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CLINICAL PERSPECTIVES

Advances in gastrointestinal endoscopy

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Key words
gastrointestinal endoscopy, endoscopic imaging, endoscopic resection, endoscopic ablation, endoscope development.

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Abstract

Gastrointestinal endoscopy has undergone a remarkable expansion in its capabilities as a result of sophisticated technological advances in recent years. New imaging technologies, novel ablation and resection techniques, cutting-edge endoscope development and creative extraluminal applications have taken gastrointestinal endoscopy to an exciting new level. An update on some of these advances is presented for the physician audience.

Introduction

Endoscopy remains an essential complement to the clinical management of patients with gastrointestinal disorders. Recent technological advances have broadened the horizons of possibility for endoscopic therapies. Several recent advances that may be encountered by the general physician audience are reviewed here.

Advances in imaging

Standard endoscopy uses white light to provide images of the gastrointestinal tract mucosa. Image-enhanced endoscopy has evolved over the past decade with the development of several modalities to increase the amount of visual data above what can be obtained with white light alone.

Four main techniques have been developed: (i) high resolution and magnification white light endoscopy; (ii) contrast enhancement; (iii) *in vivo* histology; and (iv) autofluorescence.

High resolution and magnification endoscopy

High-resolution images can now be achieved with endoscopes containing new generation charge-coupled devices (CCD), which allow the capture of more than a million digital pixels, as compared with conventional endoscopes that capture around 300 000 pixels. This increase in resolution improves image quality and results in better discrimination of detail. The application of this new CCD technology has important clinical implications – previously, dysplastic changes in Barrett's oesophagus were essentially endoscopically 'invisible', making random biopsy protocols the only way to detect abnormalities. However, high-resolution endoscopes now make it possible to specifically target biopsies of endoscopically visible abnormalities within Barrett's segments, with detection rates of up to 80% of the lesions present.[1,2]

Magnification results in enlargement of images, without necessarily increasing resolution. The new generation magnification endoscopes have an adjustable focusing mechanism that enables enlargement of the image size from 1.5 to 150 times.[3] As some mucosal abnormalities, such as intestinal metaplasia, are translucent, the addition of a tissue stain to magnification endoscopy can improve visualisation. Again, one of the major roles of these visualisation enhancements is to improve the targeting of biopsies to areas containing dysplasia: several studies suggest that this can be achieved accurately with magnification endoscopy, whereas others do not.[4,5] Most likely, it is operator-dependent, with the best results being achieved within expert centres.

Contrast enhancement

Contrast enhancement can be achieved either by applying stains or pigments to the mucosa (dye-based), or increasing the amount of blue light present by the use of a filter (equipment-based). Both techniques permit improved tissue characterisation.

Dye-based techniques

A variety of stains exists with differing mechanisms of action: absorptive stains (Lugol's iodine and methylene blue) diffuse or are absorbed across cell membranes; contrast stains (indigo carmine) define mucosal crevices to highlight surface topography and mucosal irregularities; and reactive stains (Congo red) undergo chemical reactions with various cellular components causing a colour change. These dye techniques have been demonstrated to improve the detection of lesions within conditions, such as Barrett's oesophagus[6] and ulcerative colitis.[7] However, while these techniques possess certain advantages, such as being cheap and readily available, they are time-consuming and suffer from poor reproducibility.

Equipment-based techniques

Narrow band imaging (Olympus Corporation, Tokyo, Japan) is the prototype example – it preferentially enhances the blue and green components of a digital image. This makes vascular structures dark, and therefore more easily detected. As abnormal tissue has increased vascularity and alterations in the morphology of its microvasculature,[8] these tend to stand out from surrounding normal tissue (Fig. 1). Narrow band imaging (NBI) has the advantage of being time-efficient, as it can be activated at the touch of a button on enabled endoscopes. Satisfactory data regarding its accuracy exist, particularly in the setting of detecting dysplasia within Barrett's oesophagus.[9–11] A meta-analysis has found the pooled sensitivity and specificity of NBI for detecting high-grade dysplasia within Barrett's mucosa to be 96% and 94% respectively.[12]

In vivo histology

Virtual histology, the ability to visualise histological detail *in vivo* at endoscopy, is an exciting advance in endoscopic technology. The ability to make on-the-spot management decisions based on real-time histology drives the

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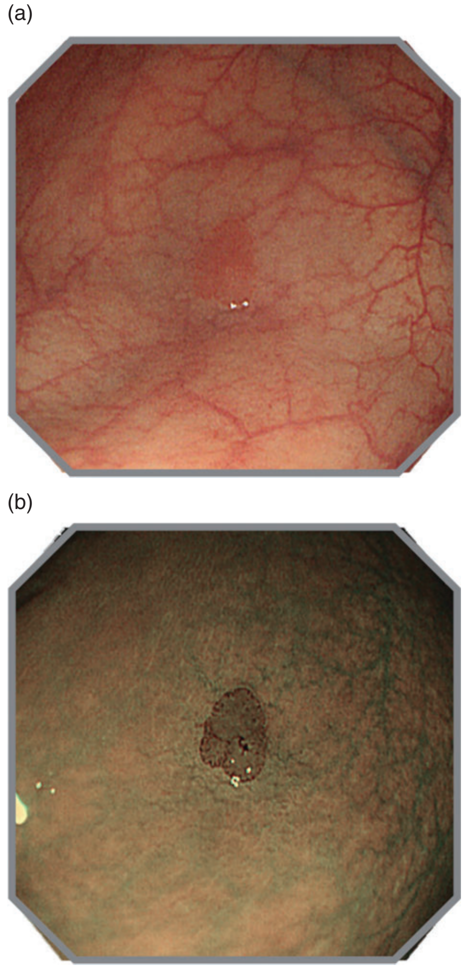

Figure 1 (a) Polyp under standard white light. (b) Polyp under NBI.

evolution of this technique. Confocal laser endomicroscopy (CLE) and endocytoscopy are the two techniques that permit *in vivo* histology.

CLE integrates a confocal laser microscope within the tip of a standard videoendoscope or can be used as a probe passed through the channel of a standard endoscope. The technology uses a laser that penetrates the mucosal surface and illuminates a microthin layer of tissue. The endomicroscope provides 7-μm thick cross-sectional tissue images parallel to the mucosal surface to a depth of 250 μm. The initial clinical trials of CLE found close to 100% accuracy for detecting neoplastic lesions at surveillance colonoscopy.[13,14] Subsequently, other disorders have been studied with CLE, including Barrett's oesophagus,[15,16] gastric adenocarcinoma[17] and oesophageal squamous cell carcinoma.[18] Overall, reported results are very good, with accuracy rates often greater than 90%. However, it should be noted that the patients were highly selected and the studies were performed in expert centres.

Endocytoscopy is based solely on high-level magnification using optical lenses. Therefore, because of a lack of a confocal plane, only the most superficial mucosal layer can be imaged and the lens must come into direct contact with the tissue. The development of endocytoscopy devices has not been as rapid and prolific as for the CLE technology, and less data have been published. It is likely that CLE will surpass endocytoscopy in this field of technological advancement.

Autofluorescence

Autofluorescence uses natural tissue fluorescence emitted by endogenous molecules (fluorophores), such as collagen, flavins and porphyrins. After excitation by a short wavelength light source, the fluorophores emit light of longer wavelengths (fluorescence). The total fluorescence emission differs between tissue types due to differences in fluorophore concentration, metabolic state and/or spatial distribution. The colour differences in fluorescence emission can be demonstrated in real time during endoscopy and provide a basis for differentiation between normal and abnormal tissue.

Initial studies demonstrated that neoplastic lesions within the colon could be accurately detected by virtue of the longer wavelength autofluorescence emitted in comparison to surrounding normal tissue.[19,20] However, it subsequently became apparent that the relatively inferior resolution of this technology, among other shortcomings, limited its utility as a stand-alone technique. The recent coupling of autofluorescence with other forms of image enhancement now offers a multimodal technique that addresses these limitations. Olympus Corporation have developed a trimodal imaging system consisting of autofluorescence followed by NBI with magnification – this has significantly improved the accuracy of Barrett's neoplasia detection,[21] as well as increased the diagnostic yield of neoplasia detection in screening of patients with ulcerative colitis.[22] Accurate results have also been found in the analysis of colonic polyps.[23]

Advances in ablation

Once neoplastic tissue has been detected through the above imaging enhancement technologies, eradication of the tissue using minimally invasive techniques is a highly sought-after goal. While surgery remains the definitive curative treatment option, it may be associated with significant morbidity and mortality. Therefore, endoscopic ablation techniques represent an important technological advance.

Three major advances have been made in this arena in recent years: (i) radiofrequency ablation (RFA), (ii) argon

Figure 2 Radiofrequency ablation catheter, HALO^{360} (BARRX Medical Inc. Sunnyvale, CA, USA).

plasma coagulation (APC) and (iii) cryotherapy. All of these techniques represent important treatment options for treating premalignant lesions in a non-surgical fashion, with the major application being for Barrett's oesophagus.

Radiofrequency ablation

RFA is the most significant advance in this field. RFA applies an alternating electrical current to tissue through an electrode array. This current creates an electromagnetic field, causing electrons and other charged ions to oscillate and create molecular friction, thereby resulting in a rapid rise in tissue heat and subsequent injury. A commercially available RFA system for oesophageal treatment is produced by BARRX Medical Inc (Sunnyvale, CA, USA), the HALO^{360} and HALO^{90} ablation catheters. The HALO^{360} catheter is passed through the working channel of an endoscope and applies a 360-degree treatment to the circumference of the oesophageal wall (Fig. 2). RFA has been demonstrated to be effective for the treatment of both high- and low-grade dysplasia in Barrett's oesophagus. In a randomised sham controlled trial, complete eradication of dysplasia was achieved in 90.5% of low-grade dysplasia patients as compared with 22.7% of controls ($P < 0.0001$), and 81% of high-grade dysplasia patients as compared with 19% of controls at 12 months ($P < 0.0001$).[24] With the ability to use standard endoscopes to employ these single-use catheters, this technology is being increasingly employed and long-term data are being generated.

Argon plasma coagulation

APC uses argon gas as the medium of transfer for electrical current, creating non-contact thermal coagulation of target tissue. The coagulation is delivered by the passage of a probe through the working channel of a standard endoscope. APC is capable of ablating a superficial area of mucosa, although prolonged application can result in deeper tissue injury.[25] Variable results have been reported for APC in the eradication of Barrett's mucosa, ranging from complete ablation rates of over 98% and no relapse at 12 months[26] to ablation rates of approximately 60% and recurrence in approximately half.[27,28] 'Buried Barrett's', the recurrence of intestinal metaplasia beneath squamous reepithelisation, is also a significant problem. For these reasons, APC is not considered to be an adequate stand-alone technique for the long-term destruction of neoplastic tissue.

Cryotherapy

Cryotherapy causes tissue destruction by spraying a cryogen (liquid nitrogen or carbon dioxide) as a gas onto tissue. It can be delivered through a catheter passed into the working channel of a standard endoscope. Cell death is caused by the production of extracellular ice. Current data are limited, with small numbers and short follow-up times, but promising early experiences have been described in the oesophagus, stomach and rectum. Perhaps its most important use is in Barrett's oesophagus. A multicentre retrospective study found a 97% eradication rate for high-grade dysplasia, but 'buried Barrett's' was found in 3%.[29]

Advances in resection

Surgery is the most established curative treatment modality for gastrointestinal tract lesions containing high-grade dysplasia. However, it carries with it significant morbidity and mortality, especially in elderly patients with comorbidities.

Endoscopic resection has evolved significantly in recent years, with sophisticated techniques now permitting even the largest lesions to be endoscopically resected. Resection techniques carry a significant advantage over ablation techniques: histological assessment can be performed on the resected specimen, confirming histological subtype and staging.

Two major technical categories exist: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR refers to the resection of mucosal tissue using a snare, whereas ESD is the direct dissection of the submucosal layer beneath the lesion. An exhaustive review of the techniques is beyond the scope of this publication.

Endoscopic mucosal resection

Three main methods have been developed to facilitate snare resection of abnormal tissue: multiband ligation, cap-assisted, and lift and cut (Fig. 3). Variations of these techniques can be employed at all levels of the

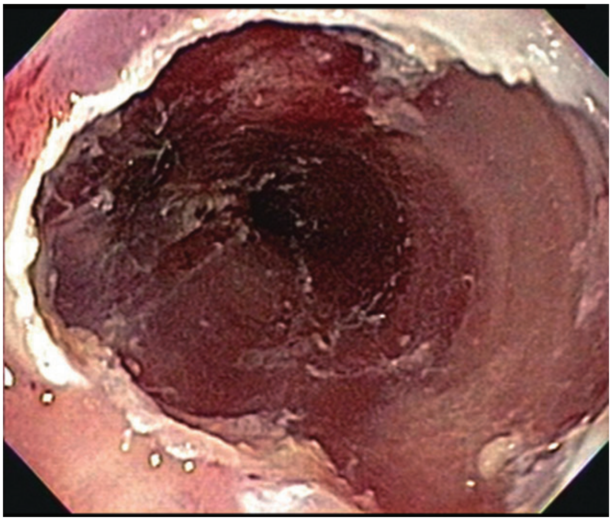

Figure 3 Multiband ligation resection.

gastrointestinal tract. In Eastern populations, the majority of published literature pertains to early lesions in the stomach. In contrast, local data are dominated by the more common Western entity of colonic polyps, with multicentre Australian data demonstrating the success of EMR technique for large laterally spreading tumours.[30]

Endoscopic submucosal dissection

Three main steps form the basis of ESD: injection of fluid into the submucosal plane to elevate the area of abnormality, cutting of the mucosa surrounding the lesion and then dissecting the submucosa beneath the lesion to remove it. It has been developed and refined in Japan where its initial use was for the treatment of early gastric cancer. ESD has subsequently been extrapolated to use in the colon for the en bloc resection of laterally spreading colonic tumours.

Excellent technical and short-term follow-up results have been reported with ESD. Perhaps of greater importance are long-term outcomes, results of which are emerging from Japan. For gastric ESD, disease-specific 5- and 10-year survival rates of 99% and 99% have been reported;[31] ongoing endoscopic surveillance is prudent, however. Complications include bleeding, both immediate and delayed, stricture formation and perforation. These occur at variable rates depending on the location of resection.

Advances in endoscopes

Colon capsule endoscopy

The demand for colonoscopy remains high, with screening programmes, such as the Australian National Bowel

Figure 4 PillCam Colon 2 (Given Imaging Ltd, Yoqneam, Israel).

Cancer Screening Program, providing an ever-increasing demand for services. The quest for an alternative colonic investigation that is less invasive and requires less manpower, yet remains equally accurate, continues.

Wireless capsule endoscopy, the ingestion of a pill-sized battery-powered camera device that captures images of the gastrointestinal tract as it moves with peristalsis, was originally developed to visualise the small intestine. In recent years, this technology has been extrapolated to the development of the colon capsule endoscopy, marketed by Given Imaging Ltd as the PillCam Colon. A second generation device, the PillCam Colon 2, has now been developed (Figs 4,5). This new generation capsule has a wider angle of view than its predecessor and conserves battery energy by adapting the frame rate of image capture according to the speed of movement.

A recently published multicentre European trial compared the performance of the PillCam Colon 2 with colonoscopy, demonstrating relatively high sensitivities

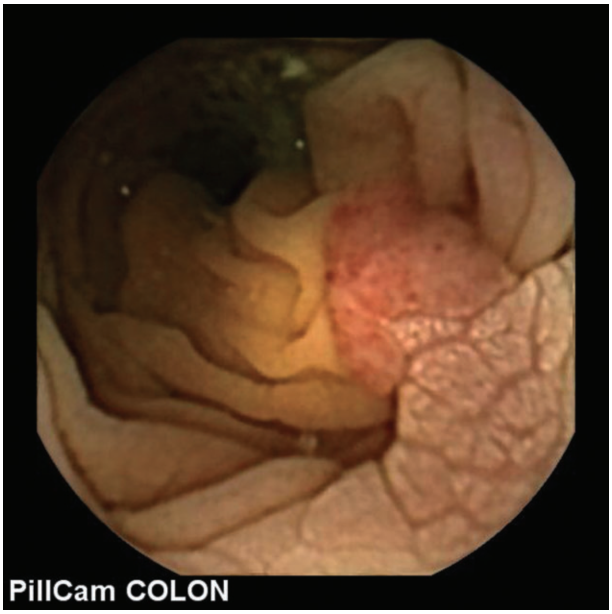

Figure 5 Colonic polyp seen at colon capsule endoscopy, PillCam Colon 2 (Given Imaging Ltd, Yoqneam, Israel).

of 84% and 88% for colonic polyps ≥6 mm and ≥10 mm respectively, and specificities of 64% and 95%.[32] While these results are promising (and represent an improvement upon previous meta-analysis for the first generation colon capsule[33]), conventional optical colonoscopy remains the gold standard as it is currently the only tool that offers both diagnostic and therapeutic capabilities. The main role for colon capsule endoscopy is likely to remain with indications, such as inability to perform complete colonoscopy and where contraindications to performing colonoscopy exist (e.g. anaesthetic risk).

Remote control and magnetic capsule endoscopy

The major limitation of all forms of capsule endoscopy to date has been the inability to control its movement and administer therapeutic intervention. Movement of the device through the gut is passive, relying on peristaltic waves for propulsion. To address these shortcomings, current advances are directed at developing a controllable device by use of techniques, such as magnets and remote control locomotion.

Currently, information transfer is unidirectional: images are captured by the device and transmitted to a data recorder. The ability to reciprocate, transmitting instructions to the capsule from an external controller, is yet to be fully realised. However, advances are being made in this regard, with magnet control currently under development. The ability to steer the capsule quickly through areas that are not of interest (e.g. the oesophagus and stomach, regions that can already be easily viewed through standard gastroscopy) to the region in question (e.g. the small bowel) has been achieved with a capsule containing neodymium boron iron cylindrical magnets – its movement can be manipulated by an external hand-held magnet.[34] A paddling-based locomotion device is also in current development.[35] In a porcine model, researchers were able to completely direct stable and active movement, both *in vitro* and *ex vivo*, without complications. Both of these developments represent promising advances towards the ultimate goal of a fully steerable device capable of delivering directed therapy.

Colonoscopy advances

Given that conventional colonoscopy remains the current gold standard in clinical practice, refining the art to improve its accuracy is of paramount importance. Many of the imaging developments discussed in the first section of this article apply to colonoscopy. Further advances specific to colonoscopy have also been developed.

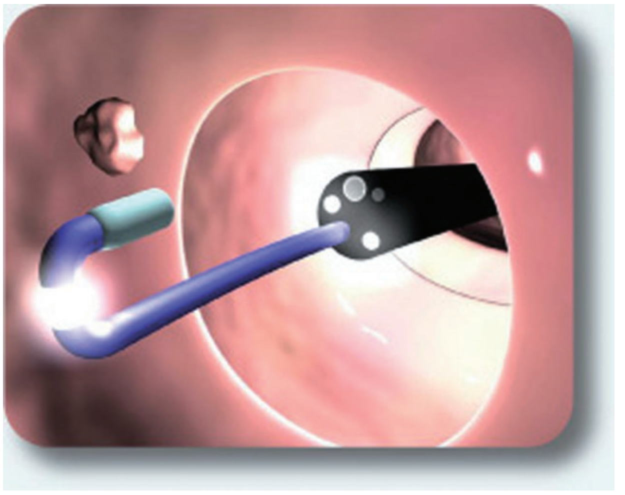

Figure 6 Third Eye Retroscope (Avantis Medical, Sunnyvale, CA, USA).

Water immersion colonoscopy

The filling of the colon with water, instead of air, has the benefit of straightening the sigmoid colon, resulting in an easier-to-traverse angle. For patients undergoing colonoscopy with light or 'on-demand' sedation, this technique results in lower sedation requirements.[36] It may also improve adenoma detection rate.[37–39]

Cap-fitted colonoscopy

The addition of a transparent cap or hood to the tip of the colonoscope may improve ease of colonoscope advancement by maintaining a distance between the tip of the colonoscope and the colonic mucosa, thereby avoiding obscuration of view by the collapse of the mucosa over the instrument tip.[40] This simple technical modification shortens time taken to reach the caecum in randomised controlled trials.[41–43]

Third Eye Retroscope

The accuracy of colonoscopy is measured by its ability to detect polyps during withdrawal of the colonoscope. Standard colonoscope withdrawal techniques only provide views of the distal side of the mucosal folds. The Third Eye Retroscope (Avantis Medical, Sunnyvale, California, USA) has been developed to address this problem. It is a separate device that is passed through the working channel of the colonoscope and advanced into the colonic lumen and retroflexed (Fig. 6), 'hooking' behind the folds to provide images of these areas. The proceduralist watches both the images from the forward and retroflexed views simultaneously on two separate screens

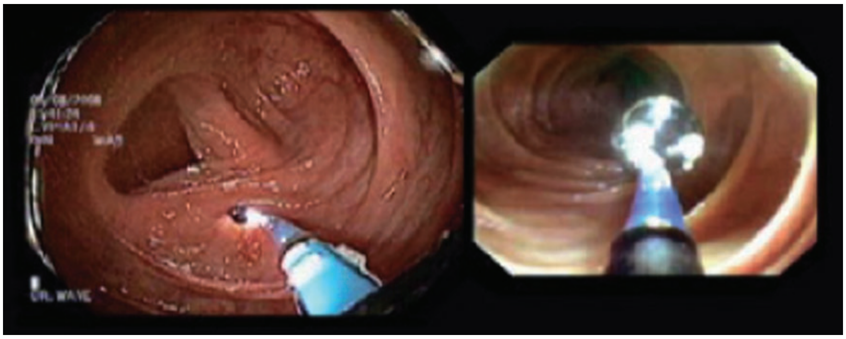

Figure 7 Simultaneous antegrade and retrograde views with Third Eye Retroscope (Avantis Medical, Sunnyvale, CA, USA).

(Fig. 7). Prospective studies have demonstrated improved adenoma detection rates using the Third Eye Retroscope, but at the expense of increased procedure duration.[44–46]

Advances beyond the gut

Venturing beyond the gastrointestinal tract wall has become a true endoscopic reality as a result of the advances in two techniques: EUS (endoscopic ultrasound) and NOTES (natural orifice transluminal endoscopic surgery).

EUS-guided therapies

EUS was originally developed to provide imaging of organs that lie in close proximity to the gastrointestinal tract wall, particularly the pancreas. A modified endoscope containing an ultrasound component at its tip provides detailed images of extraluminal structures, and also allows real-time visualisation of a needle passed through the echoendoscope to perform fine needle aspiration. Extrapolating further, the technique can be used for the drainage of pancreatic collections, such as pseudocysts and infected pancreatic necrosis. It is also emerging as a vehicle for the oncological treatment of pancreatic and other extraluminal cancers.

Pancreatic therapies

Pseudocysts complicate approximately 10% of cases of acute pancreatitis.[47] While many will resolve spontaneously, occasionally significant clinical sequelae may develop, including gastric outlet obstruction and infection. Infected pancreatic necrosis is a more sinister complication, with systemic sepsis and multiorgan failure being life-threatening complications. Laparotomy and drainage/necrosectomy is an invasive procedure, for which these patients are often too unwell to undergo. For collections lying in close proximity to the gastric or duodenal wall, endoscopic drainage provides a minimally invasive alternative (Fig. 8). Under real-time EUS guidance, the peripancreatic collection can be punctured, and stents placed between the collection and the gastric/duodenal lumen to facilitate drainage into the gastrointestinal tract (Figs 9–11). Furthermore, where there is solid necrotic debris within the collection, the endoscope can be passed through the gut wall and into the collection to perform debridement with excellent clinical outcomes (Fig. 12).[48]

Injection

Extrapolating further upon the ability to pass a needle across the gut wall into adjacent organs, several oncological applications have been developed for EUS.

The EUS-guided injection of fiducial markers to guide stereotactic radiotherapy is a novel, minimally invasive way to improve the accuracy of treatment. It is potentially more comfortable and accurate than the percutaneous route, and has been used for pancreatic, prostate and mediastinal cancers.[49–51]

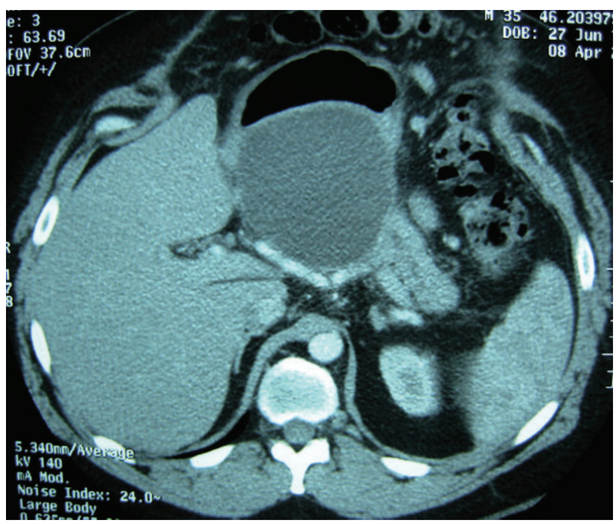

Figure 8 Peripancreatic fluid collection adjacent to gastric wall.

Figure 9 Endoscopic view of peripancreatic collection creating an external compression into stomach.

Figure 11 Stents placed between peripancreatic collection and gastric lumen.

EUS fine needle injection of various antitumour agents into pancreatic and other malignancies is also advancing. Ethanol and paclitaxel have been injected into pancreatic cystic lesions with resolution rates of over 60%.[52,53] Dendritic cells, potent antigen-presenting cells for the induction of T-cell responses, have been injected under EUS guidance into advanced pancreatic cancers, with preliminary results showing mixed outcomes but no serious toxicity.[54] Likewise, reports of EUS injection of mixed lymphocyte culture, adenovirus vectors and conventional chemotherapeutic agents have reported minimal toxicities and variable early results.[55–59]

Natural orifice transluminal endoscopic surgery

NOTES has generated significant interest in recent years. Accessing the peritoneal or thoracic spaces through internal, transvisceral incisions instead of transabdominal incisions offers potential benefits of decreased postoperative pain, fewer wound complications and better cosmetic outcome. The transgastric route has been used to perform procedures including peritoneoscopy, cholecystectomy, appendicectomy, repair of percutaneous endoscopic gastrostomy tube complications and cystogastrostomy.[60–65] However, at this time, the majority of experience and literature remains in animal models, with human experience remaining limited. The development of dedicated NOTES equipment and the resolution of challenges, such as suturing and anastomotic

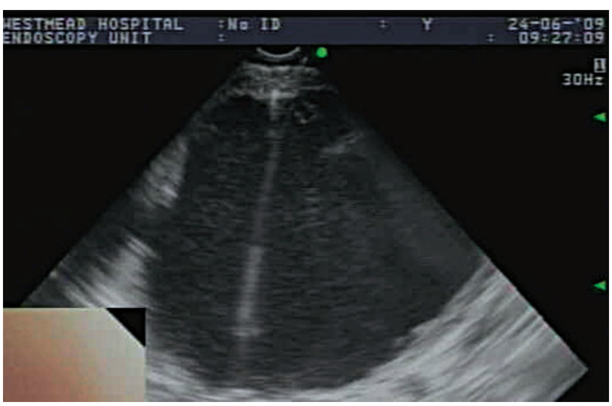

Figure 10 Endoscopic ultrasound view of needle puncture of peripancreatic collection.

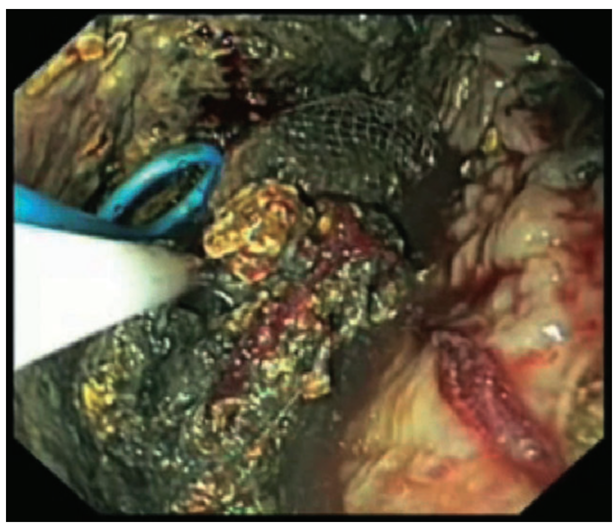

Figure 12 Endoscopic view of passage into necrotic collection, with basket being used to retrieve necrotic tissue.

techniques, need to be addressed before this technology reaches prime time human use.

Conclusion

Significant advances have been made in endoscopic technology in recent years. Endoscopists now have multiple techniques with which to visualise, resect and ablate abnormalities within and beyond the gastrointestinal tract. The judicious use of these new technologies is of paramount importance; the success of any new technology will always be dependent upon its use in appropriately selected patients.

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