut-off strain ratio of 2.25 was used [34]. Itoh et al. subjected the EUS elastographic images of the upstream pancreas and the pancreatic tumor in 58 patients to statistical analysis and then assessed how well parameters of elastography, including the mean, standard deviation, skewness and kurtosis, could diagnose the histological fibrosis of the pancreatectomy specimens, which was graded into four categories (normal, mild, marked, and severe fibrosis) [35]. The most useful EUS elastography parameter was the mean for diagnosing pancreatic fibrosis with the area under the ROC curve of 0.90.

EUS Elastography for Evaluating Lymph Nodes

The differential diagnosis of benign and malignant lymph nodes is essential for clinically staging patients with cancer. Recently published meta-analysis with seven studies involving 368 patients with 431 lymph nodes showed that the pooled sensitivity of EUS elastography for the differential diagnosis of benign and malignant lymph nodes was 88%, and the specificity was 85% [36]. For the qualitative analy-

sis, the dominance of blue color (relatively hard tissue) is used for as marker for malignancy, the accuracy reaches 85 % [37]. The quantitative analyses of the data indicated a sensitivity of 85–94 %, a specificity of 66–92 % and an overall accuracy of 86–89 % [38, 39]. The cut-off strain ratio value of 3.81 distinguished malignant lymph nodes from benign lymph nodes with a sensitivity and specificity of 86 and 85 %, respectively [40].

Contrast-Enhanced EUS

Ultrasound Contrast Agents

Intravenous ultrasound contrast agents are microbubbles consisting of gas covered with a lipid or phospholipid membrane [41]. A certain range of acoustic power induces microbubble oscillation or breakage [42, 43]. Contrast-enhanced harmonic ultrasonography selectively depicts the signals produced by microbubble oscillation or breakage. The first-generation ultrasound contrast agent was Levovist (Schering AG, Berlin, Germany), which is composed of microbubbles of room air covered with a palmitic acid membrane. Levovist requires high acoustic power to oscillate or break its microbubbles [41, 42]. The second-generation ultrasound contrast agents include SonoVue (Bracco Imaging, Milan, Italy), Sonazoid (Daiichi-Sankyo, Tokyo, Japan; GE Health care Milwaukee, WI, USA), and Definity (Lantheus Medical Imaging, North Billerica MA, USA) and are composed of gases (not room air). They can be oscillated or broken by lower acoustic powers [41, 43], and thus are more suitable for the EUS, because the small transducer of EUS produces limited acoustic power [44]. Immediately before performing contrast enhancement, the ultrasound contrast agents are reconstituted with sterile water. After images of the ideal scanning plane are displayed on the specific mode for contrast enhancement, a bolus injection of the ultrasound contrast agent is administered through a 22-gauge cannula placed in the antecubital vein.

Principle of Contrast-Enhanced EUS

Intravenous ultrasound contrast agents enhance EUS images by depicting the vessels. Contrast-enhanced EUS includes contrast-enhanced doppler EUS and contrast-enhanced harmonic EUS. The former modality is based on the principle that the phase shift of the signals received from ultrasound contrast agents produces pseudo-doppler signals [42, 43]. On contrast-enhanced doppler EUS, these pseudo-doppler signals increase the sensitivity with which color and power doppler imaging depict the doppler signals from vessels [45–51]. However, this modality remains limited in terms of real time vessel imaging, because of artefacts such as blooming.

The other contrast-enhanced EUS modality, namely, contrast-enhanced harmonic EUS, selectively depicts harmonic components that are integer multiples of the fundamental frequency [9, 10, 42–44]. When microbubbles are oscillated or broken after receiving a certain range of acoustic power, harmonic components are produced. The harmonic component derived from microbubbles is higher than that from tissues; thus, contrast harmonic imaging more intensively depicts signals from the microbubbles than those from the tissue by selectively detecting the harmonic components [9, 10, 42–44]. Contrast-enhanced harmonic EUS can be performed with a wideband transducer equipped with EUS and the second-generation ultrasound contrast agents which are oscillated or broken by low acoustic powers [9, 10, 44].

Contrast-Enhanced EUS for Pancreatic Solid Masses

On contrast-enhanced EUS, the solid pancreatic lesions can be characterized on the basis of their enhancement patterns relative to their surrounding tissue, namely, hypo-enhancement, iso-enhancement, or hyper-enhancement [52–55]. The contrast-enhanced harmonic EUS depicts pancreatic ductal carcinomas as nodules with hypo-enhancement that mostly have irregular network-like vessels (Fig. 4a) [52–55]. By contrast, most inflammatory pseudotumors exhibit iso-enhancement (Fig. 4b) and most neuroendocrine tumors exhibit hyper-enhancement (Fig. 4c) [52–55]. When Sonazoid which is the most sensitive ultrasound contrast is used for contrast-enhanced harmonic EUS, all pancreatic carcinomas possess a certain enhancement although the most are with hypo-enhancement, while benign necrotic tissues exhibit non-enhancement [54]. A recently published meta-analysis showed that when pancreatic adenocarcinomas are diagnosed on the basis of hypo-enhancement in contrast-enhanced harmonic EUS, the pooled diagnostic sensitivity and specificity are 94 and 89%, respectively [56]. Moreover, when contrast-enhanced harmonic EUS was compared to conventional EUS, the former detected pancreatic adenocarcinomas (defined as hypo-enhanced lesions) with better sensitivity and specificity (96 and 64%, respectively) than conventional EUS, where pancreatic adenocarcinomas were defined as hypoechoic lesions (86 and 18%, respectively) [52]. Contrast-enhanced harmonic EUS also improves the depiction of the outline of ductal carcinomas with uncertain conventional EUS findings [52, 54, 57].

The contrast-enhanced harmonic EUS and contrast-enhanced CT are comparable in terms of differentiating ductal carcinomas from other masses, although contrast-enhanced harmonic EUS (91% sensitivity and 94% specificity) is superior to contrast-enhanced CT (71% sensitivity and 92% specificity) for small ($\leq$2 cm) carcinomas [54]. In particular, the contrast-enhanced harmonic EUS is useful for characterizing small neoplasms that contrast-enhanced CT cannot identify [54].

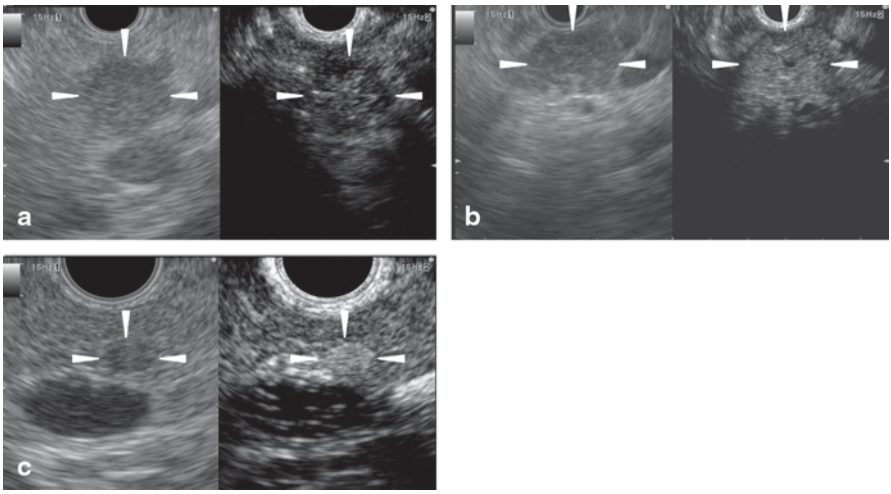

Fig. 4a-c Typical conventional (*left*) and contrast-enhanced harmonic (*right*) EUS images of the pancreatic solid tumors. **a** A ductal carcinoma with hypo-enhancement. Conventional EUS (*left*) shows a hypoechoic area (*arrowheads*) of 15 mm in diameter at the body of the pancreas. Contrast-enhanced harmonic EUS (CH-EUS) (*right*) indicates that the area exhibits hypo-enhancement (arrowheads) compared with the surrounding tissue. **b** An inflammatory pseudotumor with iso-enhancement. Conventional EUS *(left*) shows a hypoechoic area (*arrowheads*) at the body of the pancreas. CH-EUS (*right*) indicates that the area exhibits homogeneous iso-enhancement (*arrowheads*) compared with the surrounding tissue. **c** A neuroendocrine tumor with hyper-enhancement. Conventional EUS (*left*) shows a hypoechoic area (*arrowheads*) of 5 mm in diameter at the body of the pancreas. CH-EUS (*right*) indicates that the area exhibits hyper-enhancement (*arrowheads*) compared with the surrounding tissue. *EUS* endoscopic ultrasonography

Contrast-Enhanced EUS for Pancreatic Cystic Tumors

Since contrast-enhanced harmonic EUS can identify vessels in the echogenic structure of cystic lesions, it discriminates mural nodules from mucous clots more sensitively than conventional EUS (Fig. 5) [58]. Mural nodules can also be further classified by contrast-enhanced EUS into four classes; low papillary, polypoid, papillary, and invasive nodules. Of these, the papillary and invasive nodules associate frequently with malignancy [58].

Contrast-Enhanced EUS for Tumor Staging and Lymph Node Assessment

Compared to conventional EUS, contrast-enhanced harmonic EUS improves the preoperative T-staging of pancreatobiliary tumors [59]. In particular, contrast-enhanced harmonic EUS is superior in diagnosing portal invasion by pancreatobiliary

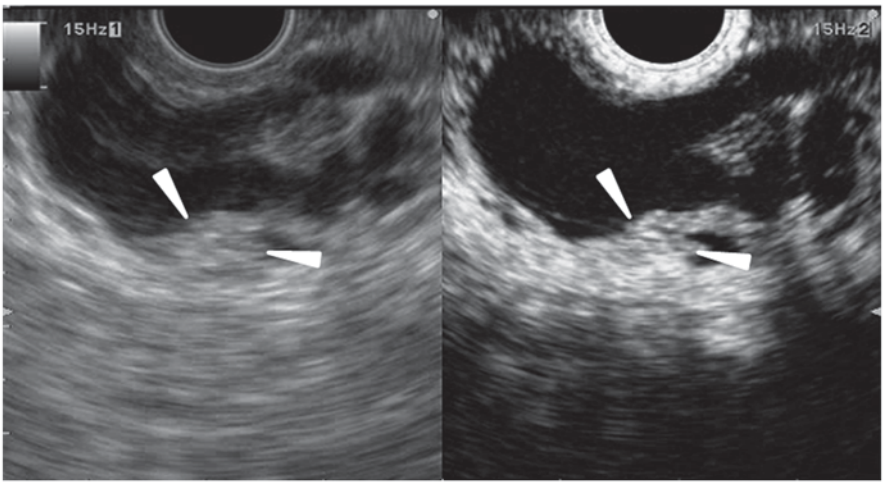

Fig. 5 Typical conventional (*left*) and contrast-enhanced harmonic (*right*) EUS images of the intraductal papillary mucinous neoplasm. Conventional EUS (*left*) shows a cystic lesion in the head of the pancreas. A mural nodule (*arrowheads*) is depicted in the lesion. Contrast-enhanced harmonic EUS (*right*) revealed the mural nodule has abundant vascularity (*arrowheads*). *EUS* endoscopic ultrasonography

adenocarcinomas. With respect to lymph node metastases, these exhibit enhancement defects on contrast-enhanced doppler EUS [51]. When this property is used, contrast-enhanced doppler EUS distinguishes benign from malignant lymph nodes with significantly higher sensitivity (100 %) and specificity (86 %) than conventional EUS variables (88 and 77 %, respectively) [51]. The contrast-enhanced harmonic EUS is also useful for diagnosing intra-abdominal lesions of undetermined origin. When it is used, 96 % of malignant lesions exhibit heterogeneous enhancement, whereas 75 % of benign lesions exhibit homogeneous enhancement [60].

Contrast-Enhanced EUS for Gallbladder Lesions

When contrast-enhanced harmonic EUS was compared to conventional EUS in terms of the differential diagnosis of gallbladder wall thickening, the former had better diagnostic accuracy [61]. On contrast-enhanced harmonic EUS, inhomogeneous enhancement is strongly predictive of malignant gallbladder wall thickening (Fig. 6) [61]. With respect to gallbladder polyps, the presence of irregular intratumoral vessels or perfusion defects seen on the contrast-enhanced harmonic EUS are sensitive and accurate predictors of malignant gallbladder polyps [62].

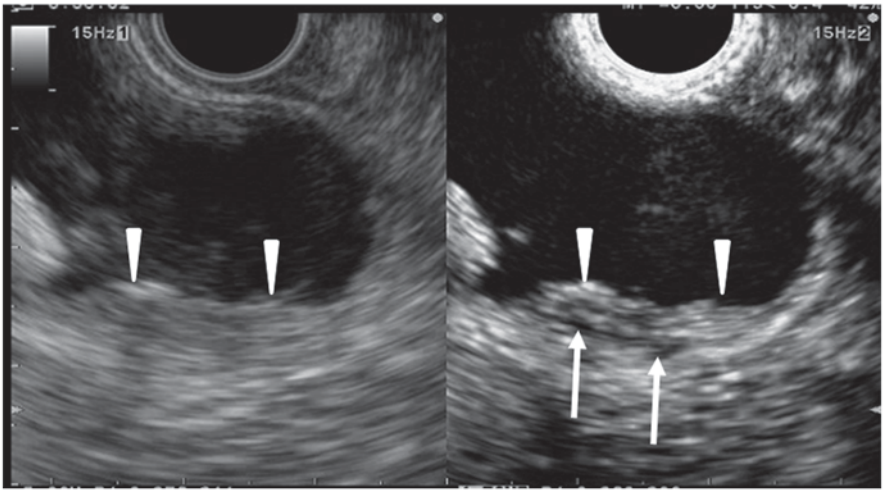

Fig. 6 Typical conventional (*left*) and contrast-enhanced harmonic (*right*) EUS images of the gallbladder carcinoma. Conventional EUS (*left*) shows a thickened wall (*arrowheads*) of the gallbladder. Contrast-enhanced harmonic EUS (*right*) reveals an enhancement in the thickened wall (*arrowheads*) and perfusion defects (*arrows*). *EUS* endoscopic ultrasonography

Contrast-Enhanced EUS for Subepithelial Tumors in the Upper Gastrointestinal Tract

The contrast-enhanced harmonic EUS studies of subepithelial tumors in the upper gastrointestinal tract revealed that gastrointestinal stromal tumors (GISTs) had significantly higher echo intensity than benign tumors such as lipomas [63]. In addition, the contrast-enhanced harmonic EUS allows the vessels flowing from the periphery to the center of GISTs to be visualized (Fig. 7) [64]. By contrast, the contrast-enhanced CT cannot identify most of these vessels. All high-grade malignancy GISTs possess these contrast-enhanced harmonic EUS-depicted irregular vessels. When using higher echo intensity and detection of irregular vessels to diagnose high-grade malignancy GISTs, the contrast-enhanced harmonic EUS is more sensitive than conventional EUS findings (namely, a large size, a lobular border, and a heterogeneous structure) [64]. These results suggest that the contrast-enhanced harmonic EUS can be used to identify GISTs and estimate their malignant potential.

Quantitative Assessment of Parenchymal Perfusion with the Contrast-Enhanced EUS

The classification of pancreatic lesions on the basis of their enhancement patterns on the contrast-enhanced harmonic EUS is a convenient way to characterize the conventional EUS-detected lesions. However, the classification system depends on

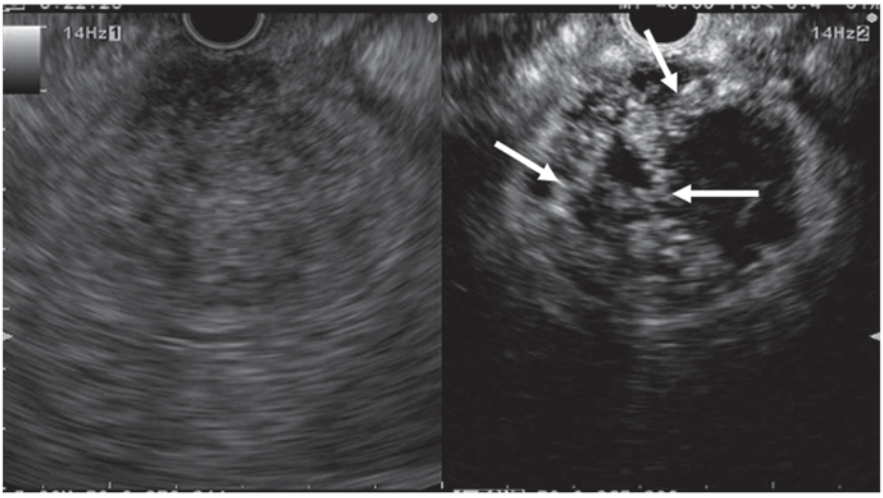

Fig. 7 Typical conventional *(left)* and contrast-enhanced harmonic (*right*) EUS images of the gastrointestinal stromal tumor. Conventional EUS (*left*) shows a tumor (*arrowheads*) of 4 cm in diameter in the fourth layer of the gastric wall. Contrast-enhanced harmonic EUS (*right*) revealed irregular vessels (*arrows*) in the tumor. *EUS* endoscopic ultrasonography

subjective assessment, which means that different readers can differ in their interpretations. This problem may be eliminated by quantitative analyses using a time-intensity curve with the contrast-enhanced harmonic EUS. Several time-intensity curve variables have been shown to be useful for the differential diagnosis of pancreatic masses. In particular, a low ratio of the uptake inside the mass to the uptake of the surrounding parenchyma [65], a low median intensity [66], a low maximum intensity [66], a long time to peak [67], a high area under the curve [67], and a high echo intensity reduction rate [68] have been found to be predictive of ductal adenocarcinomas.

Hybrid of Contrast-enhanced EUS and EUS elastography

It is unclear whether combining the contrast-enhanced EUS and EUS elastography yields a better diagnostic ability than each individual method. When Sãftoiu et al. assessed the diagnostic accuracy of the contrast-enhanced EUS and/or EUS elastography for solid masses in the pancreas, they found that the contrast-enhanced doppler EUS and EUS elastography had comparable sensitivity (91 and 85%, respectively), but their specificities were less than 70% [29]. By contrast, when hypo-enhancement on the contrast-enhanced doppler EUS and hard elasticity on EUS elastography were used to diagnose these masses, this combination was highly specific (95%); thus, combining the two methods may be useful for reducing the number of false-positive cases [29]. However, Hocke et al. reported that the com-

bination of fundamental B-mode, elastography and the contrast-enhanced doppler imaging (90 % sensitivity and 64 % specificity) did not improve on the result of the contrast-enhanced doppler EUS alone (90 % sensitivity and 92 % specificity) [26]. Further studies are needed to establish the contrast-enhanced harmonic EUS and EUS elastography criteria that can be used to diagnose pancreatic tumors.

Contrast-Enhanced EUS for EUS-FNA

The contrast-enhanced harmonic EUS can complement EUS-FNA in terms of identifying pancreatic ductal carcinomas that have false-negative EUS-FNA findings [53–55]. When pancreatic lesions with hypo-enhancement on contrast-enhanced harmonic EUS were regarded as ductal carcinomas in patients with negative EUS-FNA findings, the sensitivity of ductal carcinoma diagnosis increased from 92 % (EUS-FNA alone) to 100 % (both EUS-FNA and the contrast-enhanced harmonic EUS) [54]. Moreover, a French multicenter study showed that five false-negative EUS-FNA cases were correctly classified by the contrast-enhanced harmonic EUS [55].

Since the contrast-enhanced harmonic EUS clearly depicts subtle lesions that conventional EUS cannot identify, it can also be used to identify the target of EUS-FNA (Fig. 8) [52, 54, 57]. Moreover, it can be used to locate a specific site within a lesion that would be more suitable for EUS-FNA than other sites. Identifying and avoiding the avascular sites in a lesion may help avoid sampling necrotic areas and improve the sensitivity of pancreatic tumor diagnosis by EUS-FNA [69]. The contrast-enhanced EUS may also be helpful in terms of assessing lymph nodes that

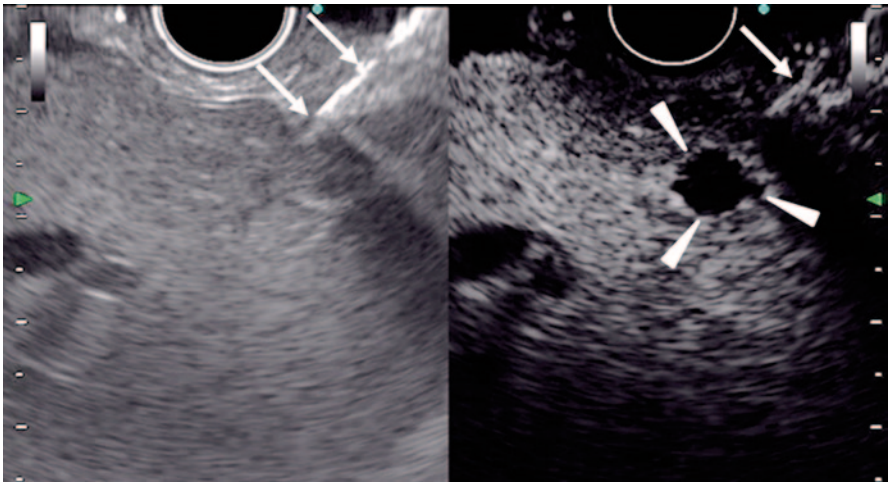

Fig. 8 Images of contrast-enhanced EUS-guided fine needle aspiration in the liver. Conventional EUS (*left*) cannot identify a nodule, while contrast-enhanced harmonic EUS (*right*) depicts a hypovascular nodule (*arrowheads*) in the liver. A needle (*arrows*) is inserted under guidance of contrast-enhanced harmonic EUS. *EUS* endoscopic ultrasonography

cannot be accessed by EUS-FNA, because of an intervening tumor or vessels; it can also help eliminate the time and risk associated with performing EUS-FNA at a second site [70].

EUS-Guided Biliary Drainage

Indication of EUS-Guided Biliary Drainage

The endoscopic biliary drainage is a common first-choice approach for obstructive jaundice. In standard endoscopic biliary drainage, a stent is inserted into the bile duct through the duodenal papilla by using a side-viewing endoscope; however, deep cannulation of the bile duct is difficult in some patients. Moreover, in some patients, the reconstruction after resection of the digestive tract or the duodenal infiltration of the tumor makes it impossible to reach the duodenal papilla. In such patients, endoscopic transpapillary treatment cannot be selected and percutaneous transhepatic biliary drainage (PTBD) and surgery had to be considered. In 2001, Giovannini et al. reported EUS-guided biliary drainage [12]. Since then, various EUS-guided biliary drainage techniques have been reported as an alternative treatment of obstructive jaundice after unsuccessful endoscopic transpapillary biliary drainage [12, 13, 71–108, 110–112].

EUS-Guided Biliary Drainage Procedures

The EUS-guided biliary drainage procedure is based on the EUS-guided pancreatic cyst drainage procedure. It consists of four steps, as follows: selection of the puncture site/route, puncture, dilation, and stenting [12, 13, 71–112]. As this procedure is performed in an organ with a specific shape, viz., the biliary tract, various puncture sites/routes and stenting methods can be used. This procedural variability is a feature of differing from EUS-guided pancreatic cyst drainage. There are two puncture routes, as follows: either from the gastric body (or small intestine after total gastrectomy with reconstruction of the digestive tract) to the intrahepatic bile duct, or from the duodenal bulb to the extrahepatic bile duct [71–112]. Another route from the duodenal bulb (or antrum) to the gallbladder may also be an option [113–121]. Stenting is classified into three methods: transmural drainage in which a stent is inserted into the site of puncture [12,13, 80, 81, 82, 90, 94, 96, 103, 104, 105, 109, 111], rendezvous drainage in which EUS-guided puncture is performed as an auxiliary procedure for transpapillary treatment [78, 88, 99, 102, 106], and antegrade stenting in which a stent is antegradely inserted/placed from the site of puncture into a stenotic site of the bile duct along a guide-wire after puncture [89, 101, 107, 110]. Because these different puncture sites/routes or stenting methods have not been systematically compared, it remains to be clarified which is the most effective method.

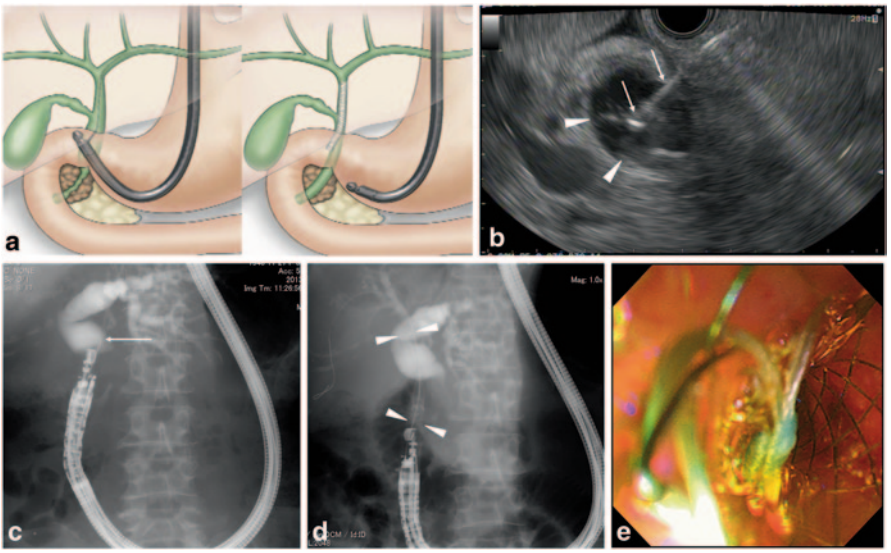

Fig. 9 Procedure of EUS-guided choledochoduodenostomy. **a** Schematic image. **b** EUS image of bile duct puncture. *Arrowheads*: extrahepatic bile duct. *Arrows*: puncture needle. **c** Fluoroscopic image of bile duct puncture; *arrow*: puncture needle. **d** Fluoroscopic image of stent deployment; *arrowheads*: metal stent. **e** Endoscopic image of stent deployment. *EUS* endoscopic ultrasonography

The treatment choice depends on whether the site of biliary obstruction and papilla can be reached. For rendezvous drainage, an endoscope is needed to reach the papilla [78, 88, 99, 102, 106]. Furthermore, the EUS-guided transduodenal treatment is indicated for obstruction of the lower bile duct [81, 82, 83, 90, 94, 96, 103, 105, 109]. It is important to review which treatment method is appropriate for individual patients prior to the start of treatment and to plan a therapeutic strategy, so that a second choice can be selected in case the first-choice route of treatment or stenting method is difficult.

1. EUS-guided choledochoduodenostomy (EUS-CDS) [12, 71–77, 81, 82, 90, 94, 96, 103, 105, 109] (Fig. 9).
   The extrahepatic bile duct can be observed closely from the duodenal bulb. Usually, the middle part of the bile duct is suitable for the target. For optimal visualization, the echoendoscope should be in a long position, with tip of the echoendoscope directed toward the hepatic hilum. The puncture should be performed so that the guidewire is inserted into the proximal bile duct. Before puncturing the bile duct, intervening vessel should be avoided using Doppler mode. Under real time EUS guidance, a 19-gauge needle is inserted transduodenally into the extrahepatic bile duct. A cholangiogram is obtained to display the dilated intrahepatic and extahepatic bile ducts proximal to the obstruction, under fluoroscopy. After the cholangiogram, a guide-wire inserted into the proximal bile duct through the needle. For the dilatation of the needle tract, a tapered catheter with a thin tip is inserted into the bile duct. Biliary dilatation catheter, balloon

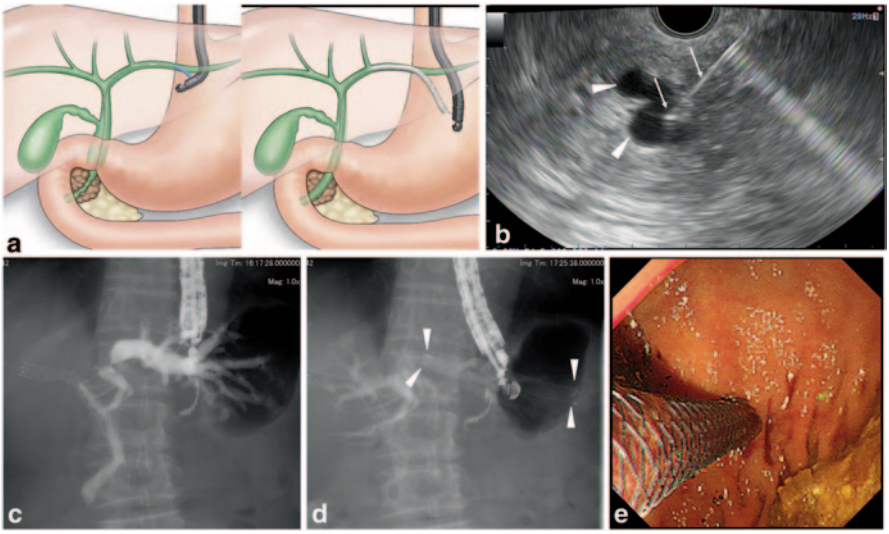

Fig. 10 Procedure of EUS-guided hepaticogastrostomy. **a** Schematic image, **b** EUS image of bile duct puncture; *arrowheads*: intrahepatic bile duct; *arrows*: puncture needle, **c** fluoroscopic image of cholangiogram; contrast is injected from the catheter inserted from the gastric wall into the intrahepatic bile duct, **d** Fluoroscopic image of stent deployment; *arrowheads*: metal stent. **e** Endoscopic image of stent deployment.

dilator, or cautery dilator is used for subsequent dilatation of the tract. After the dilatation of the tract, a plastic stent or metal stent is deployed over the guide-wire. At the initial step during the stent deployment, the position of the stent should be observed under guidance of fluoroscopy and ultrasonography. At the second half step during the stent deployment, the deployment procedure should be performed under endoscopic guidance.

2. EUS-guided hepaticogastrostomy (EUS-HGS) [13, 71–77, 80, 104, 111] (Fig. 10). The intrahepatic bile duct can be observed closely from the lesser curvature of the stomach. The anterior lateral branch (B3) of the intrahepatic bile duct is the most suitable target of EUS-HGS. Compared with EUS-CDS, it is more difficult to identify an appropriate assess route, so that the tip of a guide-wire reach the hilar bile duct, because the intrahepatic bile duct is smaller, located at more profound place, and branching. After identification of an appropriate assess route, the intrahepatic bile duct is punctured with a 19-gauge needle, through which a cholangiogram is performed. A guide-wire is inserted toward the hilar bile duct through the needle. As performed in EUS-CDS, the needle tract is dilated. In the first report of EUS-HGS, a double pigtail stent was used for EUS-HGS. However, compared with EUS-CDS, the stent is more strongly affected by peristalsis and breathing, which may cause stent migration. Therefore, metal stent which can be anchored to the bile duct and gastric wall is recommended for the EUS-HGS. Also, the luminal side of the deployed stent should be long for prevention of post-procedural stent migration.

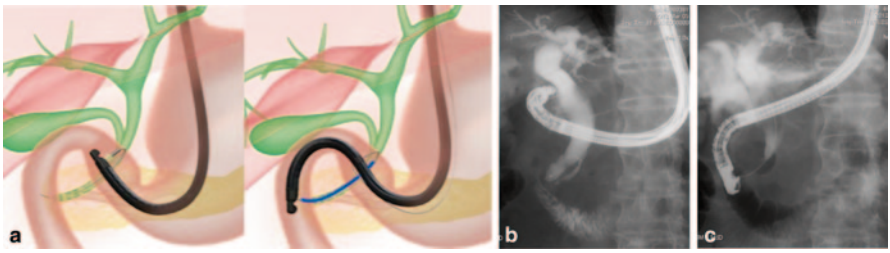

Fig. 11 Procedure of EUS-guided rendezvous drainage. **a** Schematic image. **b** Fluoroscopic image of cholangiogram. Contrast is injected from the catheter inserted from the duodenal wall into the extrahepatic bile duct. **c** Fluoroscopic image of transpapillary drainage; after grasping the tip of the guide-wire in the duodenal lumen with duodenoscope; ordinary transpappilary drainage is performed. *EUS* endoscopic ultrasonography

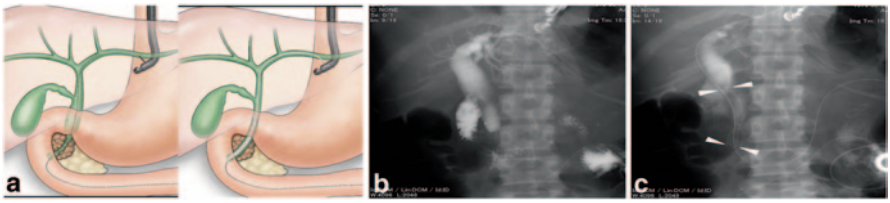

Fig. 12 Procedure of EUS-guided antegrade stenting. **a** Schematic image, **b** Fluoroscopic image of guide-wire insertion; a guide-wire is inserted from the catheter inserted from the gastric wall into the bile duct; The tip of the guide-wire passes the biliary stricture and the papilla, **c** fluoroscopic image of stent deployment. *Arrowheads*: metal stent. *EUS* endoscopic ultrasonography

3. EUS-guided rendezvous drainage (EUS-RV) [71–78, 88, 99, 102, 106] (Fig. 11).
   As the procedures previously described, a 19 gauge-needle is punctured via the duodenum or stomach. Through the needle, a guide-wire is inserted into the bile duct. The stricture and papilla should be passed by the tip of the guide-wire. The echoendoscope is exchanged to a duodenoscope, with which the guide-wire is grasped and pulled into its channel. Over the retracted guide-wire, the ordinary transpapillary drainage can be performed.

4. EUS-guided antegrade stenting (EUS-AG) [75, 76, 89, 101, 107, 108, 110] (Fig. 12).
   A cholagiogram is performed after the transhepatic needle puncture described previously. A guide-wire is inserted into the bile duct through the needle. As performed during EUS-guided rendezvous drainage (EUS-RV), the tip of the guide-wire is advanced to pass the stricture of the bile duct. Subsequently, the needle tract is dilated as performed in EUS-HGS. A delivery system for metal stent is inserted over the guide-wire through the needle tract, and advanced to the biliary stricture. The metal stent is deployed at the biliary stricture.

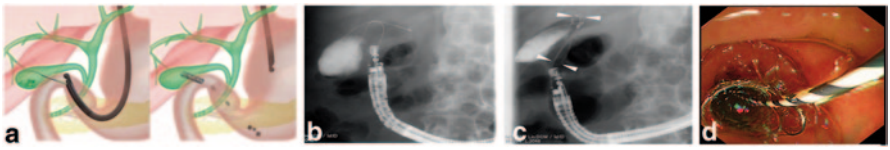

Fig. 13 Procedure of EUS-guided gallbladder drainage. **a** Schematic image, **b** fluoroscopic image of guide-wire insertion; a guide-wire is inserted from the catheter inserted from the duodenal wall into the gallbladder, **c** fluoroscopic image of stent deployment; arrowheads: metal stent, **d** endoscopic image of stent deployment. *EUS* endoscopic ultrasonography

5. EUS-guided gallbladder drainage [113–121] (Fig. 13)
   The gallbladder can be observed closely from the bulb of the duodenum or the antrum of the stomach. For optimal visualization, the echoendoscope should be in a long position. The gallbladder is punctured with a 19-gauge needle, and a cholecystogram is performed. After insertion of the guide-wire into the gallbladder, the guide-wire is coiled by more than two folds. As described previously, the needle tract is dilated. Over the guide-wire, a naso-bilairy tube, pigtail stent, or covered metal stent is inserted to create the amastomosis between the gallbladder and gastroduodenal lumen.

Outcomes of EUS-Guided Biliary Drainage

1. Success rate and incidence of complications
   Most studies on EUS-guided biliary drainage are retrospective. In those with more than 10 patients, the success rate and incidence of complications differ markedly—the success rates range from 67 to 100%, while the complication incidences range from 0 to 46% [12, 13, 71–96, 98–108]. These studies also differed in terms of the puncture sites/routes and stenting methods that were used, which may have contributed to the differences in the success rates. In a multicenter cooperative retrospective study involving 125 patients who underwent EUS-guided biliary drainage in Spain, the success rate, clinical improvement rate, and incidence of complications were 67, 63, and 23%, respectively [97]. This success rate was markedly lower than that in another study involving a single institution. The most important factor responsible for the lack of success in this procedure was the number of endoscopists who participated in the treatment—single endoscopists had significantly lower success rates (57%) than when two endoscopists were present (80%), suggesting that the assistant, who helps with guide-wire insertion and dilating operations, plays an important role and that this procedure cannot be readily completed by a single endoscopist [97]. In the Spanish multicenter study described above, the success rate of EUS-CDS(86%) was higher than those of EUS-HGS(65%) and EUS-RV(68%), although these differences did not achieve statistical significance [97]. In addition, the incidence of complications after EUS-CDS (15%) was lower than that

after EUS-HGS (29%). By contrast, the large international multicenter retrpspective study in high volume centers compared intrahepatic and extrahepatic approaches in terms of success and complication rates, and concluded both approaches are comparable [112]. These two reports suggest that the number of attending endoscopists and presence of a skilled assistant affect outcomes of EUS-HGS more than those of EUS-CDS.

EUS-RV does not require the formation of a transgastric/-enteric fistula; thus, there is no influence of a fistula on the risk of stent migration. Therefore, EUS-RV may be appropriate for patients with benign diseases or those for whom surgery is indicated. The EUS-AG can be performed even when the papilla cannot be reached, unlike EUS-RV [75, 76, 89, 101, 107, 108]. Because EUS-AG also does not require the formation of a fistula, there is no risk of posttreatment stent migration. After duodenal stenting, it is difficult to make an approach from the duodenum in some patients, for whom EUS-HGS or EUS-AG can be selected. Before treatment, all treatment options that are available must be considered. To establish which of these individual treatment methods is the safest and most effective, a randomized comparative study should be conducted.

2. Comparison with other drainage procedures

Retrospective studies of patients in whom transpapillary treatment was difficult have shown that many are advanced-stage patients, including those with duodenal stenosis/marked stenosis of the bile duct. This may have influenced the efficacy and safety of the EUS-guided biliary drainage. The EUS-guided biliary drainage is more advantageous than transpapillary treatment with ERCP, because it has a less marked effect on the pancreas. Therefore, selecting EUS-guided biliary drainage can help to reduce the risk of post-ERCP pancreatitis. When Hara et al. performed EUS-CDS as a first choice for non-resectable malignant stenosis of the lower bile duct without selecting transpapillary treatment in a phase I study, the success rate, clinical improvement rate, and incidence of complications were 94, 100, and 17%, respectively, which are similar to those for standard transpapillary treatment or PTBD [109].

Until recently, there was no evidence showing which of two procedures, namely, EUS-guided biliary drainage and PTBD, should be selected as the second choice for patients in whom transpapillary treatment is difficult. However, in 2012, Artifon et al. conducted a prospective randomized study in which PTBD was compared to EUS-CDS in 25 patients in whom transpapillary treatment was difficult [103]. They reported that the two treatment groups did not differ significantly in terms of the treatment response, incidence of complications, or cost, suggesting that EUS-CDS is as effective as PTBD [103]. This also indicates that EUS-CDS can be performed prior to PTBD, which is important, because the PTBD requires the insertion of an external fistula tube which affects the patient's quality of life (QOL), whereas the EUS-guided biliary drainage involves one-step internal fistula formation. To confirm the equivalence of EUS-guided biliary drainage to PTBD, a large-scale multicenter randomized study comparing the two techniques is warranted.

3. Stent patency period
   The patency period of EUS-guided biliary drainage depends on the subject and the stent. In their long-term follow-up study, Yamao et al. reported that the mean stent patency period after EUS-CDS with a plastic stent was 211.8 days, which is longer than the patency period of the plastic stent in standard transpapillary endoscopic treatment [81]. By contrast, in the study of advanced-stage patients (median survival, 125 days), the median stent patency period was 99 days [94]. When Horaguchi et al. examined the long-term course in patients in whom a covered metal stent was used, they reported a long average stent patency period of 433 days; thus, in patients who may require long-term patency, a metal stent should be used [95].

4. Major complications and their prevention using a metal stent
   For the EUS-guided biliary drainage, puncture/stenting is performed through the abdominal cavity between the biliary tract and digestive tract. Therefore, the most frequent complications associated with this procedure are biliary peritonitis and pneumoperitoneum related to the leakage of bile or intragastric gas from the puncture site [71]. Furthermore, the stent migration has been reported as the most dangerous complication of this procedure. Although biliary peritonitis and pneumoperitoneum may arise from the leakage of bile or intragastric gas during endoscopic treatment, this leakage may persist after endoscopic treatment. In particular, leakage from the space between the stent and the bile duct (digestive tract) wall at the puncture site may persist when a plastic stent is used. However, when a covered metal stent is used, the stent's radial force can completely prevent a space from opening up between the stent and the bile duct wall. Moreover, the metal stent can be fixed to the digestive tract/bile duct wall; therefore, reducing the risk of migration.

EUS-Guided Gallbladder Drainage

EUS-guided gallbladder drainage is a new treatment that is based on the EUS-guided biliary drainage procedure. Radical treatment for acute cholecystitis is cholecystectomy. In patients for whom surgery is not indicated or for whom early surgery is not recommended, conservative treatment is predominantly performed. However, gallbladder drainage must be promptly performed in patients who do not respond to conservative treatment or who develop serious conditions such as septic shock and disseminated intravascular coagulation. The emergency gallbladder drainage procedures for acute cholecystitis are percutaneous transhepatic gallbladder drainage (PTGBD), percutaneous transhepatic gallbladder aspiration (PTGBA), and endoscopic transpapillary nasal gallbladder drainage (ENGBD) [122]. Although the current role of EUS-guided gallbladder drainage in the treatment of acute cholecystitis is unclear, a randomized comparative study of patients with acute cholecystitis in whom emergency surgery was impossible due to a poor general condition showed that the efficacy of EUS-guided gallbladder drainage was similar to that of PTGBD [117].

In that study, the success rate, clinical improvement rate, and incidence of complications of EUS-guided gallbladder drainage were 97, 100, and 7%, respectively [117].

When a metal stent is inserted during transpapillary drainage for the malignant stenosis of the biliary tract, acute cholecystitis due to obstruction of the orifice of the cystic duct may occur [123]. Since most patients who require metal-stent insertion have advanced cancer, the selected treatment must maintain their QOL. Therefore, PTGBA, which is less invasive than PTGBD (which requires the insertion of an external fistula tube), may be appropriate; however, PTGBA is ineffective in some patients. The EUS-guided gallbladder drainage may become a treatment option for such patients [115, 116]. Furthermore, it may be indicated for elderly persons and high risk patients with acute cholecystitis; however, there are fewer case reports on EUS-guided gallbladder drainage than case reports on EUS-guided biliary drainage. The efficacy and safety of EUS-guided gallbladder drainage should be investigated further in a larger number of patients.

Limitations and Future Perspectives of EUS-Guided Biliary Drainage

Although the gallbladder and liver are adjacent to the digestive tract, there are relatively few fixed sites and there are respiration-/movement-/digestive tract peristalsis-related changes in their positional relationship; thus, the stent migration may occur even after stenting. Furthermore, a study has shown that even the covered metal stents for transpapillary treatment that were described above can dislocate. Recently, a metal stent for EUS-guided drainage that is flanged at both ends for lumen-apposing was developed to prevent such stent migrationand may contribute to a safer procedure [118, 120, 121, 124]. In addition to stent migration, the intraperitoneal leakage of bile on dilating operations may cause biliary peritonitis. To prevent the evolution of such complications during treatment, it may be useful to develop a stenting device that facilitates simultaneous puncture/dilation [125], because this device may shorten the duration of treatment and prevent bile leakage. If a metal stent can be safely and readily inserted between the digestive tract and gallbladder, the EUS-guided cholecystolithotomy [119, 120, 121] may become a standard procedure, as occurred with transpapillary common bile duct lithotripsy with ERCP.

EUS-Guided Celiac Plexus Neurolysis

Role of EUS-Guided Neurolysis in Cancer-Related Pain

Upper abdominal pain or back pain occurs in patients with advanced malignant tumors. Particularly, half of patients with pancreatic carcinoma suffered from severe pain. Recommendations for pain management from the World Health Organization

include an analgesic ladder, with medication titration progressing from nonsteroidal anti-inflammatory agents (NSAIDs) to opioid [126]. Unfortunately analgesic ladder often provide incomplete pain relief and its use is limited by frequent adverse effects. Treatment with opioid is associated with a number of side effects, including neuropsychiatric symptoms, constipation, nausea, vomiting, sweating, anorexia, dyspepsia, pruritus, micturition disorders, and diarrhea [127]. The study evaluating the efficacy of therapy according to WHO guidelines showed that the treatment was assessed as good, satisfactory and inadequate in in 76, 12, and 12%, respectively [128].

Celiac plexus neurolysis (CPN) is most commonly used as a palliative treatment in patients with pain due to pancreatic cancer [129–131]. CPN affords effective pain control in patients with pancreatic cancer and is not associated with opioid side effects. Pain impulses originating from all the abdominal and most pelvic viscera are carried by visceral nerve fibers that pass through the celiac plexus and splanchnic nerves. Therefore, interruption of nociceptive input at the level of either the celiac plexus is a potentially effective means of visceral pain control [132].

Recently, the EUS-guided celiac plexus neurolysis (EUS-CPN) has been reported as a new approach for neurolysis in pancreatic cancer patients with pain [133]. The advantages of EUS-CPN over the other CPN methods are (1) short access route without intervening organs, and (2) needle insertion with real time EUS guidance to avoid injuring vessels [131, 133, 134].

EUS-CPN Techniques (Fig. 14)

The celiac plexus is adjacent to the aorta and extends down from the origin of the celiac artery to the origin of the superior mesentery artery. The EUS-CPN is a transgastric anterior approach where a needle is advanced endoscopically into the area of the celiac truck and a neurolytic agent is injected [133–142]. The neurolytic

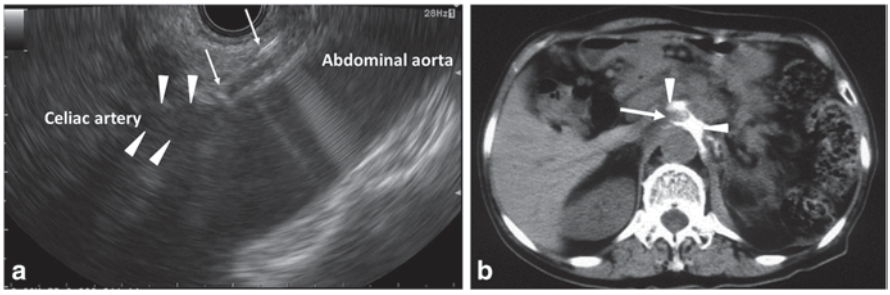

Fig. 14 Procedure of EUS-guided celiac plexus neurolysis. **a** EUS image of needle puncture; a needle (*arrows*) is inserted from the stomach to the area adjacent to the celiac artery (*arrowheads*), **b** CT image of the ethanol spread; CT depicts contrast (*arrowheads*) which is included in ethanol solution in front of the abdominal aorta. *Arrow*: celiac artery. *EUS* endoscopic ultrasonography, *CT* computed tomography

agent that is injected is usually bupivacaine or lidocaine followed by alcohol with or without contrast agent. When using a curvilinear array echoendoscope, the celiac plexus region is visualized from the lesser curve of the stomach by following the aorta to the origin of the main celiac artery (Figure 14a). The aorta is traced distally to the celiac trunk, which is the first major branch below the diaphragm. A 22-gauge needle is inserted under EUS guidance, so that the tip of the EUS-FNA needle is placed slightly anterior to the celiac trunk (Figure 14a). Bupivacaine is injected first, followed by alcohol. EUS-CPN includes two kinds of injection methods—central and bilateral injections [135]. For central injection, an injection of the entire solution into the area cephalad of the celiac trunk can be performed. For bilateral injection, echoendoscope may be rotated to one side of the celiac artery and only half of the solution is injected. The other half is then injected on the opposite side of the celiac trunk origin.

Efficacy of EUS-CPN for Abdominal Pain in Pancreatic Cancer

A meta-analysis showed 80 % of patients who underwent EUS-CPN have pain relief [138]. The pain relief usually lasts for longer than 12 weeks [133, 142]. Several reports recommend two injections (i.e., on both sides of the celiac truck). In 46–69 % of the one-injection group and 70–81 % of the two-injection group, a pain relief was obtained [135, 136]. Moreover, the median duration of pain relief in the one- and two-injection groups was 11 and 14 weeks, respectively. Distribution of ethanol on the left side of the celiac only was a significant factor for a negative response to EUS-CPN [140]. Co-injecting ethanol and contrast medium during EUS-CPN to immediately confirm the injection site by CT scan (Figure 14b) allow the relationship between the accuracy of injection and pain relief to be assessed [139]. If the CT scan indicates that the injection is inappropriate, additional EUS-CPN is recommended. The latter study found that EUS-CPN was effective in 62 % of patients overall; however, when the CT scan was performed, therefore, indicating when additional EUS-CPN was necessary, the response rate increased to 85 % [139].

The dose of alcohol used in EUS-CPN is not standardized. In the previous reports, the amount of alcohol used ranges from 2 to 20 mL [133–142]. When the safety and efficacy of 20 mL versus 10 mL alcohol during EUS-CPN were compared, both groups exhibited similar clinical efficacy, although there were no major complications in either group.

Appropriate Timing of the EUS-CPN Procedure

It remains unclear whether it is best to implement EUS-CPN for pancreatic cancer early (i.e., at the onset of pain) or late (i.e., when opiate toxicity or resistant pain develops). Wyse et al. reported their randomized controlled trial of early EUS-CPN for patients with painful pancreatic cancer in 2011 [142]. The patients were ran-

domly allocated to early EUS-CPN treatment or conventional pain management and the two groups were compared in terms of pain relief, QOL, and survival at 1 and 3 months. The EUS-CPN group had greater pain relief at both 1 and 3 months than the conventional pain management group, although only the later result achieved statistical significance. Thus early EUS-CPN (i.e., immediately after diagnosis) can be considered for patients with painful pancreatic cancer [142].

Complications of EUS-CPN

Transient diarrhea, transient hypotension, and transient pain have been reported in 44, 38, and 9% of patients undergoing EUS-CPN, respectively [134, 135, 137, 138, 143]. Severe complications occur in less than 1%. The perforation rate ranges from 0.03 to 0.07% [143]. Mild intraluminal hemorrhage occurs in 1.3–4%, and severe hemorrhage is infrequently reported [143]. However, one case report describes the case of severe end-organ ischemia that was caused by multiple EUS-CPN procedures [144]; thus, it should be noted that the EUS-CPN can associate with such severe complications.

EUS-Guided Celiac Plexus Block for Chronic Pancreatitis

For pain caused by chronic pancreatitis, the EUS-guided celiac plexus block (EUS-CPB) can be performed [145]. In EUS-CPB, a steroid solution (triamcinolone) is injected instead of ethanol; however, EUS-CPB does not appear to be very effective for chronic pancreatitis. One of the reasons for the poor efficacy of EUS-CPB for chronic pancreatitis pain is insufficient pain relief. A meta-analysis and systematic review of EUS-CPN for chronic pancreatitis and pancreatic cancer reported that while EUS-CPN relieved the pain in 80% of patients with pancreatic cancer, only 59% of patients with pancreatitis had pain relief [138]. Another reason for the poor efficacy of EUS-CPB for chronic pancreatitis pain is that it yields relatively short pain relief: Only 10% of patients have pain reduction at 24 weeks although 55% of patients have pain reduction at a mean follow-up period of 8 weeks [145]. Since surgical bypass or resection is employed as the primary treatment for chronic pancreatitis, EUS-CPN may not be appropriate for most cases of chronic pancreatitis.

EUS-Guided Celiac Ganglia Neurolysis (EUS-CGN)

The celiac plexus contains 1–5 ganglia. The dominant ones are found on the right or left side, and their level, in relation to the celiac trunk, is variable. The celiac ganglia can be identified by EUS [146, 147]. They are typically small and hypoechoic and either multi-lobulated or composed of confluent small spheres with hypoechoic bands

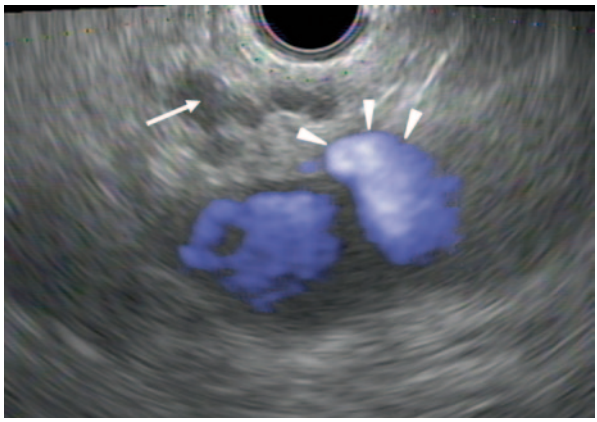

Fig. 15 EUS image of celiac ganglion. A celiac ganglion (arrow) is depicted adjacent to the celiac artery (arrowheads). *EUS* endoscopic ultrasonography

(Fig. 15). The rate of ganglia detection varies depending on the instrument used—in radial and linear EUS, the detection rates are 79.2 and 85.6%, respectively [147]. The rates of ganglia detection also vary between endosonographers (65–97%). EUS-guided celiac ganglia neurolysis (EUS-CGN) is performed by injection of mixed solution of bupivacaine and ethanol into celiac gangila. Under EUS guidance, a 22-gauge needle is inserted into as many ganglia as possible, and the mixed solution is injected into the ganglia [148]. When EUS-CGN was performed in 17 patients with pancreatic cancer, 94% reported improvement in pain scores [148]. Moreover, in a randomized multicenter trial comparing EUS-CGN with EUS-CPN in patients with abdominal cancer pain, the CGN group had significantly higher positive and complete response rates (73.5 and 50.0%, respectively) than the CPN group (45.5 and 18.2%, respectively) [149]. Therefore, it was concluded that EUS-CGN is superior to EUS-CPN in terms of relieving pain even though less neurolytic agent is injected in EUS-CGN.

EUS-Guided Broad Plexus Neurolysis (EUS-BPN)

EUS-guided broad plexus neurolysis (EUS-BPN) is performed by injection alcohol into the neural plexus around the superior mesentery artery [150]. At a point 1–2 cm inferior to the celiac trunk, the superior mesentery artery branch of the aorta can be seen. A 25-gauge needle is placed under direct EUS visualization adjacent and anterior to the lateral aspect of the aorta over the level of the superior mesenteric artery trunk (Fig. 16). Lidocaine (3 ml) is injected first, followed by 10 ml alcohol. The same process is performed on the opposite side of the aorta (with counter-clockwise rotation). EUS-BPN was more effective than EUS-CPN, particularly in cases where the cancer had expanded extensively within the abdominal cavity beyond the distribution of the celiac plexus, while it did not incur any serious complications [150].

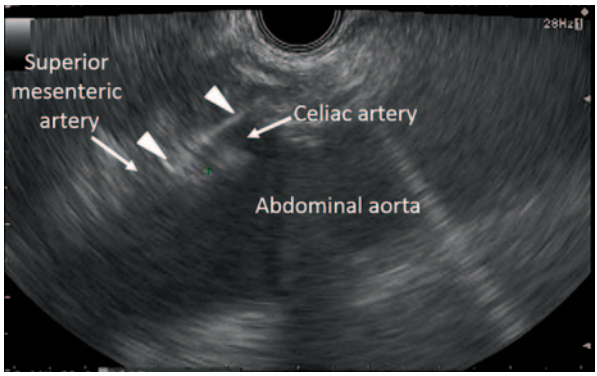

Fig. 16 Procedure of broad plexus neurolysis. A needle (*arrowheads*) is inserted from the stomach to the area adjacent to the superior mesenteric artery

Conclusion

Technological innovations such as contrast-enhanced EUS and the EUS elastography have improved the ability of EUS to detect, characterize, and stage tumors in the upper gastrointestinal tract and pancreatobiliary system. The EUS-guided interventions are also currently expanding and now include a treatment option for obstructive jaundice and a less invasive treatment for cancer-related pain.

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Endoscopic Submucosal Dissection

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Clinical Training

Endoscopic submucosal dissection (ESD) requires highly technically demanding maneuvers and skills, thus, requiring special training. Endoscopists must have a good understanding of the cognitive and technical aspects of ESD before performing the procedure, including indications, the endoscope features, ESD knives and other auxiliary equipment, injection agents, electrosurgical units (ESUs), and methods for treating possible complications.

Currently, there are no formal clinical training programs for ESD in the USA; though in Europe, there exists an endoscopy society guidance and position statement from an expert panel for adaptation and practice of ESD [1]. It is unfortunate that there are no established guidelines regarding the most effective training strategy for ESD and there are limited published reports on this specific subject [2]. In Japan and some other Asian countries, training in ESD heavily relies on the observation of more experienced endoscopists and subsequent supervision by experts, who physically assist in the procedure when the trainee faces technical difficulties or when complications occur [3]. In the Western countries, this ESD training technique is seldom practiced and the adoption of this training method is very difficult. Consequently, the optimal training strategy has yet to be determined. Experts suggest that ESD should first be carried out in harvested pig stomachs (ex vivo model) and then practiced during live animal procedures (in vivo model), before being performed in humans [4, 5]. Dinis-Ribeiro et al. published a case series of 19 ESD for gastric superficial lesions performed in humans in Portugal [6]. The ESD procedures were performed by a single endoscopist who was trained in Japan. Probst et al. reported a series of 71 epithelial and submucosal lesions treated by ESD in a single specialty center in Germany [7]. They showed that there was a learning curve; the procedural

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duration decreased over time significantly, and there was a trend in improving the R0 resection rate, size of the lesion, and complication rate in the second half of the cases. No preclinical animal training was described in that study.

It is necessary to establish the learning curve for ESD to define the optimal experience required to reduce complication rates and achieve satisfactory outcomes. It has been estimated that 30 gastric cases must be performed under the supervision of an expert to overcome this learning curve [8, 9]. Also, the institutions' case volume (at least 50 colorectal ESDs) was associated with a significantly reduced risk of complications, with an odds ratio of 0.4, and even lower if 100 or more colorectal ESDs were performed [10].

The incidence of gastric cancer is high in Japan and some other Asian countries compared to that in most Western countries, where the number of "early" gastric lesions that are detected is lower [11]. In the Western countries, colorectal and esophageal lesions (mainly Barrett's dysplasia) could be considered a reasonable therapeutic indication for ESD. However, performing ESD in the esophagus and colon is especially complex and technically demanding, thereby increasing the perforation risk [12]. Experts suggest that initial colorectal ESDs undertaken by Western endoscopists should be performed in the rectum because endoscopic treatment of rectal lesions is technically less demanding and has lower risk of perforation. They also suggested that endoscopists begin by performing colorectal ESDs on smaller lesions (20–30 mm) in the rectum reserving more challenging ESD cases (e.g., locations in the right colon and larger lesions 50 mm or larger) for endoscopists more experienced with ESD [10, 12].

Indications for ESD

Esophageal ESD

In esophageal squamous cell carcinoma (SCC), invasion depth and lymphatic invasion are known risk factors associated with lymph-node metastasis [13]. Lesions are classified according to the depth of invasion as intraepithelial carcinoma (EP), restricted within the lamina propria (LP) layer, in contact with or invading the muscularis mucosa (MM), and invading the submucosal (SM) layer to a depth of one-third (SM1), or more than one-third (SM2 and SM3) of the layer thickness. ESD with complete resection is considered curative for EP–LP esophageal SCC with negative deep and lateral margins. MM-SM1 esophageal SCC has a substantial risk of lymph node metastasis in the esophagus, yet, ESD can still be considered, especially since it is considered lower risk for metastasis when the pathological review reveals the tumor is differentiated type, invasion depth is limited (some defined <200 μm), and lymphovascular invasion is absent. The patient's age, comorbid condition, and surgical risk should be carefully taken into account especially in this setting. SM2 or deeper (≥ 200 μm) should be treated with conventional transthoracic esophagectomy with systematic lymph node dissection or chemoradiation therapy [13, 14].

Table 1 Conventional and extended criteria for endoscopic resection for gastric cancer

Conventional indications for endoscopic resection
High probability for en bloc resection
Tumor histology
Differentiated type adenocarcinoma
Intramucosal cancer
No lymphovascular invasion
Tumor size and morphology
≤20 mm elevated lesion without ulceration
≤10 mm if configuration is superficial depressed type (Paris classification IIc)
Extended indications for endoscopic resection
Intramucosal differentiated cancers of any size without ulceration and no lymphovascular invasion
Intramucosal differentiated cancers ≤30 mm with ulceration and no lymphovascular invasion
Intramucosal undifferentiated cancers ≤20 mm without ulceration
Differentiated cancer ≤3 cm with extension in the submucosa ≤500 μm and no lymphovascular invasion

In Barrett's esophageal adenocarcinoma, the degree of differentiation and the incidence of lymphatic vessel and venous invasion correlate with the depth of infiltration of the early carcinoma [15]. Complete endoscopic resection of Barrett's esophageal cancer restricted within the mucosa and with high-grade dysplasia can be considered curative if the size of tumor is limited (<3 cm), tumor is differentiated and lymphovascular invasion is absent [16, 17].

Gastric ESD

According to the 2010 guidelines published by the Japanese Gastric Cancer Association, endoscopic resection of early gastric cancer (EGC) is indicated for lesions that can be resected in one piece and have a negligible risk of lymph node metastasis [18]. The traditional and extended indications for endoscopic resection are summarized in Table 1. To ensure a resected lesion meets the curative criteria described in Table 1, complete resection and subsequent pathological reevaluation are necessary.

Colorectal ESD

The risk of lymph node metastasis for early colorectal cancer correlates with the depth of invasion. Endoscopic complete resection of neoplastic lesions that are diagnosed as benign adenoma, noninvasive or minimally invasive carcinoma without

Table 2 Indications for colorectal ESD

Korean Society of Gastrointestinal Endoscopy ESD Study Group [20]
Early colorectal cancers with no lymph node metastasis
Laterally spreading tumors (LST) ≥20 mm
Subepithelial lesions
Fibrosed lesions
Japanese Colorectal ESD Standardization Implementation Working Group [21]
Tumor for which the use of snare EMR for en bloc resection is difficult
Nongranular LST (especially pseudodepressed type)
Tumor with a type V_I pit pattern
Carcinoma with shallow submucosal invasion
Large depressed tumor
Large elevated lesion likely containing adenocarcinoma
Mucosal lesion with submucosal fibrosis
Sporadic localized lesion within chronic inflammation such as ulcerative colitis
Local residual carcinoma after EMR

ESD endoscopic submucosal dissection, *EMR* endoscopic mucosal resection

vessel infiltration is considered curative regardless of the size of the tumor [19]. The indications for colorectal ESD based on the recommendations of the Korean Working Group and the Japanese Colorectal ESD Standardization Implementation Working Group are summarized in Table 2 [20, 21].

Procedural Steps of ESD

A detailed description of the actual procedural steps is beyond the scope of this review, but can be found in the recently published *Endoscopic Submucosal Dissection* edition of *Gastrointestinal Endoscopy Clinics of North America* [22–25]. In summary, the steps include:

1. Identification and marking of the lesion with a sufficient lateral safety margin
2. Submucosal injection and tissue elevation
3. Circumferential or step-by-step incision (alternating with submucosal dissection) of the mucosa outside of the markings of lesion
4. Submucosal dissection to complete “en bloc” removal of the target lesion, and subsequent retrieval
5. Careful hemostasis and prophylactic coagulation of vessels at the resection base
6. Preparation and orientation of the retrieved specimen for histopathological evaluation

Tools, Materials, and Techniques

Electrosurgical Knives

The contact area is one of the most important factors determining the characteristics of the specific knife. A knife with a smaller contact area usually produces a rapid and effective cut due to a higher current density with limited coagulation effect. The standard needle knife and an insulation-tipped (IT) electrosurgical knife (IT knife and IT-2 knife; KD-610 L and KD-611 L; Olympus Co., Tokyo, Japan) are mainly used for performing gastric ESDs. Since the colorectal wall is thinner than the gastric wall and the submucosal space is narrower, but with less vasculature, knives for colorectal ESD should have a short blade length and, ideally, some safety feature to prevent muscularis propria injury. The conventional resection knives and the resection knives with integrated fluid injection capability used during ESD and currently available in the West are summarized in Table 3 [26–32].

Submucosal Injection Agents

Submucosal injection solutions are used to lift lesions, separating mucosa from muscularis propria, but the lengthier ESD procedure (as compared to endoscopic mucosal resection (EMR)) requires prolonged elevation of the mucosa to expose the submucosal layer to facilitate submucosal dissection. Thus, the agent used for ESD must be long-lasting, safe, easy to handle, and easy to inject. In order to meet these criteria, many injection agents have been thoroughly evaluated, with some becoming commonly used. Sodium hyaluronate is now commercially available in Japan as a dedicated injection agent for ESD (MucoUp®, Johnson and Johnson Medical Co., Tokyo, Japan).

Hypertonic saline solution and dextrose are inexpensive and readily available, but both can cause tissue damage [33]. On the other hand, fibrinogen is a good submucosal cushion [34]; but, since this agent is derived from human serum, it has been criticized as a potential vehicle for viral transmission. Sodium carboxymethylcellulose [35], endoscopic lubricant jelly (Null Jelly) [36], and photocrosslinkable chitosan hydrogel may be other choices [37], but further study is necessary to verify the safety and efficacy of these alternatives. One of the most commonly used agents in Japan is Glyceol (Chugai Pharmaceutical, Tokyo), which consists of 10% glycerol and 5% fructose in normal saline, combined with a small amount of sodium hyaluronate [38].

Diluted epinephrine (1:100,000 to 200,000) mixed into the submucosal injection agent has been reported to reduce immediate bleeding during the endoscopic procedure [39]. However, due to the limited clinical evidence, its use is variable and may not be necessary for colorectal ESD. Indigo carmine may also be added to the injection solution to help in visualizing the area to dissect (utilizing minimum

Table 3 Electrosurgical knives

Type	Description	Advantages	Manufacturer
Conventional resection knives			
Standard needle knives	Fine tip with long but regulated length	Small contact area with high cutting power	Olympus, Boston Scientific, Cook Medical
Insulated tip (IT and IT-2) knife and mini-IT knife [26, 27]	Ceramic ball at the tip of needle knife (with triangular extension for IT-2), smaller and shorter knife (mini IT)	Decreased perforation risk, long knife makes faster cutting ability	Olympus
Hook knife [28]	Tip bent at a 90° and rotatable	"Fishing" and traction of submucosal fibers toward the knife before the cutting	Olympus
Flex knife/dual knife [29]	Thin snare-like tip or fixed length tip with small rounded end	Thickened sheath end stabilize the knife and prevents deeper migration of knife	Olympus
Triangular knife [26]	Small triangular plate at the tip	Tissue capture feasible with triangle tip	Olympus
Resection knives with integrated fluid injection capability			
Hybrid knife [30]	Injection needle from the tip of the needle knife	Intermittent fluid injection then needle-knife dissection	ERBE Elektromedizin
Flush knife [31]	Roller pump variable in rotation speed from the tip of short needle-knife (variable length)	Immediate washout of blood and debris from the endoscopic field, easy addition of submucosal cushion	Fujinon (not available in the USA)
Ball-tip flush knife [32]	Broad catheter and short knife enlarged at the tip to a ball	Better coagulation with tip, stable movement and easy capture of tissue	Fujinon (not available in the USA)

amount necessary for adequate coloring). Finally, lidocaine (1 %) has been used as a local anesthesia for rectal ESD close to the dentate line, though this may not be necessary [40].

Hoods

A transparent distal attachment (hood or cap) can be mounted on the tip of the endoscope to assist the safe and controlled use of an ESD knife. The hood pushes the resected mucosa or surrounding tissue away from the cutting plane, thus, creating countertraction and allowing better and clearer visualization of the working area. It is

also useful for temporary hemostasis by tamponading the bleeding point with the tip of the hood to stop bleeding while the ESD knife is exchanged for hemostatic forceps.

The small-caliber-tip transparent (ST) hood (DH-16GR or DH-16CR; Fujifilm, Tokyo, Japan) has a tapered aperture and enables the operator to easily open up the incision to dive into the submucosal layer and accurately adjust the depth of incision that is made with the tip of the knife. Short ST hoods with a 1 mm larger opening tip than conventional ST hoods (8 mm versus 7 mm) have been developed (DH-28GR, DH-29CR, or DH-30CR; Fujifilm, Tokyo, Japan), but are not yet available in the USA [41].

Various other types of attachments can be chosen depending on the needs or situation (e.g., an attachment with holes to drain water or blood) [42]. The KUME hood (Create Medic, Yokohama, Japan) is a soft transparent distal attachment with a thin tube. It provides a jet of water via the tube attached to a water-filled syringe. Impact Shooter (Top Co., Tokyo, Japan) enables the endoscope to work like a dual-channel scope. Air Assist (Top Co., Tokyo, Japan) is a soft balloon that fits outside the endoscope, proximal to the bending area of the endoscope. It enables the endoscope to mimic a multibending scope. The EndoLifter (Olympus, Tokyo, Japan) is a distal attachment with grasping forceps that can be used to grasp the mucosa. Once the proximal area is cut and the mucosa grasped with the EndoLifter, the submucosal layer is revealed, creating easier access to the dissection plane of the submucosa; however, the proposed benefit is not consistently provided [42].

Electrosurgical Units

A high-performance ESU is indispensable for every step of the ESD procedure: marking, precutting, circumferential cutting, submucosal dissection, and hemostasis. Older ESUs only had one power setting, but the VIO series ESUs (VIO 200D, VIO 300D, ICC350, ERBE Elektromedizin, Tuebingen, Germany) have a sensor that can control the power automatically and adjust to the circumstance [20]. Each unit detects and monitors the current, power, and spark that create the cutting by controlling voltage. Therefore, the procedure can be performed in a smooth and steady manner.

There are various kinds of electric modes, each of which is used for a different purpose. The indications and characteristics of each type of current are summarized in Table 4.

Countertraction Techniques

An additional or "second hand" can certainly facilitate the endoscopic resection procedure while reducing the technical difficulty [43]. Counteraction to assist ESD has been attempted with various methods.

1. Position change—the use of gravity
   This technique involves positioning the lesion (and the patient) to maximize gravitational pull, which allows the field of vision to be clear of blood and water.

Table 4 Electrosurgical unit (ESU) currents

Types	Indications	Characteristics
Endocut Q and I	Markings, mucosal incision, and submucosal dissection Hemostasis during the cut procedure	Computer-programmed mode that alternatively applying the cut and coagulation (soft or forced) current with voltage control
Auto cut	Rarely used in ESD	Power dosing is automated (software controlled) with constant voltage
Dry cut	Mucosal incision and submucosal dissection	Cutting mode mixed with coagulation effect
Forced coagulation	Dissection under a strongly vascularized lesion Trimming (additional incision at the submucosal layer along the mucosal incision line)	High voltage with low duty cycle allowing effective coagulation with some cutting effect
Swift coagulation	Submucosal dissection (sometimes used for mucosal incision)	Similar to dry cut but it has more of a coagulation effect
Soft coagulation	Markings and bleeding control with hemostatic forceps	Low-voltage current (< 200 V) that coagulates adjacent tissues slowly without char effect, no cutting effect
Spray coagulation	Peroral endoscopic myotomy (POEM)—muscle incision, submucosal dissection	Highest voltage creating arcs

Additionally, gravity can be used to pull the mucosa away from the muscularis propria, which provides a countertraction effect, and further assists with a clear field of vision.

2. Clip-line methods
   The clip with line (thread) method is a simple and useful method not only for gastric ESD (mainly at the greater curvature), but also for esophageal, colonic, and duodenal ESD [44].
3. External grasping forceps
   The external grasping forceps are carried into the endoscopic resection field by the other grasping forceps inserted into the working channel after the circumferential mucosal incision. The distance from the tip of the endoscope to the dissection site can be adjusted by pulling and/or pushing the grasping forceps, adjusting to create the best countertraction effect [45].
4. The internal traction method
   A set of two clips connected by a rubber ring or nylon line is used. The first clip with rubber ring or nylon line is attached at the target part after circumferential mucosal incision. After that, the second clip is attached at the opposite side of the lesion. This pulls the lesion and opens up the resection margin, making access for submucosal dissection easier [46].

5. The double-channel scope method
   Either grasping forceps or the outer sheath of an injection needle can be inserted into the available channel of a double-channel scope to create countertraction during ESD [47]. However, movement of the equipment is restricted since the assisting device (forceps or injection needle) moves together with the endoscope tip and dissecting needle.
6. The double-scope method
   Countertraction is provided by a second small-caliber endoscope with forceps inserted alongside the conventional upper endoscope. Once adequate grasping of the edge of the tissue is obtained, the second endoscope can be disconnected from a light source in order to allow the procedure to continue with a single light source [48, 49].
7. Magnetic-anchor-guided ESD
   The magnetic anchor is placed at the edge of the incised mucosa of the lesion. Magnetic traction can be applied to the anchor using an extracorporeal electromagnet control system and the incised mucosa can be opened to expose the submucosal layer for further dissection [50]. However, this technique is not practiced very often in the USA due to the limited availability of suitable extracorporeal electromagnet control systems.

Future Directions

Effective traction and countertraction for opening and stabilizing the operating field are the keys to a successful resection with a shorter duration. During endoscopic therapies using a conventional endoscope, all instruments are deployed in line with the axis of the endoscope. Therefore, off-axis motions are impossible, including triangulation of the instruments, which is an essential motion in any surgical procedure.

Ho et al. reported the feasibility of using the master and slave transluminal endoscopic robot (MASTER) to perform ESD in a pig model [51]. This novel robotics-enhanced endosurgical system enables off-axis motions of endoscopic instruments deployed at the distal end of the endoscope.

Other similar systems are being developed to increase dexterity and maneuverability in complex endoluminal and natural orifice translumenal endoscopic surgery. These include: The EndoSamurai® (Olympus Medical Systems, Tokyo, Japan), TransPort™ Multi-Lumen Operating Platform (USGI Medical, San Clemente, CA, USA), and Direct Drive Endoscopic System™ (Boston Scientific, Natick, MA, USA) [52–54]. These promising prototypes still require considerable improvement, and their applicability to ESD is still under investigation.

Conclusion

ESD is a novel technique that emerged at the end of the twentieth century and expanded endoscopic treatment for EGC with improved outcomes. It quickly became accepted as the primary endoscopic treatment modality for larger and difficult gastric tumors. ESD has rapidly expanded to other difficult mucosal and submucosal tumors throughout the gastrointestinal tract, enabling less invasive endoscopic treatment for lesions that were traditionally treated with surgery. We have summarized the indications for ESD in the esophagus, stomach, and colorectum, as well as introduced some of the technical aspects of ESD, including proper equipment and tools. The current issues facing ESD in the USA are the need for a proper, standardized training programs, as well as well-designed clinical trials to study the efficacy of ESD for disease more commonly seen in our population, such as Barrett's related neoplasms and colorectal neoplasms. We have little doubt that ESD will become widely accepted and utilized more as an advanced endoscopic treatment modality in the West.

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Colon Widefield Endoscopic Mucosal Resection

Michael J. Bourke and Nicholas J. Tutticci

Introduction

Colonoscopy has a central role in the prevention and detection of colorectal cancer, which remains the third most common cancer diagnosis and the fourth leading cause of cancer-related mortality worldwide [1]. A reduction in both colorectal cancer incidence and mortality has been consistently associated with colonoscopy and polypectomy [2–4]; however, its efficacy in cancer prevention varies between colonoscopists and has been linked to quality indicators [5, 6]. The majority of polyps encountered at colonoscopy are less than 10 mm in size and are readily removed by snare resection with, or without, electrocautery [7–9]. Adenomas with villous change, high-grade dysplasia or size ≥10 mm are termed advanced adenomas and are encountered in 2.5–10 % of colonoscopies [10, 11]. In contrast to pedunculated lesions, the removal of flat and sessile lesions greater than 10 mm is more challenging and may require the aid of submucosal (SM) injection. Usually, lesions up to 20 mm in size are resected when encountered at index colonoscopy [12, 13]. Large sessile polyps and laterally spreading tumours (LSTs) ≥20 mm are forms of advanced mucosal neoplasia (AMN) [14] and are removed by wide field endoscopic mucosal resection (WF-EMR) usually at a second dedicated colonoscopy [15]. The techniques involved in WF-EMR remain an evolving field of knowledge and are the focus of this chapter.

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Endoscopic Resection

The colonic wall is thin, approximately 1.5 mm in the proximal colon and 3 mm in the distal colon, rendering it susceptible to deep thermal injury or entrapment during snare electrocautery [16]. Injection of fluid into the SM space to protect against thermal injury was initially described over half a century ago in a small case series of electrocautery for rectal polyp fulguration at rigid sigmoidoscopy [17]. In 1973, SM injection prior to snare polypectomy was performed in a canine model followed by a small clinical series in the proximal colon without complication [18]. Subsequently, this technique has been termed endoscopic mucosal resection (EMR); however, as a variable amount of SM tissue is intentionally resected in addition to the mucosal layer, endoscopic resection (ER) may be considered a more correct term [14]. Conventional EMR (or ER) generally refers to attempted en bloc resection of mucosal lesions of 10–25 mm. WF-EMR may be used to describe ER of larger lesions ≥ 30 mm requiring piecemeal resection with a resultant broad mucosal defect, often hemi-circumferential or greater in extent [14].

Lesion Assessment

Accurate lesion assessment informs the therapeutic strategy. The mucosal layer of the colon does not contain lymphatics and hence, in the absence of SM invasion (SMI) the risk of lymph node metastases is negligible [19]. Invasion through the muscularis mucosa is the defining feature of colorectal adenocarcinoma [19]. It is important to recognise differences in reporting when interpreting clinical studies with intra-mucosal carcinoma in Japan representing high-grade dysplasia in the West [19–21]. As colorectal cancer progressively invades the submucosa, the risk of lymph node metastasis increases with increasing width and depth [22–24]. SM (T1) [25] adenocarcinoma may be classified as either low or high risk for lymph node metastases with rates of <5 and 6–35%, respectively [24, 26, 27]. Low-risk lesions are: well or moderately differentiated with absence of lymphovascular invasion, absolute invasion depth into the submucosa of ≤ 1000 μm and complete excision [21, 27, 28]. Lesions at risk for lymph node metastasis require consideration of surgical treatment. As the standard of care for colorectal cancer (CRC) with lymph nodes metastases remains surgical resection and lymph node dissection [26, 27, 29, 30] rather than endoscopic therapy, accurate prediction is imperative at endoscopy.

Morphology and Surface Pattern

Lesion interrogation incorporates overview and focal modes and involves size, morphology and surface pattern assessment [15, 21]. Ulcerated, firm lesions usually represent deeply invasive carcinoma, the appearance of superficial lesions may be more subtle. Lesion size can be accurately gauged against a fully opened snare

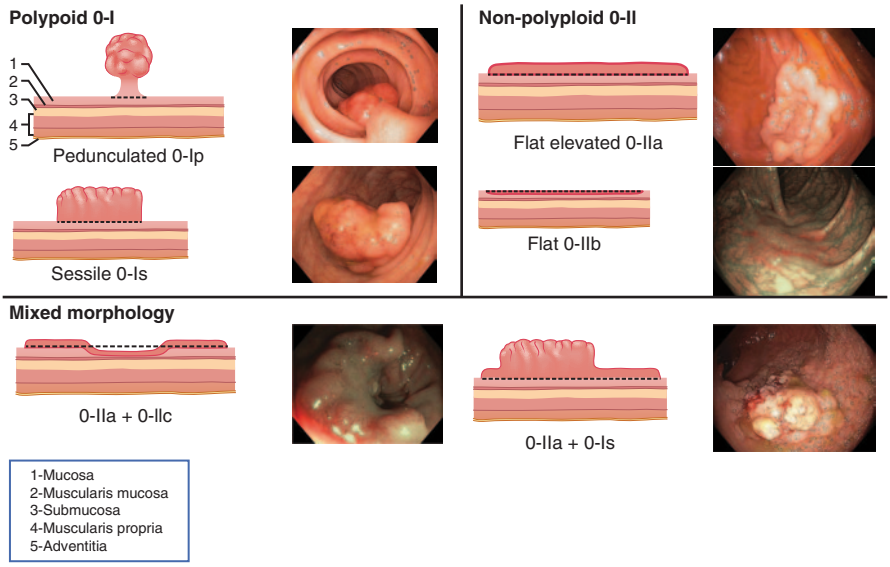

Fig. 1 Schematic of Paris classification of superficial neoplasia and corresponding endoscopic images examples of common AMN morphologies encountered. Lesions are broadly divided into polypoid (0-I) and flat (0-II) morphologies on the basis of protrusion >2.5 mm above the mucosal surface in 0-I lesions in contrast to the lower vertical height of 0-II lesions. The margin of 0-IIb lesions or the depressed area within nongranular flat lesions may be indistinct and is best appreciated in these cases under narrow-band imaging (NBI). Mixed morphologies may exist with an elevated risk of SMI associated with depressed areas (0-IIc) or flat lesions with large nodule (0-IIa+0-Is)

of known dimension, though size alone is a poor predictor of SMI [21]. The Paris classification system (Fig. 1) arose through international collaboration and has been well validated[21, 31]. Lesions that appear limited to the mucosa or submucosa are described as superficial '0' lesions and are divided into three groups: polypoid (0-Ip = pendunculated, 0-Is = sessile and 0-Isp = semipedunculated), flat or non-polypoid (0-IIa = slightly or flat elevated, 0-IIb = completely flat or 0-IIc = depressed) and excavated (0-IIIc = ulcer). Historically, the discrimination in reporting between sessile and flat lesions by the Western endoscopists has been poor with both types labelled as sessile [21]. The key discriminator between sessile (0-Is) and the most common flat polyp (0-IIa) is elevation greater than 2.5 mm above the surrounding mucosa. This may be assessed by comparison to a closed biopsy forceps. Lesions with multiple morphologies are described with the predominant morphology listed first with a '+' symbol separating the remainder. Common examples with clinical implications include 0-IIa+Is and 0-IIa+IIc.

An additional descriptor for lesions larger than 10 mm in diameter demonstrating a predominately horizontal pattern of growth with a low vertical trajectory is laterally spreading tumor (LST). LSTs are classified as 0-IIa or 0-IIb by elevation criteria under the Paris classification [22]. Adenomatous (either conventional or traditional serrated adenomas) may be further categorised by their surface granularity as granular (G), non-granular (NG) (Fig. 2) [32]. Although hyperplastic and sessile

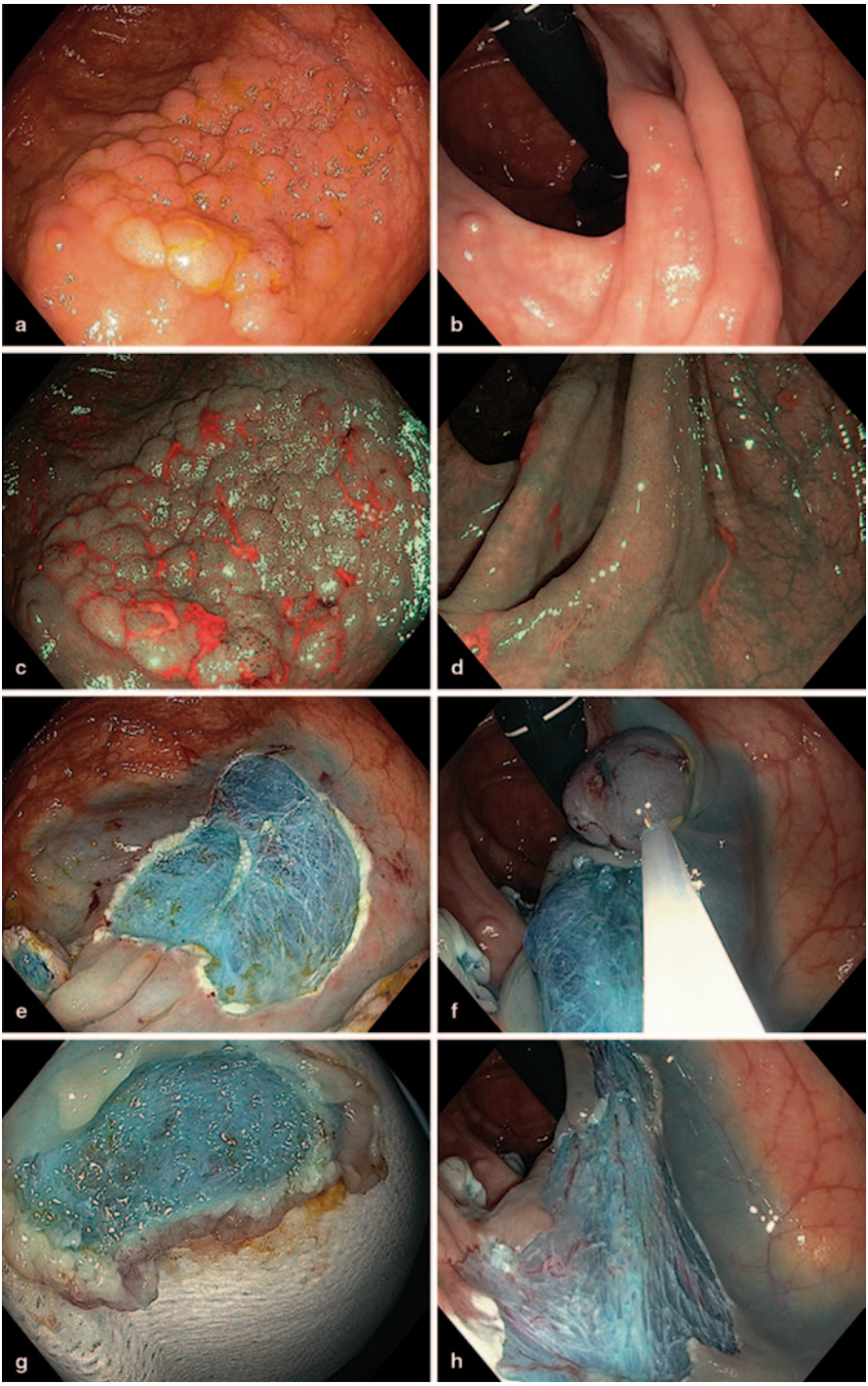

Fig. 2 Series of comparative images of granular and non-granular homogenous LSTs in the proximal colon. Thirty millimetres caecal granular LST (Paris 0-IIa) WL (**a**) and narrow-band imaging

serrated adenomas/polyps may often exhibit the morphology of LSTs, they are not described within this system [32] and the approach to these lesions is described later.

Association Between Morphology and Risk of SMI

LST-G (0-IIa and 0-IIa+Is) are prevalent in cohorts of colonic polyps referred for resection and overall represent a low rate (3.2%) of SMI in this setting [15]. A homogeneous 0-IIa LST-G has a risk of SMI of approximately 1% [15, 33, 34]. They are ideal for endoscopic therapy even when very large. A sessile component in a flat elevated lesion (0-IIa+0-Is) has a higher risk of SMI at 6–10% [33]. LST-NG and LST-G are biologically distinct with different rates of oncogene expression [33, 35]. The NG pattern represents a higher risk of SMI which ranges from 5 to 15% in a homogeneous lesion up to 70% in those with a depressed area [15, 32, 33, 36]. In the majority of cases, the area of SMI lies under the Is nodule or depressed area which allows targeting of this area for initial resection [33].

Surface Pattern

The surface of a lesion may be assessed either in terms of pit (Kudo pit pattern) [37] or vascular pattern (multiple classifications) [38]. Kudo's anatomic pit pattern was described with magnifying colonscopes and chromoendoscopy [37] and has been utilised for prediction of depth of invasion [39, 40]. In summary type I and II are typical of normal mucosa or hyperplastic lesions, type IIIL and IV of adenoma and IIIs and Vi with high-grade changes or SMI <1000 μm. Vi pattern within a demarcated area or Vn pattern is associated with deeply invasive adenocarcinoma [41–43].

Surface microvascular classification is based on the observation that tumourogenesis involves angiogenesis with altered microvessels [44, 45], which may be better appreciated with push-button modalities such as narrow-band imaging (NBI). The central concept is that with advancing histological grade vessels become thicker and more tortuous before then becoming irregular and obliterated. In the strictest sense, NBI does not allow assessment of the Kudo pit pattern [38], but rather demonstrates a pit-like pattern. Given the diversity of NBI classifications (Sano, Hiroshima, Showa, Jikei and additional Japanese University classifications) [38] a unified classification which does not require magnifying colonoscopes has been proposed (NBI International Colorectal Endoscopic (NICE) classification)

(NBI) (**c**). Piecemeal resection defect (**e**) and underside specimen (**g**) both demonstrating homogenous blue submucosal (SM) staining. Thirty-five millimetres ascending colon nongranular LST (Paris 0-IIb) with subtle appearance under WL (**b**) and enhanced margin visualisation under NBI (**d**). Sequential resection (**f**) and resultant defect (**h**)

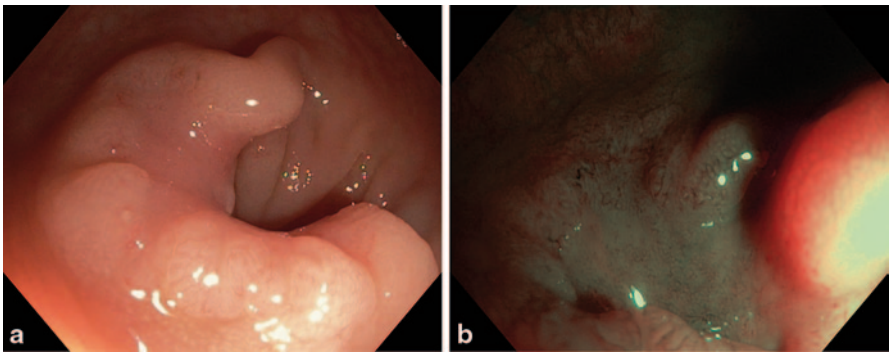

Fig. 3 **a** 30 mm nongranular LST with depression (0-IIa + 0-II c). **b** Loss of regular dark vascular pattern in the depressed area in non-magnified NBI view highlighting irregular to absent vascular pattern and Vi-n pit-like pattern. Biopsies taken after non-lifting demonstrated high-grade dysplasia; histopathology of the surgical specimen confirmed adenocarcinoma with deep submucosal invasion (SMI)

[38, 46, 47]. Classifications have significant predictive capability; however, in the absence of magnifying colonoscopy evidence is predominately limited to discrimination between adenomatous and serrated polyps [48–51] rather than identifying SMI [38, 42, 52, 53]. Further studies validating both pit and vascular classification in predicting SMI are required. Surface pattern assessment is more accurate in flat and sessile lesions rather than pedunculated lesions [54] and is additive when combined with morphology, for example, NG-LSTs with depressed (0-IIc) area and type V Kudo pit pattern has predictive power of 50 % for invasive disease (Fig. 3), in the hands of Western endoscopists without magnification [15].

If deeply invasive disease is predicted endoscopically, our practice is to perform targeted biopsies, place a localising tattoo if required and refer the patient for staging imaging and surgery. Multiple tunnelling biopsies should not be taken when a large flat lesion is first encountered if it is potentially considered suitable for endoscopic resection basedon endoscopic features due to the risk of SM fibrosis and subsequent non-lifting.

The WF-EMR Procedure

Pre-Procedural Preparation

Although no guidelines exist on the consent for WF-EMR, risks, alternative therapies and consequences of no action should be conveyed [55]. Specific consent reflecting the increased risks of WF-EMR of AMN over those of routine colonoscopy and polypectomy should be obtained. All patients including those with distal

sigmoid or rectal lesions should receive full bowel preparation to facilitate optimal views and mitigate against the risk of contamination in the event of perforation. Carbon dioxide (CO_2) insufflation reduces colonoscopy procedural and post-procedural discomfort [56, 57] and post-procedural admission after WF-EMR [58] in a large prospective cohort study.

Guidelines for management of anti-platelet therapy prior to WF-EMR do not exist. General guidelines for endoscopic procedures are a useful template [59, 60]. However an individualised approach to peri-procedural anti-platelet and anti-coagulation management should be employed and the use of these agents must always be factored into the therapeutic approach. Cardiologist consultation should be considered before anti-platelet or anti-coagulation discontinuation in patients with coronary stents or metal prosthetic valves. If a compelling indication for ongoing anti-platelet therapy exists, we continue with low-dose aspirin in preference to alternative anti-platelet agents. Enoxaparin window technique may be used for prosthetic valves with the drug omitted on the day of the procedure only. The post-procedural bleeding risk is significant but generally amenable to therapy and must be balanced against the more serious risk of cardiac thromboembolism which is frequently catastrophic.

EMR Procedure

The colonoscope position for resection should be optimised prior to commencement. Reduce loops to the shortest most stable scope position. Rotate the colonoscope so that the lesion lies at the 5–6 o'clock position; however, this should not be considered mandatory, if an ideal resection aspect exists at an alternative position. Wash, inspect and photo-document whilst assessing morphology and interrogating surface pattern. Complete assessment or optimal resection position may require retroflexion, particularly in the distal rectum or ascending colon/hepatic flexure. Routine retroflexion with an adult scope is achievable and safe in the majority of patients in these locations [61]. If colonic spasm is problematic intravenous hyoscine bromide 10–20 mg or glucagon 0.5–1 IU may be helpful.

Injection

SM injection is a critical component of WF-EMR. The ideal injectate should be safe, affordable and provide a sustained and localised elevation when injected into the SM space [62, 63]. Normal saline is most commonly used; however, it may disperse along the SM space limiting the magnitude and duration of elevation. Alternatives include: glycerol, hyaluronic acid and succinylated gelatin. Fluid selection is influence by local availability and cost [63, 64]. In randomised trials, succinylated gelatin increases ER en bloc resection size in a porcine model [65] and reduces procedure duration and number of resection pieces in humans [62]. Dilute

indigocarmine is added to the injectate. This dye is avid for the loose areolar tissue of the SM. The benefits are threefold.

1. Delineate the area of successful SM injection where resection may be safely performed.
2. Highlight the margin of the lesion especially of indistinct and flat neoplasms, for example, 0-IIb NG lesions.
3. Stain the mucosal defect creating a homogenous blue mat expanse of obliquely orientated SM fibres. This facilitates the evaluation for deep injury.

Methylene blue is an alternative dye; however, it does not perform as well. Epinephrine (adrenaline) is added with the aims of reducing minor intra-procedural bleeding (IPB) to facilitate a clear endoscopic view and to reduce dispersion of the SM injectate through vasoconstriction of draining vessels [14]. Its effect upon post-polypectomy bleeding is unclear [66–68]. Practically, we add 80 mg of indigocarmine to a 500 ml bag of succinylated gelatin (Gelofusine ® B. Braun Australia), 9 ml of this solution is drawn into a 10 ml syringe with 1 ml of 1:10,000 epinephrines (adrenaline) in normal saline.

Injection Technique

Approach the mucosa at an angle of approximately 30 %. A tangential approach reduces the risk of trans-mural injection. Use the 'touch and inject' technique, where the injecting catheter with the needle 'out' is advanced until it touches the mucosa. The assistant then begins injection whilst simultaneously the endoscopist advances the catheter rapidly with a short 'stab'. This method rapidly finds the SM plane. Immediate elevation should occur. If elevation is not seen deep injection has likely occurred. Unless excessive this is inconsequential, and the needle should be slowly withdrawn till satisfactory mucosal elevation occurs. Whilst elevation of the entire lesion is essential for en bloc resection; for WF-EMR, this may hamper piecemeal resection due to an excessive tension within the fluid cushion limiting tissue capture within the snare. It may also crowd the lumen restricting access to the whole lesion. Tissue elevation tends to be transient so repeat injection is necessary in any case. Whilst injection occurs, the catheter and scope may be gently moved as one to 'guide' the formation of the tissue elevation in the desired direction [14, 69, 70]. Translesional injection should be avoided, if SMI is suspected.

Electrosurgical Device

In contrast to pedunculated lesions, where a low-power coagulation current is used to coapt feeding vessels, for ER of flat or sessile lesions more sophisticated electrosurgical outputs are required. Microprocessor (e.g., ERBE VIO 300, Tubingen, Germany, Olympus ESG-100, Tokyo, Japan) controlled alternating cut and coagulation cycles with automatic adjustment of power output in relation to tissue impedance

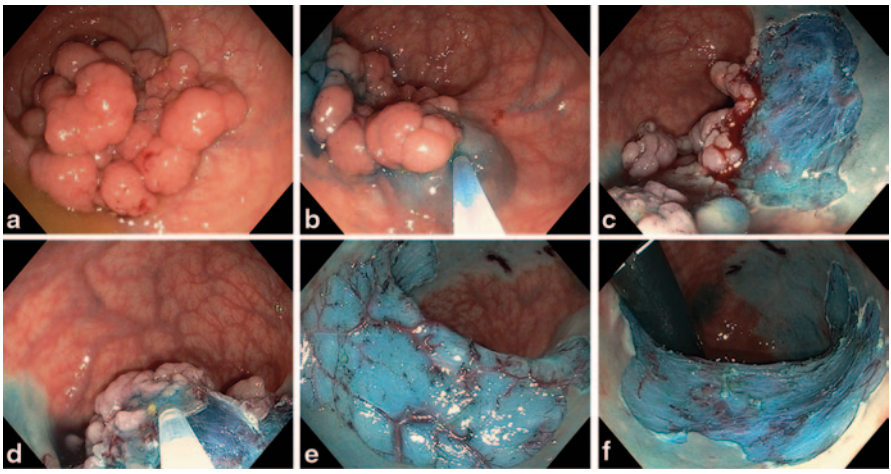

Fig. 4 **a** 50 mm hemi-circumferential rectal granular LST (0-IIa + 0-Is). Submucosal (SM) injection **b** then resection **c** of distal margin. **d** Injection of central portion. Hemi-circumferential mucosal defect with prominent non-bleeding vessels on forward **e** and retroflexion **f** views.

changes during polypectomy are preferable [14]. This approach is based on sound electrophysiological principles, but is unproven in clinical trials.

Snare Selection

A range of snares is required. We utilise a 20 mm spiral snare for most WF-EMR cases. The serrated wire aids tissue capture, crucial to the inclusion of a margin of normal mucosa in the resection. A small thin-wire snare should be available for resection of residual disease within and at the margin of the defect. It is also useful for areas with fibrosis, poor lifting or difficult access. Multiple snare types with varied shape and size on opening and different wire characteristics are available and may be utilised in specific circumstances largely guided by proceduralist preference.

Resection

En bloc resection is ideal; however, it is limited by lesion size and location with current ER techniques. During piecemeal ER each resection has the potential to create complications and leave disease; hence, the aim should be safe resection in the fewest number of pieces possible (an oligo-piecemeal resection). Start resection in the area most likely to contain SMI if present, e.g., the Is component of a IIa + Is lesion, a IIc component of an LST-NG lesion or demarcated area with advanced pit or surface pattern (Fig. 4). For homogeneous lesions commence at the area anticipated most challenging to resect. After injection the lesion;

- Work sequentially from the point of first entry into the SM plane. Align the snare with the edge of the advancing mucosal defect and continue this technique as the lesion is removed. This reduces the risk of tissue islands (within the defect), which are difficult to subsequently remove.
- With the snare open over the lesion push down very firmly with the up-down control onto the SM cushion whilst aspirating gas to; reduce colonic wall tension, decrease the mucosal footprint of the lesion, and maximise tissue capture.
- Perform a staged snare closure, advancing the catheter to maintain the snare base at the lesion edge, whilst monitoring the lesion for 'buckling' or loss of the margin, which requires snare repositioning.
- Close the snare very tightly to exclude muscularis propria (MP) from the captured tissue. If using a spiral (serrated) snare, it is not possible to transect ensnared tissue of more than 10 mm diameter without the use of diathermy.
- Tent the captured tissue away from the wall of the colon. If concern for MP entrapment exists at this point, slightly open the snare so the MP can 'drop out'. This technique can also be used, if an adjacent fold has been inadvertently entrapped.
- The proceduralist should take the snare for the final transection phase. The sensory feedback is invaluable to inform on the safety and efficacy of the excision. Safe tissue capture is confirmed by three manoeuvres:
  - Assess the mobility of the ensnared tissue by moving the snare catheter quickly back and forth; it should move freely relative to the underlying colonic wall.
  - The snare should close fully with minimal 'puckering' of the surrounding tissue. If concerned once again the MP release manoeuvre can be repeated as before. The snare is, thus, partially opened and tented into the lumen to release the deeper tissue before repeat closure.
  - Transection should be fast; the snare is kept tightly closed whilst the foot pedal is depressed. With a microprocessor-controlled generator, using alternating cycles of high-frequency short-pulse cutting on a background of coagulation current, generally between one and three pulses, but occasionally up to 5–6, to transect the tissue. A longer transection phase raises concerns for either the MP entrapment or deeper neoplastic invasion [71]. These features are less reliable in the presence of SM fibrosis or with the scope in retroflexion.
- The defect is washed and examined after each resection for evidence of deep injury or residual tissue. NBI and topical SM chromoendoscopy (TSC) [72] are used to evaluate potential areas of residual adenoma, MP injury or non-staining.

Residual tissue may remain, particularly at resection margins. We attempt complete snare excision of all endoscopically visualised polyp with a margin of normal tissue wherever possible. Minute areas can be difficult to ensnare even with smaller thin wired snares and tissue ablation may be required. The use of argon plasma coagulation (APC) has been studied in two settings. Firstly, when applied to a defect which appears to have had all tissue resected has been shown to reduce residual/recurrent tissue at surveillance in a small cohort of lesions > 15 mm [73]. The second setting

is use of APC to endoscopically visible disease not amenable to snare resection, where if no therapy is initiated persistent disease is apparent in 100% of patients at surveillance [74]. When APC is applied to endoscopically visible residual tissue, the described recurrence rates are disappointingly high: 14 [75], 39.5 [15], 46.5 [73], 47.5% [76] and 50% [74] indicating it has limited efficacy in this setting. The optimal treatment modality for this type of residual disease is not known.

Risk factors for primary resection failure on multivariate analysis are as follows: previous attempt at resection, ileocaecal valve (ICV) involvement and difficult position, as defined by the proceduralist [15].

Specimen Retrieval and Assessment

When several resection fragments exist a net is used. For very large lesions, the scope may need to be withdrawn and reinserted. The underside of the retrieved fragments is assessed quickly ex vivo, preferably with the colonoscope, for evidence of a target sign. Large pieces are pinned flat prior to submission for histopathologic examination. En face ex-vivo interrogation with the enhanced imaging functions of the colonoscope confirms the primary endoscopic assessment. These specimens are submitted separately. As the en face view maybe superior to the in vivo endoscopic image, this type of controlled analysis is a convenient means of improving the endoscopists imaging skills. We undertake extensive photo-documentation with subsequent histological correlation to improve our imaging skills and diagnostic accuracy. Smaller fragments collected from the suction channel via a trap or gauze are also submitted.

Lesion Localisation

The site of the lesion should be readily localised so surveillance colonoscopy or if necessary, laparoscopic surgery, can be performed. For rectal lesions, record the distance with a straight scope from the distal margin of the lesion to the anal verge. Lesions in the caecum or very proximal ascending colon may be described in relation to the ICV referenced at the 9 o'clock position on the medial wall. For other regions of the colon, tattoo placement should be considered. Sterile carbon suspension is not biologically inert and can be associated with complications [77, 64]. Fibrosis may occur when tattoo tracks to the site of a lesion or resection site, resulting in challenging resection [64]. Unintended transmural injection has been associated with phlegmon formation and peritoneal staining making localisation at surgery difficult. Guidelines on colonic tattoo have been proposed [64]; tattoo with sterile carbon should be placed 3 cm distal to the lesion/defect with saline pre-injection technique. The injectate used for the preceding ER may also suffice. An injection technique identical to that described above for lesion elevation is employed. When elevation occurs the saline/injectate syringe is exchanged for the tattoo syringe and

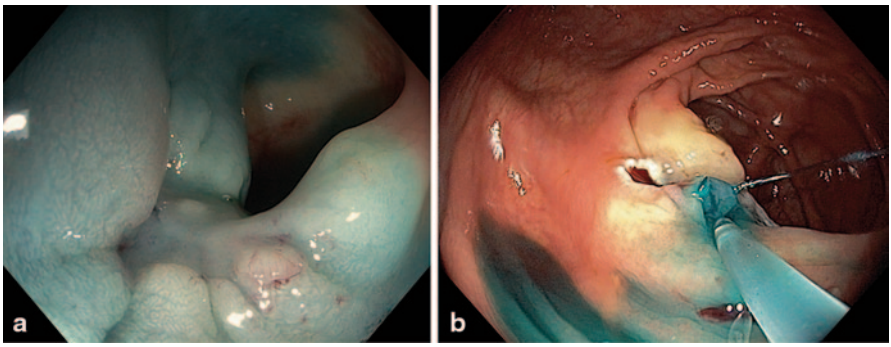

Fig. 5 Analogous signs of submucosal (SM) fibrosis elicited at lesion injection. **a** Non-lifting with elevation of the surrounding mucosa, the 'cannyoning' effect. **b** The jet sign

3 ml of tattoo solution injected. A switch back to the saline syringe and injection of a further 2 ml will clear the injection catheter of the remaining tattoo and allow rapid progression to pre-injection at the second tattoo site. A minimum of two tattoos with the second on the contralateral wall is recommended for surgical localisation.

Limited Elevation with SM Injection

A failure to achieve elevation during SM injection, despite the needle situated within the correct anatomic layer, is known as the non-lifting sign. An analogous sign may be demonstrated, where a stream of injectate exits the area for elevation at the same speed as it is injected, the 'jet sign' [14] (Fig. 5). These signs indicate that the SM space has been obliterated usually by fibrosis or uncommonly by direct carcinomatous involvement. In 2013, the application of correct enhanced imaging strategies should avoid the clinical scenario where a deeply invasive disease is attempted to be elevated. Fibrosis may be induced by mechanical or thermal injury from previous resection attempts, reaction to tattoo [64] placed for localisation or reaction to SM tumour invasion. The accuracy of the lifting sign in discriminating between lesions with or without SMI is often misconceived. Several studies [78–80] have evaluated the lifting sign in colonic lesions; overall adenomatous lesions and adenocarcinoma with SMI limited to $\leq$1000 μm (i.e., SM1) generally lift. Deep invasion beyond 2000 μm is generally not associated with lifting; however, lesions with intermediate depth of SMI (1000–2000 μm), which is beyond the current criteria for ER, may lift [81]. Thus, a lesion with concerning morphology and or surface pattern may lift for resection yet ultimately return histology with SMI depth requiring surgical management (Fig. 6). Conversely, if a lesion fails to lift in the absence of prior significant biopsy or resection attempts, deep invasion is possible particularly, where Is morphology is present as this may conceal cancer deep within the lesion. Where there is a history of resection attempts or multiple biopsies in a flat lesion and this histology does not indicate SMI, attempts at elevation and resection of a poorly lifting lesion can be considered and is discussed below.

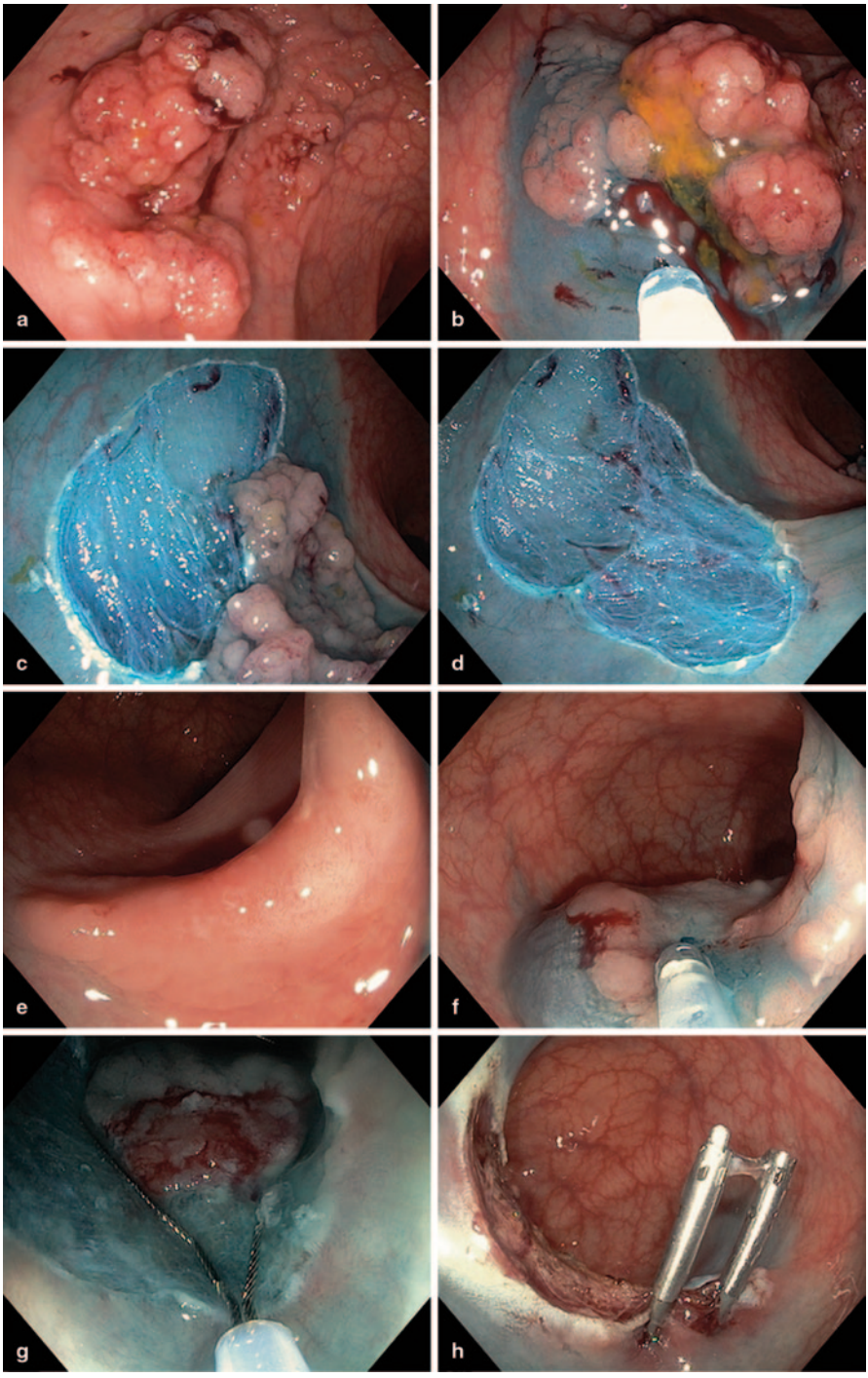

Fig. 6 Comparative images of granular and nongranular LST resection. **a** Forty-five millimetres Granular LST with sessile components (IIa+Is). **b** Elevation of the dominant Is component for initial resection. **c** Resection with margin of normal tissue. **d** Homogenous blue stained defect.

Complications

Intra-Procedural Bleeding

Significant IPB occurs in approximately 10–20 % of WF-EMR procedure. It is readily amenable to endoscopic haemostasis. First, the area is irrigated to identify the bleeding point, ideally via a foot pedal operated pump though a dedicated flushing channel. Techniques for haemostasis include: injection of adrenaline, APC, coagulation via snare tip or grasper forceps and endoscopic clipping. The technique of snare tip soft coagulation (STSC) requires 1–2 mm of snare tip to be exposed which is then used to deliver soft coagulation current (80W, effect 4, ERBE VIO) in a targeted fashion to a bleeding site. In a prospective study of 196 patients, a mean lesion size 41.5 mm undergoing WF-EMR, the STSC was effective in 40/44 cases of IPB without complication [82]. For large vessels or pulsatile bleeding, coagulating forceps (utilising the same generator setting, 80W, effect 4) or clips are necessary. These techniques have the disadvantage of additional expense and device exchange time. Clips may also hamper subsequent resection or bury residual adenoma.

Delayed Bleeding

Bleeding is the commonest complication of WF-EMR with the majority occurring within 48 hours of resection. Clinically significant bleeding which is defined as bleeding requiring hospital admission, is seen in 3–7 % of resections in prospective studies [15, 83]. Risk factors for lesions > 20 mm in size include: lesion location in the proximal colon, recent aspirin use and increasing patient age [83, 84]. Most bleeding will settle with conservative management; however, patients with ongoing bleeding or hemodynamic compromise despite resuscitation require intervention. Repeat colonoscopy with endoscopic haemostasis predominately by use of endoscopic clips is usually effective. As the site of bleeding is known and the patient is auto-prepared from the bleeding, additional oral bowel preparation is often not required within this 48 h window. Rarely angiographic embolisation is necessary for cases of failed endoscopic haemostasis or severe bleeding.

Post-Procedural Pain

Mild self-limiting pain is not uncommon after WF EMR and is reduced by use of CO2 insufflation [58]. After WF-EMR for lesions > 30–40 mm, the patients are kept

e Thirty millimetres nongranular LST with central depression (IIa + IIc). **f** Limited elevation of the depressed area which corresponded with adenocarcinoma with superficial submucosal invasion (SMI) on histopathological examination. **f** Change to small thin-wire snare for resection of poorly lifting component. **g** Intra-procedural bleeding (IPB) managed with endoscopic clips

nil by mouth for 2 hours prior to proceduralist review, whilst supine in first-stage recovery. The abdomen is quickly examined and should be soft and non-tender. Patients may then commence clear fluids and be discharged after a further 2 hour period of observation. Persistent pain warrants admission and further evaluation. Computer tomography (CT) is the imaging modality of choice, where perforation is suspected as plain x-ray is relatively insensitive in this setting [85, 86]. Confirmed perforation requires multidiscliplinary management including a colorectal surgical service. Some free air may be seen on CT even after successful endoscopic closure; thus, the management decisions should be driven primarily by the patient's clinical status.

Perforation and Endoscopic Detection of MP Injury

Although perforation remains a feared complication of EMR, the majority of cases identified at resection may be managed endoscopically [15, 87, 88]. Systematic inspection of the resection defect and the underside of the resected specimen are crucial. Both indigo carmine and methylene blue are avid for the loose connective tissue in the submucosa, thus the typical homogenous blue mat staining of the defect reassures the proceduralist that injury to the MP has not occurred. The MP does not stain and is seen as a white to grey ellipse within the mucosal defect. This may represent a full or partial thickness injury, the latter may present at delayed perforation, if not closed endoscopically. A proportion of non-stained areas will occur due to focally limited dye contact or limited infiltration at SM lift rather than representing muscle injury. TSC allows for a rapid test of staining for interrogation of these areas [72]. The technique involves focused irrigation with dye containing injectate over the unstained area via the injection catheter with the needle retracted. Staining of the submucosa is swift and relatively resistant to water irrigation. Yellow adipose tissue may often be seen in resection defects in the proximal colon and does not represent deep injury.

The target sign is a specific marker for MP resection [87]. It may be seen on the underside of the resection specimen and formed by concentric rings of unstained mucosa and MP (Fig. 7). The mirror target sign may also be appreciated within the colonic resection defect. When identified, it should prompt suctioning of residual faecal fluid and the patient repositioning, so that the defect lies opposite the dependant area to avoid fluid contaminating the defect. Unless there is a clear hole, the residual polyp tissue should be cleared from the adjacent to the defect if feasible, before an attempt at closure as tissue in or under clips may be 'buried'. Defect closure with endoscopic clips is effective in the majority of cases and can provide closure comparable to surgically placed sutures, as demonstrated in an animal model [89]. Clipping should commence at one end with sequential clips in a 'zipper' technique as the placement of a central clip initially can result in unopposed bowed tissue edges ('dogs ears'). Gentle suction is applied to maximise tissue capture prior to the closure and deployment. Post-procedure these patients are observed and remain nil by mouth for 2 hours before further clinical review by the proceduralist. Patients in

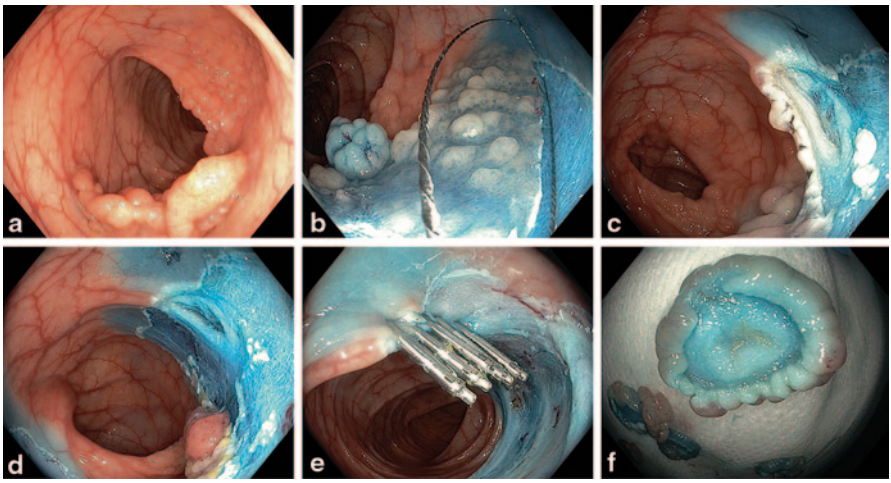

Fig. 7 **a** Forty-five millimetres sigmoid granular LST (Paris 0-IIa+Is). **b** Sequential resection. **c** Mirror target sign indicating MP injury. **d** Resection of adenomatous tissue adjacent to site of MP injury to avoid buried tissue after closure. **e** Endoscopic closure with clips and complete resection of the lesion. **f** Target sign on resection specimen. The patient was admitted overnight for observation and discharged the next day well

whom endoscopic closure is satisfactory and are clinically well without abdominal pain on examination may commence clear liquids orally and after further period of observation may be potentially be discharged home on clear liquid diet the same day.

Specific Resection Scenarios

Serrated Lesions

The serrated polyp family includes hyperplastic polyps, sessile serrated adenomas/polyps (SSA/Ps) with or without dysplasia and traditional serrated adenomas [19]. Hyperplastic polyps and SSA/Ps without dysplasia are most often flat (0-IIa) by Paris morphology; however, they are not classified by the granular or nongranular surface descriptor. TSAs have the endoscopic appearance and are managed as conventional adenomatous polyps [32]. The majority of large proximal serrated polyps are SSA/Ps [90] which are endoscopically subtle and may has a significant role in the relative failure of colonoscopy to provide similar protection from CRC in the proximal to the distal colon [91–94]. Surveillance guidelines have been updated recognising their significance [95] and their complete endoscopic removal is recommended. Endoscopic predictors of these lesions include adherent mucous or debris [96], pale appearance under NBI [97] and type II-O (open) Kudo-Kimura

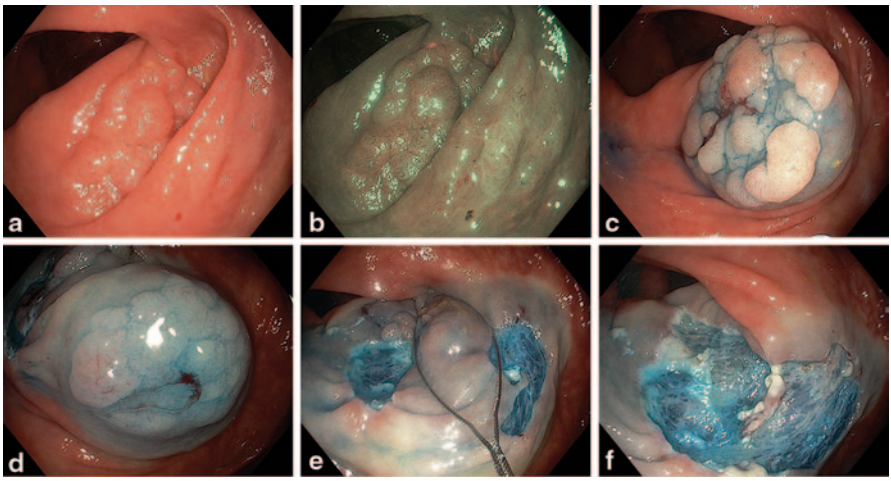

Fig. 8 Thirty millimetres granular LST (Paris 0-IIa) tubular adenoma and adjacent 25 mm (Paris 0-IIa) sessile serrated adenoma in HD WL (**a**) and NBI (**b**). Sumucosal injection of the adenomatous (**c**) and serrated (**d**) lesions. The SSA margin is clear after injection (**e**). Resection of rim of intervening normal tissue (**f**). Resultant wide mucosal defect (**g**)

pit pattern [98]. The low vertical growth and often indistinct margins which make endoscopic detection difficult can lead to challenges during ER. Although the lesion margin may become more obvious after SM injection with dye solution, coagulated margins of normal tissue are difficult to distinguish from the pale tissue of the polyp despite high definition colonoscopes (Fig. 8). A prospective trial of completeness of polyp resection identified SSA/P histology as an independent predictor of residual polyp at polypectomy [99] with residual tissue approaching 50% for SSAs >10 mm in size. Although the incomplete resection rate of SSAs has not been reported upon from a resection series of lesions >20 mm in size, it is clear that these lesions warrant particular attention when identified. The optimal techniques for complete and safe serrated lesion removal remain unknown and are the subject of ongoing research.

Ileocaecal Valve Involvement

The ileocecal valve represents a challenge for complete resection and is a risk factor for recurrence after ER [15]. The margin between villous small intestinal mucosa and adenomatous tissue may be more difficult to appreciate than the junction to colonic mucosa and the smaller ileal lumen may reduce access. Resection may be optimised by use of a clear plastic cap attachment and judicious injection volume along with suitable snare selection.

Periappendiceal

Caecal polyps involving the peri-appendiceal area may be completely resected without perforation providing the appendiceal mucosa can be visualised proximal to the polyp and accessed for snaring after injection. Greater than > 50 % of the appendiceal orifice circumference involvement is a relative contraindication to resection. Prior appendicectomy allows greater confidence during resection in the caecal pole and is a salient history point to note.

Anorectum

Lesions located in the rectum warrant special consideration due to inherent differences in innervation and vascular drainage. For lesions approaching the anal verge, somatic nerve fibres may relay pain post procedure, which can be reduced by addition of long-acting local anaesthesia to the injectate (e.g., 1 % ropivacaine). As the prominent rectal venous network drains directly to the systemic circulation from the distal rectum, prophylactic intravenous broad spectrum antibiotics should be considered to reduce the risk of bacteraemia. The systemic circulatory drainage also dictates that continuous electrocardiograph monitoring be performed when adrenaline and or local anaesthetic is added to the injectate. Access and views may be limited for anorectal lesions and may be improved with a clear cap attachment. Additionally, the confines of the rectum may overcome with use of a gastroscope, with the shorter bending section than a colonoscope resulting in greater manoeuvrability in retroflexion (Fig. 9).

Residual Tissue at Surveillance and the Previously Attempted Lesion

The term recurrence is used to denote recurrence of endoscopically appreciable polyp tissue or consistent histology on biopsies at surveillance. This presumably arises from persistence and growth of residual, albeit potentially microscopic, disease at the time of resection rather than de novo re-emergence of dysplasia. Thus, the term residual tissue may be more correct than recurrence per se.

Residual tissue is detected at surveillance in 10–20 % of lesions completely cleared endoscopically. It is usually unifocal, diminutive and easily treated [15].

When a portion of a lesion has been removed in a failed previous attempt, the remaining polyp mass may be significant and fibrosis induced by previous electocautery may make resection challenging. In general, begin resection in an area without SM fibrosis. Here, you will easily be able to find the SM plane. Use of a small stiff thin-wire snare may improve success. Care must be taken with SM injection in this setting as the non-lifting fibrotic area may be obscured by elevated adjacent mucosa or ‘canyonning’. ESD may be superior to ER in managing large areas of recurrence

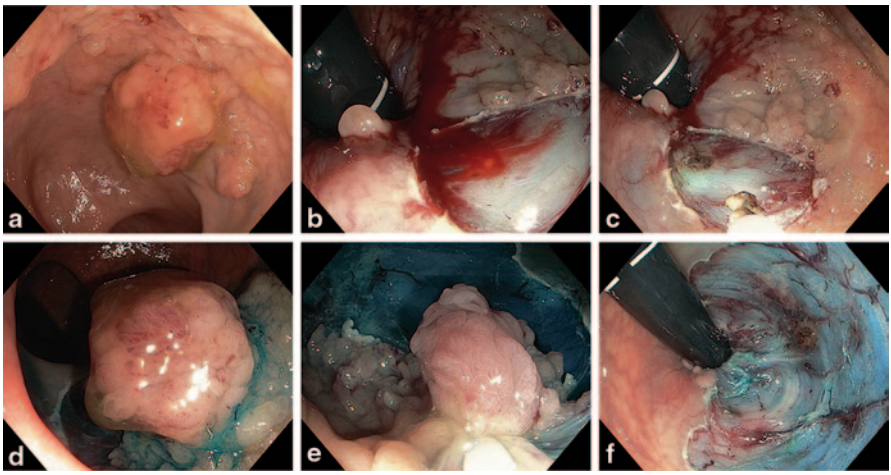

Fig. 9 **a** Fifty millimetres granular rectal LST with dominant Is nodule (Paris 0-IIa+0-Is) involving the anorectal margin. **b** Resection of polyp involving anorectal margin with intra-procedural bleeding (IPB). **c** Haemostasis after snare tip soft coagulation (STSC). **d** and **e** Resection of dominant Is nodule and remaining tissue. **f** Resultant wide mucosal defect with intact muscularis propria (MP) visible

[100]. The optimal endoscopic strategy for dealing with residual disease remains unknown. We take a two-step approach to the residual disease:

1. Using low-voltage coagulation current, we excise (if possible) or destroy the scarred residual by slowly closing the stiff thin-wire snare over the recurrence whilst applying the diathermy.
2. Once the area is flattened, we then apply STSC by a contact technique until the target tissue and surrounds are well coagulated appearing white. Because of the low-voltage generator output, there is minimal risk of transmural injury especially when employed over a scar.

Early Adenocarcinoma

Early adenocarcinomas may be treated by ER in selected cases, influenced by patient preference, comorbidity and the surgical procedure proposed. For example, the laparoscope right hemicolectomy is associated with lower morbidity than low anterior resection. Colonic adenocarcinoma with SM invasion carries a lymph node metastases rate than can be quantified by classification into low- or high-risk categories for lymph node spread [21, 27]. Low-risk criteria are: well or moderately differentiated tumour grade, absence of lymphovascular invasion and absolute invasion depth into the submucosa of $\leq$1000 μm. Although tumour budding, isolated cancer cells seen in normal tissue at margin of tumour growth, is not included in

the criteria, it is an independent predictor of lymph node metastasis [19, 101–103] and may be considered in treatment decisions. Colorectal adenocarcinoma with low-risk features, including complete resection, may be considered for endoscopic therapy alone; however, it is our recommendation that all such patients be discussed at a multidisciplinary meeting and that meeting recommendations, relevant risks and benefits to such a strategy be discussed with the patient. Although size is not a predictor of lymph node metastases (LNM) or grade [104] smaller lesions are more amenable to en bloc resection, the preferred ER technique for lesions with SM invasion. Whilst patients with lesions which fall into the high-risk category may occasionally elect to be managed endoscopically, careful follow-up is required. Evidence suggests that the rectal lesions are at greater risk for recurrence [105].

Outcomes of WF-EMR and Comparison with Alternative Treatments

WF-EMR of AMN is effective with an acceptable safety profile, when performed by appropriately trained proceduralists in tertiary centres. Large prospective multicentre studies of WF-EMR for colonic AMN are limited. These provide the best evidence to gauge technical success, short- and long-term efficacy and complication rates. Most studies are retrospective without true intention to treat case accrual methodology; thus, subject to selection bias [106–109]. The largest prospective multicentre observational study on WF-EMR with more than 470 patients reported that over 90% of patients referred for resection can be managed endoscopically with a low rate of complications which are mostly managed without the need for surgery [15]. This group has recently reported long-term follow-up data in a cohort of 940 patients. At 12 months 97% of patients are free of disease and surgery is rarely required for persisting disease [110]. Although recurrence was seen in 15–20%, it is usually unifocal, diminutive and managed endoscopically at initial surveillance [15]. ER remains the predominate technique for endoscopic removal of large (>20 mm) lesions in the Western countries with shorter procedure times, lower risk of serious complications and easier training requirements compared with endoscopic SM dissection (ESD) [111]. The primary advantage of ESD over ER is a higher en bloc histopathologically complete (R0) resection rate of approximately 80%, with a corresponding lower recurrence rate [112–116]. This is balanced, however, by routine multi-day post-procedural hospital stay and a higher risk of perforation [112, 113]. The potential for R0 resection is most relevant for known or suspected early colorectal cancer cases to be managed with endoscopic intent [21, 27]. Endoscopic management of early colorectal cancer is not well established in the West however and therefore the benefit of ESD in surgically fit patients is limited [111].

Laparascopic colorectal surgery has demonstrated superior short-term post-operative outcomes for length of hospital stay, pain scores, blood loss and equivalence in rates of recurrence and cancer-related survival when compared to open surgery [117–122]. However, morbidity, cost and length of hospital stay remain higher than that of endoscopic treatment of colonic AMN, with a predicted difference of approx-

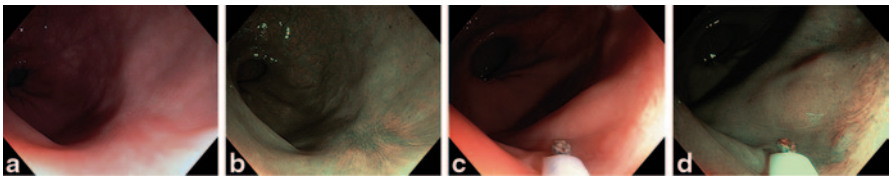

Fig. 10 WFEMR scar at surveillance under high definition WL and NBI. **a** and **b** Healthy scar without residual polyp. **c** and **d** Scar with diminutive focus of residual adenoma (to the *right* of the snare tip)

imately 6 days hospital stay and approximately US$ 10,000 per patient [15, 123, 124]. A significant mortality benefit is also seen in endoscopic treatment when modelling using the Colorectal Physiologic and Operative Severity Score for Enumeration of Mortality and Morbidity (CR-POSSUM) and Association of Coloproctology of Great Britian and Ireland (ACPGBI) scores was applied in a large prospective multicentre AMN cohort [125]. Surgical management of polyps remains prevalent; however, [126] as does surgical referral, as selected surgical units report that up to two-thirds of polyps referred for surgery ultimately can be removed endoscopically when colonoscopy is repeated [127, 128]. Surgical management of endoscopically resectable polyps exposes patients to unnecessary risk and health funding to unnecessary costs and thus, should be minimised. Guidelines have previously stated that lesions <20 mm in size should not be referred for surgery without attempt at ER or documentation of challenges to resection [129]. As selected AMN has low rates of SM invasions at even great size and may be completely removed endoscopically [15] lesion size alone is not a justifiable indication for surgical referral, rather systematic interrogation of colonic lesions and consideration of recognised risk factors for resection failure should, guide this decision. Regarding rectal lesions, non-randomised retrospective comparison of ER and TEM demonstrate greater safety and shorter hospital stay with ER however given the propensity for recurrence equivalence of polyp clearance is not seen until 6 months after follow-up ER [130].

Surveillance

The surveillance interval is based on polypectomy technique and histology. For en bloc resections of lesions 20–25 mm with clear margins histologically, a follow-up examination at 12 months may be appropriate. For lesions, resected piecemeal early surveillance is required due to the risk of residual tissue and polyp recurrence. Initial surveillance should be performed at 4–6 months. An assessment of the scar should entail careful inspection with a high definition colonoscope including retroflexion views as appropriate. Systematic assessment of the margin, where residual tissue appears more commonly, and the central area is essential. A transition point in the surface pattern (either microvascular or pit pattern) is an endoscopic clue for residual disease and should be actively sought (Fig. 10). A normal endoscopic

appearance and negative biopsy of the scar is predictive of long-term eradication [131]. Subsequent surveillance interval is at a further 12 months (i.e., 15–18 months after resection).

Training

No specific training guidelines exist for WF-EMR in contrast advanced endoscopic procedures such as endoscopic ultrasound or endoscopic retrograde cholangiopancreatography. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend that training in advanced endoscopic procedures has to be commenced after completion of basic endoscopy and colonoscopy training requirements. Although WF-EMR represents an extension of basic snare and injection skills gained during general endoscopic training, the specific challenges and techniques in managing large lesions and complications of therapy requires further experience and dedicated training. We feel that this is best obtained within centres with a high volume of referred complex lesions under the direct supervision of an experienced proceduralist.

Referral Pathways

As AMN is relatively uncommon in patients undergoing routine colonoscopy and specific skills, techniques and endoscopy unit setup are required for endoscopic management, we recommend the development of an advanced resection network [123]. At referral to the service a detailed colonoscopy report ideally describing the morphology and the site of the lesion with the addition of colour images aids in assessing the suitability for endoscopic treatment.

Future Directions

WF-EMR has advantages over both ESD and surgical management of AMN though recurrence and bleeding remain therapeutic challenges. Improving en bloc resection size for WF-EMR will allow expansion of endoscopic treatment of lesions with SMI and reduce recurrence. Hybrid ESD/EMR techniques have the potential to improve en bloc resection size whilst maintaining low procedure times [132–135]. Advances in technology miniaturisation may allow robotic assisted resection to enter routine practice [136]. Novel injectates are under investigation to provide superior focal and sustained mucosal elevation and drug delivery [137]. Reduction in post-polypectomy bleeding remains a priority with research into topical treatments [138] and closure of the resection site [139]; however, currently available closure devices are limited by the size of the defects at WF-EMR necessitating novel closure device

development. As novel treatment advancements enter endoscopic practice focus on maintaining WF-EMR as a safe and effective, the outpatient treatment must remain a priority.

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