Novel gastrointestinal procedures

Wladyslaw Januszewicz
Massimiliano di Pietro

Abstract

Over the last 20 years, a large proportion of research in the field of gastroenterology has focused on improving endoscopic imaging and developing minimally invasive therapy for benign and malignant conditions. Both conceptually and practically, these avenues advance concomitantly: refinement of endoscopic imaging leads to earlier diagnosis, and a growing number of endoscopic treatment modalities can be offered. In addition, preventive medicine has triggered studies on the natural history of premalignant conditions, aiming to define the boundaries for early therapeutic intervention. Endoscopic therapy plays a key role in the treatment of pre-cancerous and early cancerous conditions of the gastrointestinal (GI) tract, for which it has been increasingly replacing conventional surgical approaches, with improved tolerability and comparable or better outcomes. Simultaneously, the rising global burden of obesity and its complications has opened a new interventional area in endoscopy. Endoscopic approaches for the treatment of obesity, gastro-oesophageal reflux disease and diabetes have emerged in recent years. In this review, novel GI procedures for the diagnosis and treatment of common GI or GI-related conditions are illustrated. These are at different stages of introduction into routine practice but are likely to have a significant impact on patient management in the near future.

Keywords Barrett's oesophagus; biliary tract neoplasms; colorectal neoplasms; diabetes mellitus; diagnostic imaging; early detection of cancer; gastro-oesophageal reflux; gastrointestinal haemorrhage; image quality enhancement; MRCP; obesity; oesophageal motility disorders

Key points

- Blue laser imaging is a new virtual chomoendoscopic technique that may allow better characterization and detection of early gastrointestinal (GI) neoplasia
- The wireless motility capsule technique combines endoscopy with functional assessment of GI motility, representing an interesting new area of research in GI physiology
- Computer-aided detection in real-time classification of neoplastic lesions during endoscopy will hopefully assist endoscopists in identifying and delineating early GI neoplasia
- New evidence on minimally invasive alternatives to conventional antireflux surgery for gastro-oesophageal reflux disease (Linx®, EsophyX®) supports their routine use in the near future
- New endoscopic modalities for the treatment of type 2 diabetes and obesity are in different stages of clinical validation but are likely to become valid alternatives to existing medical and surgical interventions
- Gastric per-oral endoscopic myotomy is a new minimally invasive treatment for gastroparesis
- Hybrid argon plasma coagulation and cryotherapy for the treatment of dysplastic Barrett's oesophagus add to the existing endoscopic armamentarium for this condition, particularly for lesions resistant to radiofrequency ablation

Diagnostic procedures

Detection of early cancer and prediction of histological outcome represent the two most common research endpoints in the field of endoscopic imaging. Conventional dye and electronic chromoendoscopy modalities have been extensively studied in both the upper and lower gastrointestinal (GI) tract. To date, however, none has proved superior to conventional high-resolution endoscopy for detecting early neoplasia. Put simply, prolonging the inspection time seems sufficient to increase the yield of detecting colonic polyps, gastric premalignant conditions and 'invisible' dysplasia in Barrett's oesophagus (BO).

Virtual chromoendoscopy

Blue laser imaging (BLI; Fujifilm, Japan) is a new system for image-enhanced endoscopy that uses two monochromatic lasers of different wavelengths. The white light laser (wavelength 450 ± 10 nm) excites phosphors to create white light illumination, and the BLI-mode laser (wavelength 410 ± 10 nm) produces a high-contrast signal highlighting the mucosal surface and its vascular microarchitecture (Figure 1).

To date, most studies on BLI have been performed in the lower GI tract; these have included multicentre randomized controlled trials (RCTs) to assess the utility of BLI for detecting colorectal adenomas. A multicentre RCT comparing BLI colonoscopy ($n = 489$) with standard white light imaging (WLI; $n = 474$) found that a higher mean number of adenomas per patient were identified by BLI than WLI (1.27 versus 1.01, $p = 0.008$).[1] A tandem colonoscopy trial randomizing 127 patients to BLI or WLI, followed by a second WLI colonoscopy, found that the

Wladyslaw Januszewicz *MD is a Research Associate at the MRC Cancer Unit Hutchinson/MRC Research Centre, University of Cambridge and an Honorary Endoscopy Clinical Fellow in the Gastroenterology Department, Cambridge University Hospitals NHSFT, UK. Competing interests: none declared.*

Massimiliano di Pietro *MD is a Senior Clinical Investigator Scientist at the MRC Cancer Unit, University of Cambridge and Honorary Consultant Gastroenterologist at Cambridge University Hospital, UK. His research focuses on advanced endoscopic imaging for detection of early neoplasia, endoscopic treatment of pre-neoplastic and early upper gastrointestinal cancer. Competing interests: educational grants from Covidien and Olympus/KeyMed, and Mauna Kea Technologies.*

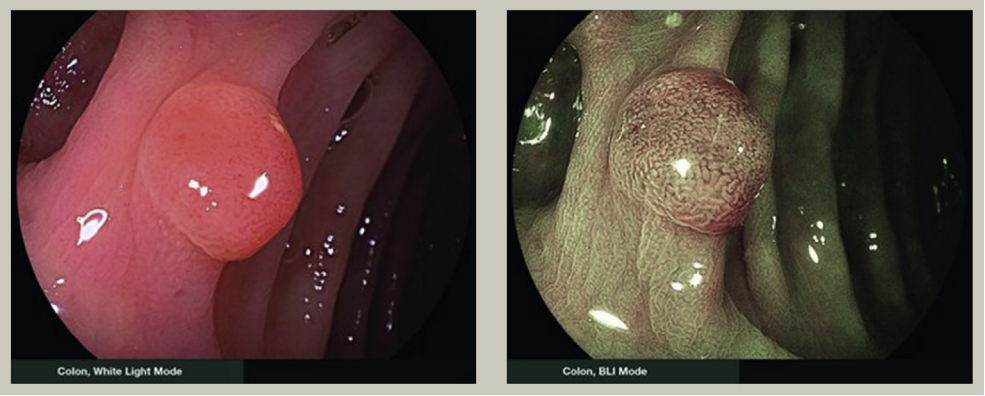

Figure 1 High-resolution WLI (left) and BLI (right) showing a colonic polyp. Image credit: Dr J Weight from the University Hospital of Magdeburg. Reproduced from Fujifilm with permission.

adenoma miss rate in the BLI group (1.6%) was significantly lower that in the WLI group (10.0%, $p = 0.001$).

The utility of BLI in the upper GI tract has also been investigated. The most recent tandem RCT examined 629 patients with known atrophic gastritis or previous endoscopic resection of early gastric cancer. BLI endoscopy had a significantly higher detection rate of early gastric cancer (93.1%) than WLI endoscopy (50.0%, $p = 0.001$). Because the afore-mentioned studies were carried out in an Asian population, validation of these promising results is warranted in Western cohorts.

Video capsule endoscopy (VCE)

VCE has a well-established role in the investigation of small bowel in obscure GI bleeding, with more recently proposed indications for the assessment of coeliac disease, small bowel tumours and hereditary polyposis syndromes. New VCE models adapted for evaluation of the oesophagus (PillCam™ ESO, Given Imaging, Israel) and the colon (PillCam™ COLON, Given Imaging) have been introduced. However, large prospective studies are required to assess the diagnostic accuracy of oesophageal and colon capsule endoscopy and provide information on how current diagnostic pathways can be improved using minimally invasive endoscopic examinations.

There is currently interest in combining endoscopy and motility assessments in a single test. Initially, attempts were made to characterize small intestine motility by analyzing the luminal image patterns from VCE video recordings. More recently, however, a wireless motility capsule (WMC; SmartPill™, Given Imaging) was introduced, which does not provide luminal images, however, uses pH, temperature and pressure measurements to evaluate both gastric emptying and transit times in the small bowel, colon and whole gut.[2] In a recent study, a WMC test was performed in a group of 100 patients with diabetes. The WMC evaluation showed evidence of GI dysmotility in 72% of patients, of whom 40% demonstrated multiregional involvement of the dysmotility. WMC testing led to treatment modification in 24 patients from this cohort (73%). Pharmacological interventions included treatment with various prokinetic agents, with the highest treatment response noted for linaclotide (64%) and the lowest for metoclopramide (19%).

Computer-aided detection (CAD)

In the attempt to detect lesions at the earliest possible stage, high-resolution endoscopes have been developed in conjunction with high-definition monitors and optical magnification. This generates an increasing amount of information, which challenges the human ability to interpret imaging data. To overcome this problem, a growing body of research is aiming to develop CAD systems that could help endoscopists to extract information from complex images. CAD is based on algorithms that, after a dedicated process of machine learning, can automatically recognize image patterns, such as an abnormal vascular pattern of the GI mucosa or subtle changes in the appearance of the mucosa.

For example, a CAD system with a deep neural network system (DNN-CAD) was used to differentiate neoplastic from hyperplastic colonic polyps. In this study, >2000 images of adenomas and hyperplastic polyps were used to train the system. After the machine learning process, an independent selection of 300 hyperplastic and neoplastic diminutive polyps (diameter <5 mm) was used to test the CAD system as well as a group of six endoscopists (two experts, four trainees). The DNN-CAD system was able to differentiate neoplastic from hyperplastic polyps with a sensitivity of 96.3% and a specificity of 78.1%. The sensitivity and specificity of the endoscopists varied between 81.9% and 96.3%, and 65.6% and 88.5%, respectively. The DNN-CAD system had a shorter time to classification than the endoscopists and a perfect intraobserver agreement (kappa score = 1).

More recently, CAD technology has been introduced for the detection of oesophageal neoplasms of both squamous and glandular origin, with sensitivity ranging between 84% and 87%, and specificity between 84% and 97%. Lastly, CAD technology was combined with capsule endoscopy to be used in detecting vascular malformations within the small intestine. In a recent study using two datasets of still frames (600 normal images and 600 GI angiectasia's), the machine learning algorithm based on a convolutional neural network could identify GI angiectasia's with a sensitivity of 100% and a specificity of 96%. A retrospective design and small cohort of patients are, however, main limitations of this study.

This is an exciting field of research stemming from collaborative work between the areas of medicine and mathematics, but

it remains to be seen how CAD will be able to assist endoscopists in daily practice.

Functional oesophageal lumen imaging probe

In the last decade, high-resolution manometry has provided fundamental insights into the dynamic function of the oesophagus, with practical clinical impact in the management of oesophageal motor disorders.

More recently, a novel functional lumen imaging probe – FLIP™ (Crospon, Ireland) – has been developed that could offer an additional tool for morphological and functional characterization of the oesophagus. FLIP™ consists of a 24 cm long catheter with a balloon mounted on the distal end, which measures the mechanical properties of the oesophagus using volume-controlled distension. The pressure is applied with a fluid-filled bag equipped with high-resolution impedance planimeters that measure multiple cross-sectional areas of pressure along the axial plane. The main advantage of FLIP™ is that it provides a measurement of the distensibility of the oesophago-gastric junction (OGJ), and simultaneously obtains information on the contractile activity and distensibility of the oesophageal body. Hence, FLIP™ is an additional test for the diagnosis of achalasia, but could also be potentially useful in the assessment of GOJ distensibility in gastro-oesophageal reflux disease (GORD), and of oesophageal wall stiffness in eosinophilic oesophagitis.

Research studies have shown that the measurements of OGJ distensibility by FLIP™ in achalasia patients correlated with symptom severity and could guide prediction of the response to endoscopic treatment. In a recent study of 54 achalasia patients (treatment naive, $n = 23$; poor treatment response, $n = 14$; good treatment response, $n = 17$) and 20 healthy volunteers, the OGJ distensibility indices were significantly different between the four groups, and the OGJ distensibility index (defined as the 'waist' of the FLIP™ bag during volumetric distension, expressed in mm^2/mmHg) was greatest in the control subjects and lowest in the participants with untreated achalasia. Further research is required to clarify indications for using FLIP™ in the diagnosis of oesophageal motor disorder and the clinical advantage of using it in other oesophageal pathologies.

Therapeutic interventions

Treatments for GORD

GORD is the most common GI diagnosis in an outpatient setting, and proton pump inhibitors (PPIs) are the mainstay of its medical management. As many as 30% of patients have an incomplete response to PPIs because these medications do not resolve the main pathophysiological cause of GORD, which is incompetence of the lower oesophageal sphincter (LOS). Laparoscopic antireflux surgery is traditionally indicated in these patients, as well as in those who are intolerant of PPIs or seek a definitive solution for a hiatus hernia. Several new, minimally invasive procedures aim to resolve LOS incompetence, including the LINX® and EsophyX® devices. These were reviewed in the previous article published in this journal (see Medicine 2015: 43:**6**. pages 341–346) and we report here only new evidence in support of some of them.

LINX® (Torax Medical, USA) is a magnetic sphincter augmentation (MSA) device that consists of a flexible band of magnetic beads connected by small wires that is placed laparoscopically around the LOS. A multicentre RCT of 152 GORD patients with moderate to severe regurgitation despite 8 weeks of PPI therapy showed symptom relief in 89% of patients treated with MSA versus 10% of patients in the PPI group ($p < 0.001$), while GORD health-related quality-of-life scores improved by at least 50% in 81% of participants, compared with 8% in the control group ($p < 0.001$). Most importantly, 91% of patients treated with MSA remained off PPI therapy. Although no serious adverse events were reported in this trial, longer follow-up studies are required as intraluminal migration has been reported in three cases.

EsophyX® (Endogastric Solutions, USA) is an endoscopic device to perform trans-oral incisionless fundoplication (TIF). It repositions the LOS in its normal anatomical site by fixing it to the fundus. In a primary RCT of 63 patients with GORD comparing EsophyX® with a high-dose PPI, both interventions corrected the oesophageal acid exposure at 6 months in just over half the patients, but EsophyX® was more effective at controlling symptoms (97% versus 50%, $p = 0.006$).[3] No significant long-term adverse effects were reported. A recent meta-analysis summarizing 32 studies involving 1475 patients with refractory GORD showed that hiatus hernia reduction could be achieved in 91% of the patients treated with the TIF technique, with an adverse event rate of 2%.

New endoscopic therapeutic modalities for obesity

With the increasing global burden of obesity and its complications, new minimally invasive treatments have been investigated. The first attempts at endoscopic weight management were undertaken in the early 1980s with the introduction of endoscopically placed intragastric balloons (IGBs). Since then, several improvements have had to be made to avoid adverse events, such as gastric mucosal damage and migration into the small bowel. IGBs promote weight loss in obese patients by partially filling their stomach and inducing a sense of early satiety.

Orbera® intragastric balloon (Apollo Endosurgery, USA) is a new-generation elastic spherical balloon made of silicone, filled with 450–700 ml of sodium chloride solution. The deflated balloon is advanced trans-orally into the stomach on a catheter over a guidewire and then filled with sodium chloride under direct endoscopic supervision. In a retrospective study assessing the efficacy of the Orbera® balloon in 321 obese patients, this intervention achieved an 8.5% body weight reduction at 3 months, 11.8% at 6 months, and 13.3% at 9 months. An improvement in lipid profile, glycated haemoglobin (HbA_{1c}) concentration, and systolic and diastolic blood pressure was also achieved at 6 months after IGB placement.

Endoscopic sleeve gastroplasty is an incisionless, minimally invasive bariatric procedure that reduces the volume of the stomach by inserting full-thickness stitches that bring together opposite gastric walls. This procedure is usually performed using a double-channel therapeutic endoscope equipped with an overstitch endoscopic suturing device (Apollo Endosurgery, USA). In a prospective single-centre study, this technique induced an average 14.4% reduction of total body weight at 6 months, 17.6% at 12 months, and 20.9% at 24 months. Moreover, at 12 months after endoscopic sleeve gastroplasty, patients had a significant reduction in HbA_{1c} concentrations and an

improvement in systolic blood pressure, waist circumference and lipid profile. There was one (1.1%) serious adverse event (perigastric leak), which was managed non-operatively.

Gastrointestinal interventions for diabetes

The duodenal mucosa is equipped with endocrine cells, which produce a variety of incretin hormones to regulate insulin secretion in response to meals. In diabetes, the duodenal mucosa exhibits abnormal hypertrophy and endocrine hyperplasia, which leads to abnormal hormonal signalling and insulin resistance. It is known from surgical series that Roux-en-Y gastric bypass, which excludes contact of the duodenum with ingested food, improves insulin tolerance.

Duodenal mucosal resurfacing (DMR) is a new endoscopic treatment of diabetes that is based on hydrothermal ablation of the duodenal mucosa to allow re-epithelialization with normal duodenal mucosa. DMR uses a 3 cm balloon catheter that delivers circumferential thermal ablations along a variable length of the duodenum (up to 12 cm). The first-in-human trial on 39 patients with type 2 diabetes showed a reduction in HbA_{1c} of 1.2% at 6 months of follow-up after this procedure.[4] Overall, DMR was well tolerated, with minimal gastrointestinal symptoms. Three patients experienced duodenal stenosis that was successfully treated by balloon dilation. Although it appears promising, larger studies with longer follow-up are awaited to draw conclusions on the long-term efficacy and safety of this treatment.

Another approach includes endoscopic duodenal bypass through placement of a duodenal-jejunal sleeve device - EndoBarrier® (GI Dynamics, US, which acts as an impermeable barrier to nutrients (Figure 2). In practical terms, this creates a functional bypass from the stomach into the proximal jejunum, excluding the duodenal mucosa from contact with food. A single-centre retrospective study with >7 years of follow-up of 152 patients with type 2 diabetes and obesity showed that significant GI symptoms were noted in nearly half the patients, leading to early removal of the device in 16 (10%). Of the 152 patients given the device, 11 had serious adverse events, which included seven cases of GI bleeding, two mild cases of pancreatitis, one hepatic abscess requiring intravenous and oral antibiotic therapy, and two cases of oesophageal perforation during device removal (the removal system has since been modified). An ongoing multicentre RCT comparing the EndoBarrier® with conventional medical therapy for the treatment of type 2 diabetes and obesity might provide more adequate data on the safety and feasibility of this device. Until then, its use outside clinical trials is not recommended.

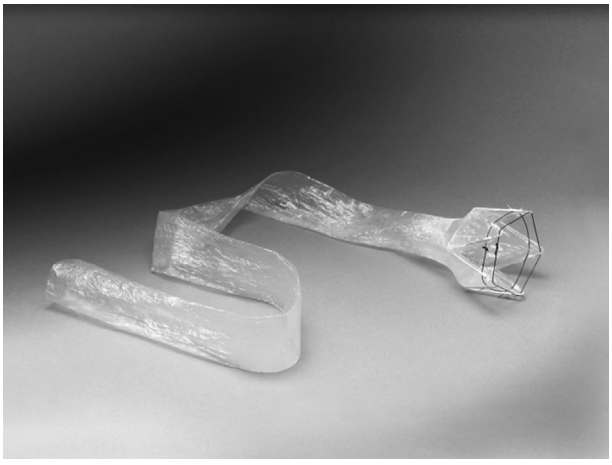

Figure 2 EndoBarrier® gastrointestinal bypass liner. Reproduced from GI Dynamics (http://www.gidynamics.com/index.php) with permission.

Endoscopic therapy for motility disorders

POEM: originally described in 2008 in Japan for the treatment of achalasia, per-oral endoscopic myotomy (POEM) has now been performed in several thousand patients, mostly in East Asia but increasingly in Western countries. This technique involves three steps; (1) submucosal tunnelling; (2) longitudinal dissection of the oesophageal muscle layer from the mid-third of the oesophagus down to the OGJ; and (3) clip closure of the tunnel entry to seal the mucosal defect. However, despite widespread use in the far East and increasing adoption in many Western institutions, RCTs are still lacking.

A recent meta-analysis assessing the efficacy of POEM versus laparoscopic Heller's myotomy (LHM) showed that POEM is slightly more effective than LHM in relieving dysphagia at 2 years in patients with achalasia (92.7% for POEM, 90.0% for LHM; $p = 0.01$). However, another meta-analysis showed that LHM is associated with less symptomatic reflux than POEM (8.8% versus 19.0%), a lower incidence of oesophagitis (7.6% versus 29.4%) and a lower incidence of pathological oesophageal acid exposure (16.8% versus 39.0%). POEM remains a very attractive endoscopic treatment for achalasia and possibly other oesophageal motility disorders, such as diffuse oesophageal spasm and nutcracker oesophagus; RCTs are underway to provide definitive evidence from comparing it with surgical treatment.

Gastric per-oral endoscopic myotomy (G-POEM): with a similar approach, G-POEM has recently been proposed as a treatment for gastroparesis. The steps of G-POEM are similar to those of POEM. A recent prospective trial in 20 patients with refractory gastroparesis (10 diabetic, 10 non-diabetic) showed that G-POEM significantly improved patients' symptoms, quality of life and gastric emptying (measured using 4-hour scintigraphy) at 3 months after the procedure. Even though the evidence for G-POEM is still sparse, given the lack of effective treatments for gastroparesis this new technique represents a promising opportunity to improve the therapeutic armamentarium for this complex disease.

Endoscopic therapy for gastrointestinal precancerous conditions and early cancer

Advances in resection techniques: over the last 20 years, endoscopic mucosal resection and endoscopic submucosal dissection have revolutionized the therapy of early neoplasia in the GI tract, moving a large proportion of patients from surgical treatment towards minimally invasive endoscopic treatment. However, some localized epithelial and most subepithelial lesions are not amenable to conventional resection techniques. Endoscopic full-thickness resection (EFTR) represents a paradigm shift in the treatment of such lesions in the GI tract. It includes at least three different techniques: clip-assisted-EFTR, exposed EFTR and non-exposed or neo-EFTR. For the purpose of this review, only the former will be discussed.

Clip-assisted-EFTR relies on the 'close then cut' principle, whereby an over-the-scope (OTS) clip is first placed around the tissue of interest, securing the defect, before the full-thickness resection is performed. The OTS clip is advanced to the target lesion, which is then retracted into the cap using a dedicated tissue retraction device (OTSC® Anchor, Ovesco Endoscopy, Germany) or grasping forceps; this is followed by clip deployment. The pseudopolyp of tissue created by the clip is then resected using an electrosurgical snare (Figure 3). This technique is particularly useful in resecting non-lifting epithelial lesions, such as adenomas embedded in severe fibrosis from prior resection attempts, as well as small subepithelial lesions (<1 cm in the upper GI tract, <2 cm in the colorectum), including neuroendocrine tumours and gastrointestinal stromal tumours.

The efficacy and safety of clip-assisted EFTR was first assessed in a case-series of nine patients with subepithelial lesions in the duodenum ($n = 4$), rectosigmoid colon ($n = 2$) or stomach ($n = 1$), or appendiceal orifice polyps ($n = 2$). The mean procedure time was 53 ± 21 minutes, and the mean size of the resected specimens was 11 ± 3 mm R0 resection was achieved in all cases. Subsequently, a large European prospective multicentre trial involving 181 patients with colorectal lesions up to 3 cm in diameter showed that the R0 resection rate could be reached for 81.2% of lesions <2 cm, although this fell to 58.1% for lesions >2 cm in size ($p = 0.0038$). The rate of adverse events was approximately 10%, and these included six perforations, four instances of bleeding, three cases of appendicitis, three post-polypectomy syndromes, one enterocolic fistula and one case of abdominal pain. Prospective comparative studies are needed to assess long-term efficacy and safety of EFTR.

Advances in ablation techniques

The advent of radiofrequency ablation (RFA; Barrx™, Medtronic, US) has revolutionized the management of BO with dysplasia. An impressive number of prospective studies, including two RCTs, have shown rates of eradication of B0 >90% and set the bar high for novel ablative modalities trying to make their way into clinical practice. New applications for RFA are currently being investigated, including gastric antral vascular ectasia, radiation proctitis and symptomatic inlet patches.

One of these techniques is hybrid argon plasma coagulation (Hybrid-APC), an evolution of the standard APC technique, developed for ablation of flat areas of BO. In animal studies, the combination of APC with prior submucosal injection reduced the coagulation depth by half in comparison with standard APC; this has potential benefits in terms of the safety profile, particularly in relation to the risk of stricture. One of the first studies performed involved 60 patients with a residual BO segment of at least 1 cm after endoscopic resection of early Barrett's neoplasia; this showed that 48 out of 50 patients (96%; intention-to-treat 49/60, 82%) achieved macroscopically complete remission after a median of 3.5 Hybrid-APC sessions (10 patients being excluded from the study). There was only one treatment-related stricture (2%). A recent pilot RCT comparing Hybrid-APC with RFA showed that the two techniques had similar rates of eradication at 12 months and adverse events; however, Hybrid-APC had a more favourable cost profile.

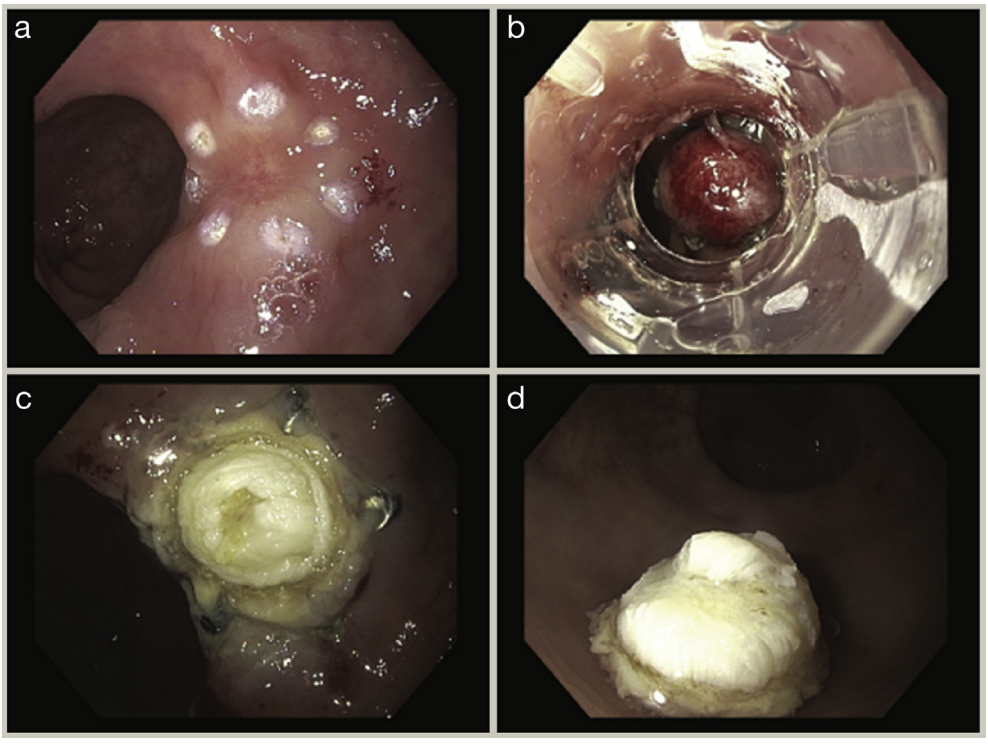

Figure 3 2. OTS clip-assisted EFTR. **(a)** Incompletely resected, scarred, neuro-endocrine tumour outlined with argon plasma coagulation dots. **(b)** The lesion, a pseudopolyp above a deployed OTS clip. **(c)** The post-resection appearance, and **(d)** the resected specimen in one piece. Reproduced from Rajan E, Wong Kee Song LM. Endoscopic full-thickness resection. *Gastroenterol* 2018; **154**(7): 1925–37, with permission from Elsevier.

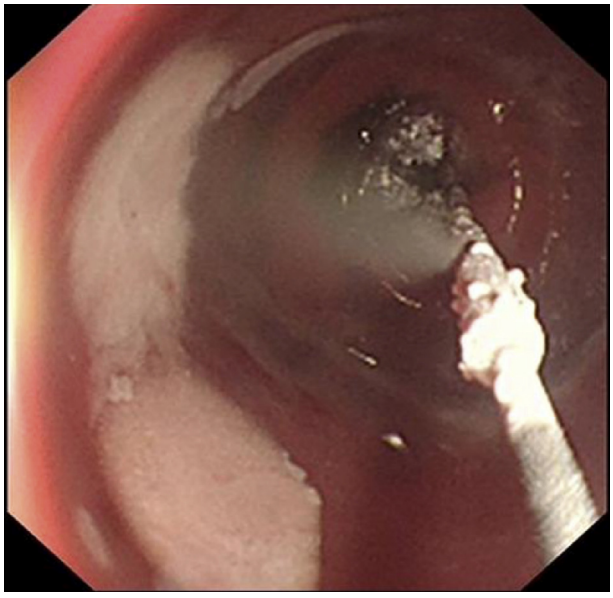

Figure 4 Endoscopic image presenting spray cryotherapy.

Cryoablation represents an additional alternative to RFA. Different cryoablation devices are now available. Liquid nitrogen spray cryotherapy (LNSCT) uses liquid nitrogen at a temperature of −196°C topically applied through a low-pressure spray catheter to the oesophageal mucosa (Figure 4). LNSCT has been shown in small retrospective studies to be a safe, well-tolerated and effective therapy for BO-associated high-grade dysplasia; complete eradication of dysplasia occurred in 82−100% of cases, and eradication of intestinal metaplasia in 70−81%. A second cryoablation system employs a balloon inflated in the oesophagus and uses a nitrous oxide gas spray to freeze targeted mucosa in contact with the balloon to −85°C. In a recent prospective, multicentre study, the cryoballoon ablation system was assessed in the treatment of 41 patients with dysplastic BO.[5] Complete eradication of dysplasia was achieved in 95% of individuals and complete eradication of intestinal metaplasia in 88% 1 year after the procedure. Four patients (9.7%) developed mild dysphagia from stenoses that required dilation. ◆

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