Advances in diagnostic and therapeutic endoscopy

Rehan Haidry
David Graham
Adil Butt
Laurence Lovat

Abstract
The burden to healthcare and the impact of disease to humans from luminal disorders of the gastrointestinal tract have driven the requirement for more efficient endoscopic visualization and instrumentation over the past decade. The push for greater diagnostic yield has driven advances in optical physics and bioengineering which are revolutionizing diagnostic and therapeutic endoscopy. This article will highlight emerging technologies since our last review, focusing on advances in imaging, endoscope design and how this is shaping the therapeutic approach to diseases of the human gastrointestinal tract. Their application to improve diagnostic ability, patient care and their limitations are discussed.

Keywords Ablation; colonoscopy; endoscopic resection; endoscopy; optical biopsy; therapeutic endoscopy

Introduction
High-definition digital technology has moved endoscopic imaging to a new dimension. Endoscopic innovations have arisen from the explosion of technical achievements through the interaction between physicians and engineers and the incorporation of technology from other fields such as computing, artificial intelligence and physics.

Rehan Haidry BSc (Hons) MRCP is a Consultant in Gastroenterology and Director of Endoscopy at University College Hospital, London, UK. Competing interests: he has received funding from Pentax Europe, Cook Endoscopy and Covidien Ltd to support research infrastructure.

David Graham BSc (Hons) MRCP is a Specialist Registrar in Gastroenterology at University College Hospital and a Research Fellow at the National Medical Laser Centre, UCL, London, UK. Competing interests: none declared.

Adil Butt BSc (Hons) MRCP is a Specialist Registrar in Gastroenterology at Chelsea and Westminster Hospital, London, UK, and Research Fellow at the National Medical Laser Centre, UCL, London, UK. Competing interests: none declared.

Laurence Lovat BSc PhD FRCP is Consultant Gastroenterologist at University College Hospital NHS Trust, London, UK, and Reader in Laser Medicine at the National Medical Laser Centre, UCL, London, UK. Competing interests: Professor Lovat has received research support from a number of endoscopy device companies which are described in this article.

What’s new?
- Ever-improving resolution and the widespread use of high-definition endoscopes continues to improve visualization. Alongside this, the introduction of image enhancement technology such as i-Scan and FICE allows for improved lesion recognition. Endoscopists are now capable of detecting subtle but significant pathology, greatly enhancing patient care.
- Technologies for accurate in vivo endoscopic diagnosis (optical biopsies) are developing rapidly with promising trial outcomes. Focus, at present, is on confocal endomicroscopy, spectroscopy (elastic scattering and Raman), autofluorescence, molecular imaging and optical coherence tomography.
- Progressively smaller, more flexible endoscopes and transnasal endoscopes have improved patient comfort whilst novel endoscope designs such as Third Eye Retroscope and Spyglass cholangioscope are allowing visualization of previously inaccessible areas of the GI tract.
- Capsule technology has advanced to allow more accurate visualization of the oesophagus and large bowel in addition to the small bowel. This approach allows for non-invasive visualization of the GI tract but its use remains limited due to, amongst other factors, the inability to gain a histological diagnosis.
- Alongside improved lesion recognition comes improved endoscopic therapy. Resection and ablative techniques are transforming patient care and successfully treating patients with conditions for which surgery was once the only option. Developing techniques, such as POEM, continues to expand the endoscopic therapeutic horizons.

Hand in hand with these advancements in imaging there is continuing evolution of the ergonomic design of the endoscopes, with dedicated accessories that allow increasing applications of therapeutic endoscopy. Advances in the treatment of early cancers of the GI tract continue and are being constantly driven by improved imaging. Endoscopic resective and ablative interventions now shape the future for early neoplasms of the gastrointestinal (GI) tract. From submucosal dissection of established cancer to radiofrequency ablation and cryoablation of precancerous dysplasia, the therapeutic armoury at the disposal of the interventional endoscopist continues to accumulate.

Advances in imaging
Improved digital imaging and virtual chromoendoscopy
Video endoscopes use white light from a xenon or halogen source for illumination and rely on a charge-coupled device (CCD) chip to enhance image resolution and magnification, in order to reconstruct the images. Standard definition (SD) white light endoscopy (WLE) has been rapidly replaced by the introduction of high definition (HD) endoscopes. Whereas CCD chips produce an image signal of 100,000 to 400,000 pixels that is displayed in SD format, the chips currently in use in HD endoscopes produce resolutions that range from 850,000 to 1.3 million pixels. These latest innovations have exponentially...
increased our ability to inspect and visualize subtle mucosal details.

Manipulation of the image using additional post-processing optical technologies, such as i-Scan, narrow-band imaging (NBI) or Fujifilm intelligent chromoendoscopy (FICE), can further enhance detection of previously invisible small lesions and is often referred to as virtual chromoendoscopy (Table 1).

### Narrow-band imaging

conventional WLE uses the entire spectrum of visible light (400–700 nm) to examine tissue. NBI developed by Olympus Medical Systems (Olympus, Japan) uses optic filters to isolate two specific bands of light: 415 nm blue and 540 nm green. By isolating these two bands of light and taking into account their absorptive and reflective properties on the mucosal surface, an image that enhances visualization of superficial mucosal and vascular structures is created. The quality of the surface pit pattern morphology is also clearly enhanced by this technology (Figure 1).

**i-Scan:** a new endoscopic image enhancement technology, i-Scan, has been developed by PENTAX (HOYA Corporation, Japan). i-Scan uses the EPKi processor technology, which enables resolution above standard HDTV, with distinct digital filters for special post-processing online imaging, which can provide detailed analysis. The computer controlled digital processing provides resolution of about 1.25 mega pixels per image. The operator enhances different elements of the mucosa by pressing a button on the hand piece of the HD endoscope. i-Scan can be used for surface analysis to recognize lesions using three modes of image enhancement:

1. **Surface enhancement (SE)/i-scan 1** – enhancement of the structure through recognition of the edges.
2. **Contrast enhancement (CE)/i-scan 2** – enhancement of depressed areas and differences in structure through coloured presentation of low-density areas.
3. **Surface and tone enhancement (TE)/i-scan 3** – enhancement tailored to individual organs through modification of the combination of red, green and blue (RGB) components for each pixel (Figure 2).

**FICE:** FICE (Fujinon, Japan) is a post-processor technology that captures spectral reflectance via a colour CCD video endoscope. This is sent to a spectral estimation matrix processing circuit contained in the video processor. The reflectance spectra of corresponding pixels that make up the conventional image are estimated mathematically. From these spectra, it is feasible to reconstruct a virtual image of a single wavelength. Three such single-wavelength images can be selected and assigned to the RGB monitor inputs, respectively, to display a composite colour-enhanced multi band image in real time. In practice this can be used like narrow band imaging to remove data from the red part of the waveband and narrow the green and blue spectra.

### Real-time in vivo diagnosis

Even with advancements in endoscopic imaging, current practice still relies widely on endoscopic sampling of suspicious areas for histological confirmation of neoplasia. New technologies now exist that allow in vivo diagnosis of cellular atypia and guide therapy.

**Confocal laser endomicroscopy (CLE):** Confocal laser endomicroscopy (CLE) is a developing technology that enables the high-resolution in vivo imaging of tissue microstructures at or near the level of histopathology without requiring tissue excision. CLE uses depth-specific tissue illumination and pinhole-limited detection to create an image from the fluorescent light reflected back from a very thin focal plane. Tissue fluorescence is achieved using intravenously or topically applied contrast agents, usually intravenous fluorescein. There are currently two commercially available devices: an endoscope-based system (eCLE) that is fully integrated into the tip of a conventional endoscope (Optiscan Pty., Ltd., Notting Hill, Australia; Pentax); and a probe-based system (pCLE) that can be passed down the working channels of a range of standard endoscopes (Cellvizio; Mauna Kea Technologies, Paris, France).

**Spectroscopy and ‘optical biopsies’:** spectroscopy is based on light interaction with tissue. The incident light directed on the tissue may be reflected in different patterns, called ‘scattering

### Digital imaging techniques

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<td>Narrow-band</td>
<td>Taking into account absorptive and reflective properties of mucosal surface,</td>
<td>These techniques allow for significantly improved mucosal visualization by</td>
<td>The principal drawback for all these techniques lies in the need for careful observation of the mucosa followed by detailed inspection using image manipulation. This is time consuming and requires considerable expertise.</td>
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<tr>
<td>imaging</td>
<td>optic filters isolate two specific bands of light (415 nm blue and 540 nm green) to enhance visualization.</td>
<td>highlighting subtle architectural or vascular differences on the mucosal surface. This improves detection of subtle irregularities and improves therapeutic outcomes.</td>
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<tr>
<td>i-Scan</td>
<td>Digital image enhancement settings such as tonal, contrast and surface filters that improve visualization of vascularity and topography.</td>
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<tr>
<td>FICE</td>
<td>Post-processing technique that reconstructs a virtual image of a single wavelength (red, green and blue) in real time enhancing visualization.</td>
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Table 1

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events’. Light may also be absorbed and re-emitted at longer wavelengths, or it may be shifted slightly to a different wavelength. These characterizations may correlate with histopathology, subcellular architecture (e.g., enlarged nuclei), specific molecular bonds, or differing tissue absorptions of light driven by exogenous or endogenous fluorescent compounds (fluorophores). Elastic scattering spectroscopy (ESS) refers to the way that light is reflected from the tissue after scattering events. Light may reflect back from tissue once (single scatter) or may ricochet within the cellular components of tissue multiple times before reflecting back toward the source (multiple scatter). Elastic scattering spectroscopy exploits the fact that light scatters differently in normal tissue compared with neoplastic tissue, and it measures the scatter characteristics to examine tissue microarchitecture. Inelastic (Raman) scattering spectroscopy measures the signals obtained when the incident light undergoes wavelength shifts caused by energy transfer in the tissue. Both ESS and RS have been shown to improve detection of neoplasia in the GI tract but they remain confined to the research setting for now and are not yet available in routine clinical practice.1,5

**Autofluorescence:** the use of autofluorescence (AF) during endoscopy is based on the principle that the mucosa contains variable amounts of fluorophores (biological substances that emit fluorescent light when exposed to light of a shorter wavelength), allowing the use of different fluorescent signatures or...
patterns to distinguish normal mucosa from dysplasia. This is a virtual chromoendoscopy imaging technique that has been evaluated in surveillance scenarios primarily in the oesophagus, stomach, and colon. Spectroscopy studies have shown that Barrett’s neoplasia has a different autofluorescence spectrum compared with non-neoplastic Barrett’s mucosa. These findings led to the development of wide-field AFI, which was integrated with HD-WLE and NBI into an ‘endoscopic trimodal imaging’ (ETMI) system. In uncontrolled ETMI studies, AFI increased the detection of early neoplasia, while NBI reduced the false-positive rate associated with AFI6,7 (Figure 3 and Table 2).

**Molecular imaging**

Molecular imaging has emerged as a new discipline in gastrointestinal endoscopy. This technology encompasses modalities that can visualize disease-specific morphological or functional tissue changes based on the molecular signature of individual cells. Molecular imaging has several advantages including minimal damage to tissues, repetitive visualization, and utility for conducting quantitative analyses. Lesion identification and characterization based on molecular changes, rather than alterations in morphology or topography, has the inherent potential to increase the effectiveness of endoscopic surveillance and screening programmes. It has recently been reported that the use of a fluorescently conjugated wheat germ agglutinin (lectin) improved the endoscopic visualization of high-grade dysplastic lesions in patients with Barrett’s oesophagus, which were not detectable by conventional endoscopy, with a high signal to background ratio of >5.8 Molecular imaging methods could revolutionize the detection of dysplasia when combined with an appropriate endoscopic imaging device that provides a wide field of view and highlights abnormalities in real time with a high level of accuracy.9

**Optical coherence tomography**

Optical coherence tomography (OCT) is a novel technique that relies on light backscattering to obtain both cross-sectional and 3-dimensional (3D) images of tissue microstructures. These images are visually analogous to viewing a coarse black and white histological specimen. OCT uses reflected light to construct an image, similar to the use of acoustic waves in ultrasound. To date, GI tract scanning has been achieved by inserting a probe through the working channel of a regular endoscope. While neither a water interface nor tissue apposition is required, the depth of scanning achieved is generally limited to 1–2 mm due to light scattering by tissues. A study that assessed the presence of dysplasia in Barrett’s oesophagus used 177 biopsy-correlated images to evaluate a novel dysplasia index, yielding sensitivity and specificity rates for high-grade dysplasia/oesophageal cancer of 83% and 75%, respectively.10

**Advances in endoscope design**

**Improved colonoscopic field of vision**

**Third eye retroscope (TER):** in colonoscopy, it is difficult to view the proximal aspect of folds or flexures, which equates to 7.8% of colonic surface area. TER passes through the instrument channel providing retrograde viewing to compliment the forward view during withdrawal. In a recent multicentre study, 14.8% more polyps were detected without detriment to procedure time or complications with TER.11

**G-EYE colonoscope:** the G-EYE (Hoya, Pentax) endoscope provides enhanced visualization of the colon, and has been shown in recent clinical studies to enable a significant increase in polyp and adenoma detection alongside a considerable reduction in polyp and adenoma miss-rate, compared with conventional colonoscopy. The G-EYE endoscope is a conventional colonoscope on to which a balloon is permanently integrated. Controlled withdrawal of the G-EYE endoscope with the balloon moderately inflated flattens colon folds, straightens lumen topography, centralizes the optical image and reduces bowel slippage, altogether increasing detection yield. Once a polyp is detected, balloon anchoring in the colon facilitates fast and accurate polyp removal.

**Full-spectrum view colonoscopy:** the most important aspect of colonoscopy is the adenoma detection rate with lesions missed as they lie behind colonic folds. A new colonoscope was introduced this year, the PeerScope (PeerMedical Ltd, Caesarea, Israel), to increase the adenoma detection rate thanks to its ability to see behind folds. It maintains the standard features of a colonoscope...
Endoscopy

but has two viewing modes: a 160-degree forward-viewing mode and a 330-degree or greater full-spectrum view.

Spyglass cholangioscopy
Per-oral cholangioscopy is appealing to therapeutic endoscopists because a direct intraluminal view of the biliary duct system offers possibilities for diagnosis and interventions beyond that which other imaging or endoscopic modalities can provide. As the image quality of cholangioscopies improves, so too does their diagnostic capability, and as their durability and manoeuvrability increases, so too does their potential use for therapeutic applications. Spyglass is a single-operator cholangioscope with four-way deflected steering and a working channel allowing visual examination of bile ducts, tissue sampling, and therapy to evaluate and treat various pancreaticobiliary diseases.

Transnasal endoscopy (TNE)
TNE utilizes ultrathin endoscopes to perform oesophagastroduodenoscopy via the nasal route. It is reported to reduce patient discomfort and is well tolerated by patients undergoing unsedated endoscopy, but studies have shown reduced completion rates and complications such as epistaxis.12

Colon capsule and radio-controlled motor-driven capsule
Second-generation colon capsules have improved sensitivity from earlier capsules, with speed-sensitive adaptable frame rates up to 35 frames/second and new software for polyp size estimation. The inability to clean, insufflate air and biopsy limits this technique. A new capsule technology able to control both the direction and transit speed resulting in a more adequate visualization of the GI tract was introduced recently (radio-controlled motor-driven capsule). If refined, the remote-control capsule system will increase the ability to screen the GI tract in a less invasive manner.

Advances in therapeutic endoscopy
All the above-mentioned advances in endoscopic imaging and design have led to improved lesion recognition but have also uncovered a spectrum of pathology that is now amenable to endoscopic therapy. The lympho-vascular distribution of the human GI tract informs us that pathology and neoplasia confined to the superficial layers such as the mucosa and submucosa can be successfully treated with endoscopic therapy because the long-term risk of nodal metastases is minimal. Mortality and morbidity associated with more established maximally invasive surgical approaches to these same pathologies can therefore be avoided.

Endoscopic mucosal resection
Endoscopic mucosal resection (EMR) is a technique used for the staging and treatment of superficial neoplasms of the gastrointestinal tract. The technique was first developed in Japan for the treatment of early gastric cancer and has since spread in use throughout the world for various indications, including removal of dysplastic Barrett’s mucosa and sessile colonic neoplasms. The utility of EMR rests in its ability to:
- Provide accurate histological staging of superficial GI neoplasms
- Provide a minimally invasive technique for removal of superficial malignancies.

Several variations of EMR are currently used, including injection-assisted, cap-assisted, and ligation-assisted techniques. All adhere to the basic principles of identification and demarcation of the lesion, submucosal injection to lift the lesion, and endoscopic snare resection.

In Barrett’s oesophagus, EMR is now part of the established management algorithm for patients with early neoplasia with several large studies showing that EMR before radiofrequency ablation (RFA) can achieve high rates of neoplasia reversal.13 (Figure 4).

Radiofrequency ablation
This is a field ablation technique (Covidien Ltd) used for the treatment of superficial neoplasia in the oesophagus. Balloon-based or focal endoscope-mounted devices are used to provide a pulse of radiofrequency energy to ablate the mucosal surface of the oesophagus. Both Barrett’s oesophagus and related neoplasia and early squamous cell neoplasia have been treated successfully and safely by this intervention. Repeated treatments have been shown to clear neoplasia and Barrett’s in several high-volume studies with durable response.14

The use of RFA in treating mucosal haemorrhagic conditions such as radiation proctopathy and gastric antral vascular ectasia is less well established but there is increasing interest in its use in these chronic and debilitating conditions. Small studies have shown promising results.15

Cryoaulation
Cryoaulation involves the use of extreme cold to destroy diseased tissue. Shaheen (2010) reported on a retrospective analysis of 98

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<td><strong>Modality</strong></td>
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Table 2
subjects who underwent cryoablation for Barrett’s oesophagus and high-grade dysplasia. Of the 98 subjects enrolled in the study, 60 completed all planned cryoablation treatments. Fifty-eight participants (97%) had complete eradication of high-grade dysplasia. No serious adverse events or perforations were reported. However, the study is limited by short follow-up of 10.5 months, no randomization and retrospective nature without a control group. 16

Endoscopic submucosal dissection

Over the past decade endoscopic submucosal dissection (ESD) has been introduced as an endoscopic treatment for gastrointestinal intraepithelial neoplasia. The limitations of EMR are low en bloc resection rate and limitation of the size of lesions that can be resected. As a result ESD has gained interest as a technique without these disadvantages and has become widely used. ESD allows removal of submucosal tumours arising from the muscularis propria by using the submucosal tunnelling technique. The problems associated with ESD are the difficulty in training physicians, long procedure time, and rate of complications. ESD has been shown to be an effective treatment for cancers of the oesophagus, stomach, and colon. 17,18

POEM: per-oral endoscopic myotomy (POEM) is a novel modality for the treatment of achalasia performed by gastroenterologists and surgeons. It represents a natural orifice transluminal endoscopic surgery (NOTES) approach to Heller myotomy. POEM has the minimal invasiveness of an endoscopic procedure that can duplicate results of the surgical Heller myotomy. The technique of POEM is centred on creation of a submucosal tunnel within the distal oesophagus in which a myotomy is performed with dissection of the inner circular muscle of the oesophagus and minimal dissection of the circular muscle of the lower oesophageal sphincter. The equipment required for POEM is readily available and compatible with existing endoscopy instruments.

REFERENCES


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