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ORIGINAL ARTICLE

DRAMATIC ADVANCES IN THE DIAGNOSIS OF DISEASE IN THE GI TRACK HAVE BEEN MADE WITH IMAGE ENHANCE ENDOSCOPY INCLUDING NBI AND AFI .DIAGONOSIS AND THERAPEUTIC ADVANCEMENT

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ABSTRACT

Gastrointestinal malignancy accounts for approximately a fifth of all cancer deaths in the United Kingdom. By the time patients are symptomatic, lesions are often advanced, with limited treatment options available. The development of effective endoscopic therapies means that neoplastic lesions can now be treated with improved patient outcomes. This has led to a paradigm shift, whereby the aim of digestive endoscopy is to identify premalignant conditions or early neoplastic change, in order to make an impact on their natural history. This has necessitated an improvement in imaging techniques in order to identify subtle mucosal changes that may harbour precancerous cells. At present there is an array of available imaging modalities, each with implications on cost, training and lesion detection. Here we describe the scientific rationale behind the major commercially available techniques as well as offering a glimpse at possible future directions.

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INTRODUCTION

Since its inception in the 1800s, endoscopic visualization has offered us the unique ability to correlate gastrointestinal mucosal change with patient symptoms. Over time, development in scope technology has meant that endoscopy has become both more comfortable and effective, making this indispensible in daily clinical practice. As the focus of endoscopy has evolved towards to detecting asymptomatic premalignant change, the goal posts of acceptable image quality have also shifted. The advanced imaging modalities create the opportunity to make a real time in vivo histological prediction, a so-called 'optical biopsy.' This may eventually allow for dispensation with random non-targeted biopsies, possibly with cost savings, but more importantly offering greater accuracy in endoscopic diagnosis. Here we discuss the technology behind the most recent advances.

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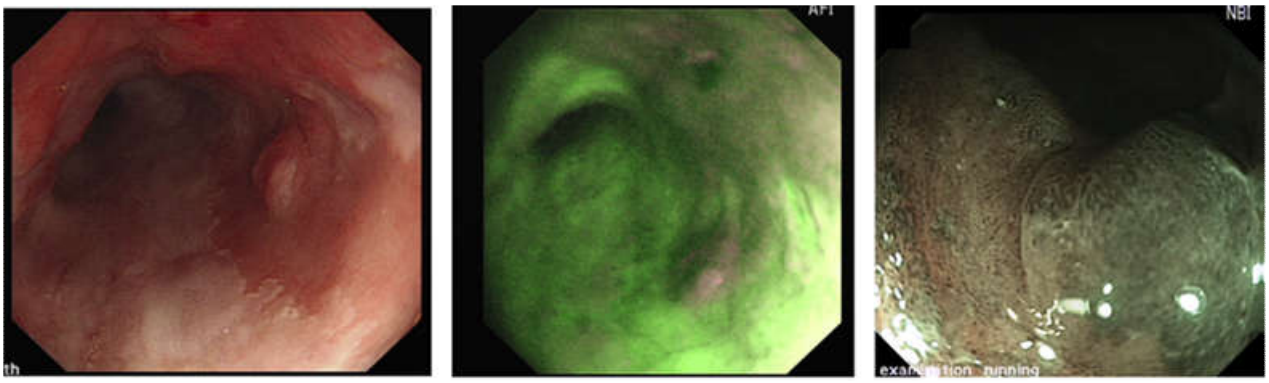
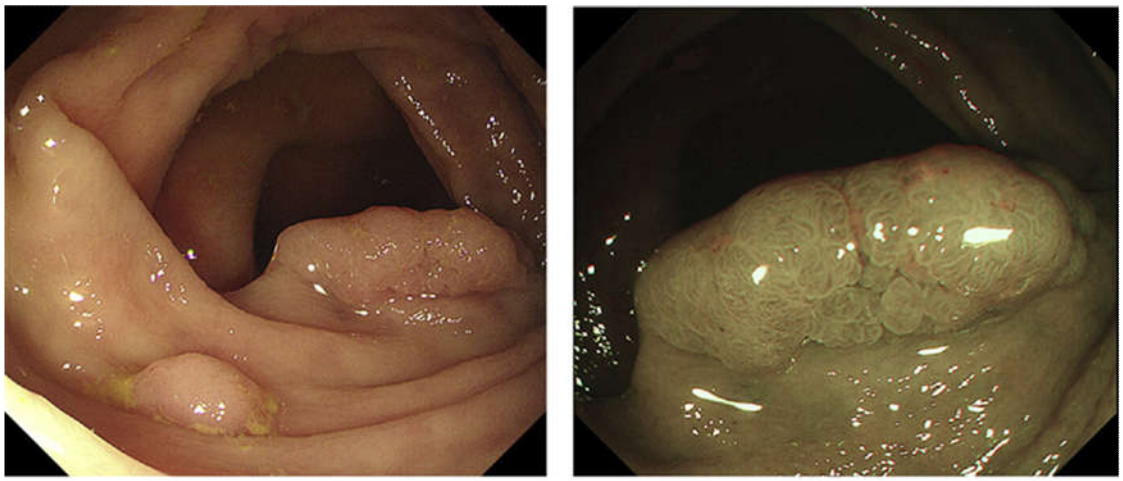
High definition and magnification white light endoscopy Technology: The current standard of care is White Light Endoscopy (WLE), which produces a true to life depiction of the gastrointestinal mucosa. Whilst this concept remains unchanged, advances in technology means that the level of detail achievable with modern endoscopes is much improved.

The major revolution in endoscope design occurred in the 1950s with the introduction of fibreoptic technology. Despite a huge leap forward in imaging quality, this modality was subject to several limitations. Resolution capabilities were dependent on the number of fibres contained within the fibreoptic bundle and therefore constrained by the finite diameter of an endoscope. The inevitable rupture of fibres associated with endoscope flexion meant that image quality decreased throughout the lifetime of the scope, eventually requiring costly replacement (Kwon, 2009 and Tanaka, 2006). In order to improve upon imaging capabilities there has had to be a departure from fibreoptic technology towards a distal digital sensor technique.



a b c

Fig. 1. Dysplastic lesion within Barrett's esophagus seen in a) HD WLE b) AFI c) NBI with magnification



a b

Fig. 2. Colonic adenoma seen in a) WLE b) NBI- demonstrating pit pattern

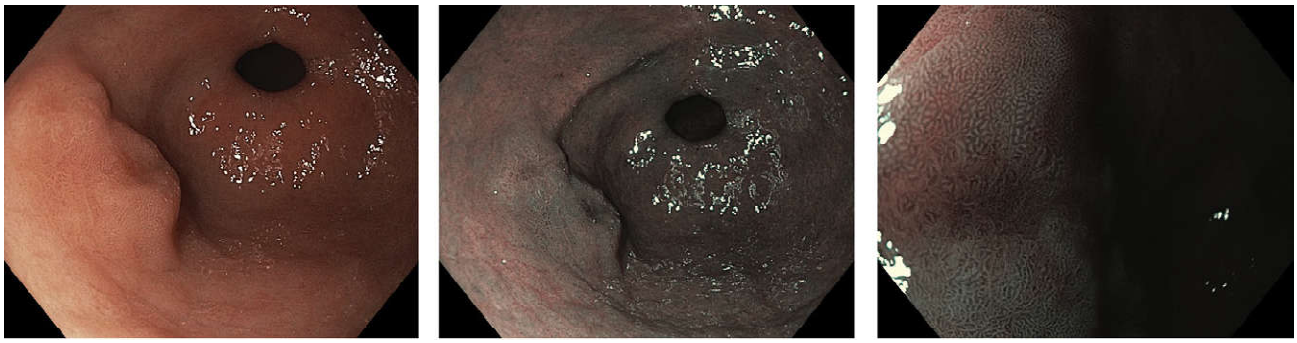
Contemporary endoscope systems consist of an external xenon arc lamp that illuminates the mucosa using the full spectrum of visible white light. Reflected light is projected through the endoscope lens onto the photoactive region of a Charge-Coupled Device (CCD) located within the endoscope tip. The consequent electric charge is transmitted to a video processor where it is interpreted as a digital image. The quality of the image produced is dependent on the pixel density of the CCD and the resolution of the screen on which the image is displayed (Kwon, 2009 and Tanaka, 2006).

Standard Definition (SD) endoscopes are equipped with CCDs that permit resolutions of up to 400,000 pixels. Developments in chip technology means that High Definition (HD) endoscopes boast CCDs capable of producing images of over one million pixels, enabling the visualisation of fine mucosal architecture and vascular detail (Figs. 1a, 2a and 3a) (1e4). This effect is augmented when combined with magnification technology, whereby a selected region can be visualised in greater detail, with no loss in resolution. Magnification of up to 150 times occurs by adjusting the position of the lens at the endoscope tip by means of a button or lever integrated onto the scope controls (Bruno, 2003 and ASGE, 2014).. Image clarity is dependent on maintaining a stable position of the scope, which is susceptible to motion artifact caused by patient movement. This can be overcome by the placement of cap on the endoscope tip that allows the scope tip to be anchored on the mucosal surface (ASGE, 2014). Images are displayed on monitors in either a 4:3 or a 5:4 ratio.

The projected image is refreshed at a rate of 60 frames per second either on a line-by-line or alternate line basis. The speed of image display enables real time viewing, even in the context of rapid movements (ASGE, 2014).

Clinical applicability: It is difficult to isolate the clinical impact of HD WLE, as in most scenarios this has been studied in combination with either dye-based or virtual chromo endoscopy. Additionally, as HD WLE has fast become the standard of care this is often used as the control method in imaging studies (ASGE, 2014). To date HD WLE has been used in combination with Narrow Band Imaging (NBI) to develop classification systems for detecting dysplasia within Barrett's esophagus (Silva, 2011).

A large meta-analysis has suggested a somewhat modest improvement in colonic adenoma detection rate of 3.5% compared to SD WLE (Subramanian, 2011). Whilst in the context of chronic inflammatory bowel disease, HD WLE guided targeted biopsies yields a three-fold greater dysplasia detection rate compared to SD WLE (Kuiper, 2012). HD WLE is widely available and has on the whole has replaced SD WLE endoscopy in daily practice. As technology has improved incrementally over time the use of HD scopes do not require a specific change in practice. In order to draw meaningful conclusions using magnification HD WLE, training in effective image acquisition and mucosal pattern recognition is likely to be important (ASGE, 2014).



a b c

Fig. 3. Low grade dysplasia in the stomach seen in a) WLE b) NBI c) NBI with near focus

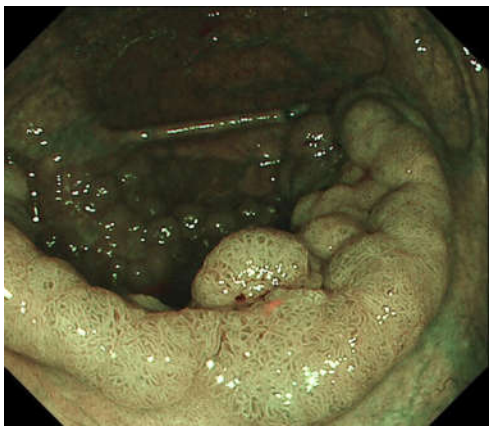


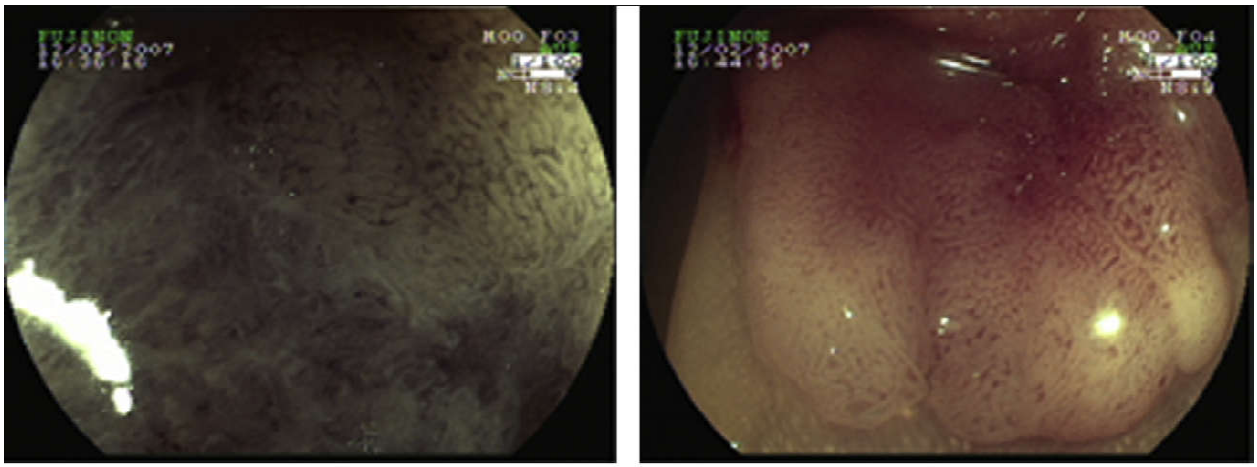
Figure 4. Colonic polyp under narrow band imaging inspection, with clearer demarcation and characterization of pit pattern compared with white light endoscopy

Virtual chromoendoscopy: The use of dyes applied to the mucosal surface have long been used to highlight abnormalities, by means of either differential uptake (Lugol's iodine and methylene blue), chemical reactions (acetic acid) or by simply by enhancing topography (indigo carmine). Whilst effective these techniques are cumbersome and time consuming. Virtual chromo endoscopy aims to obviate the need for dyes by using filters and software developments to provide instant lesion enhancement.

Narrow band imaging (NBI)

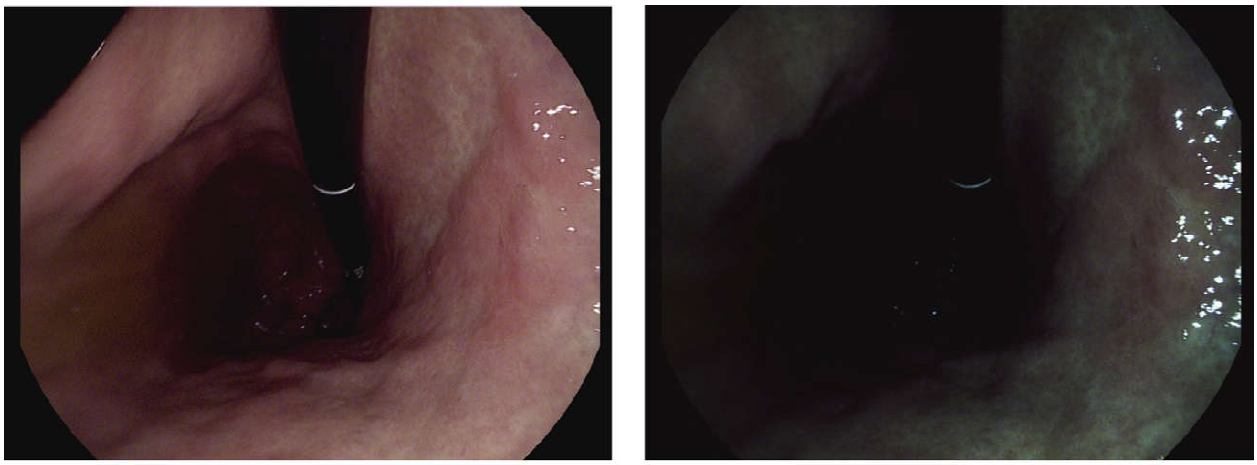
Technology: NBI is perhaps the most widely studied of the non dye-based chromoendoscopy techniques. This modality, available on Olympus endoscopy systems, utilises an electronically activated filter placed in front of the endoscope light source. White light is filtered in order to allow only the limited wavelengths of 415 nm and 540 nm to reach the mucosa. This technique exploits the principle that the depth of light penetration is proportional to wavelength (8e10). By restricting the spectrum to visible blue and green light, penetration is limited to the superficial mucosal layers. Additionally these wavelengths coincide with the optimal light absorption peaks of haemoglobin, causing haem-rich structures such as capillaries to appear darker (Song, 2008 and Gono, 2004). Mucosal blood vessels appear brown due to the reflection of blue light while submucosalvessels have a green discolouration. Given that angiogenesis is an early feature in premalignant lesions, NBI creates sharp contrast with the background normal mucosa (Figs. 1b, 2b and 3b and 3c) (Gono, 2004).

Clinical applicability: NBI has been intrinsically linked with the characterisation of mucosal morphology and as a consequence several classification systems to describe both Barrett's associated dysplasia and colonic polyps have emanated from this modality. NBI with magnification was able to detect high-grade dysplasia in Barrett's oesophagus with 96% sensitivity in a large meta-analysis (Mannath, 2010). However, at present there is insufficient evidence to dispense with quadrantic biopsies, primarily due to a variation in diagnostic sensitivity associated with operator experience (Fitzgerald, 2014). Similarly, pooled studies examining the use of NBI in the characterisation of diminutive polyps have demonstrated 91% accuracy at predicting histology (McGill, 2013). This effect is most marked when used by expert endoscopists, with studies in community-based settings failing to show such promising results (15e18). Data for the utility of NBI in the context of inflammatory bowel disease is lacking. There have been several trials, each with a small number of patients. NBI targeted biopsies in the largest ulcerative colitis surveillance study demonstrated a diagnostic yield of 9% compared to 0.04% in random segmental biopsies (Ignjatovic, 2012). It is difficult to know whether these results can be extrapolated to a more general population. Given the widespread use of the Olympus endoscopy system NBI is widely available. Familiarity with this technique in combination with no additional equipment costs makes this an attractive tool (Song, *et al*., 2008; Kuznetsov *et al*., 2008). Training is still however, a prerequisite for effective use. A major limitation of NBI is the acquisition of dark images that occurs as a consequence of narrowing the wavelength spectrum. This can make the inspection of broad areas of mucosa or lesions within a large lumen challenging.



a b

Fig. 5. Rectal polyp characterized with a) FICE preset 4 b) FICE preset 9



a b

Fig. 6. Gastric lesion characterized with a) WLE with surface enhancement b) I-Scan

This may account for the lack of additional benefit in using NBI to improve adenoma detection rate in the colon (Kuznetsov *et al*., 2006; A1 Nagorni *et al*., 2012; Dinesen *et al*., 2012). This limitation has in part been addressed by the new NBI systems that produce greater illumination to create a brighter image.

Post-processing image enhancement

Technology

Fujinon Intelligent Colour Enhancement (FICE) and I-Scan are post processing image enhancement techniques produced by Fujinon and Pentax respectively. These extend on the principles used in NBI of narrowing the spectrum of visible white light. Instead of using mechanical filters, white light images are detected and re-interpreted by use of proprietary software. Each wavelength is detected, isolated and then reinterpreted to form an enhanced image (Manfredi, 2015).

FICE

FICE, also known as optimal band imaging, selects specific wavelengths before reassigning these to either the red,blueor green elements of the light spectrum. Sixtypossible permutations of potential colourcombinations are created, ten of which can be stored as presets and are activated by the use of endoscopy system keyboard (Fig. 4a, b). Three of these presets can be assigned to a button on the endoscope, allowing for rapid alternation between the white light image and the most commonly used FICE settings.

I-SCAN

I-Scan is able to create three different imaging options by using different processing algorithms; tone enhancement, surface enhancement and contrast enhancement, with an appropriate setting selected based on lesion characteristics (Fig. 5a, b) (Kodashima, 2010).

Clinical applicability

A relatively small number of studies mean that the role of FICE and I-Scan is yet to be established. A study examining the impact of FICE in combination acetic acid in Barrett's esophagus proved a modest improvement in high-grade dysplasia detection compared to random biopsies (Pohl, 2007). Two large studies have shown that there is no additive benefit for the use of FICE in colorectal adenoma detection (Chung, 2010 and Aminalai, 2010). While characterization of colonic polyps reaches 87% when FICE with magnification is used (Kim, 2011).

I-Scan has not been proven to be superior HD WLE in the characterization of colonic polyps (Basford, 2014). A large study showed equivalent adenoma detection rates between HD WLE and I-Scan, this study did however show that the I-Scan-2 setting characterized the detected polyps with improved accuracy (Hong, 2012). Further evaluation of these modalities is required before routine use can be advocated.

Blue laser light

Technology: Some of the limitations of NBI and FICE are addressed by an imaging technique called Blue Laser light Imaging (BLI), also known as Lasereo, developed by Fujinon. This combines the properties of two lasers, one of which provides enhanced mucosal delineation using the same principles as NBI, due to its limited wavelength spectrum of 415 nm blue laser light. The second laser induces fluorescent light equivalent to that produced by a traditional xenon lamp, thereby allowing for improved illumination. By maintaining a ratio between these two lasers, bright images with sharp contrast are achieved. This allows for visualization of large lesions as well as inspection of large surface areas such as that of the capacious gastric lumen. If required additional characterization of lesions can be accomplished with FICE, which is activated by the switch of a button (Osawa, 2014).

Clinical applicability

This technology is relatively new, having only been commercially available since 2012. It has been used predominately in the Far East, with a focus on the detection of gastric lesions (Osawa, 2014). Whilst promising, data regarding the clinical utility of BLI is still emerging, with further evaluation required.

Auto-Fluorescence Imaging (AFI)

Technology: Auto-Fluorescence Imaging (AFI) takes advantage of naturally occurring fluorophores within the gastrointestinal lining. When exposed to short wavelengths endogenous fluorophores such collagen, flavins and porphyrins are excited, resulting in the emission of longer wavelengths of fluorescent light. Changes in the composition of metabolites that occur in premalignant cells cause an alteration in the emitted fluorescence spectra (Song, 2011). The AFI endoscope (Olympus Medical Systems) produces short wavelength light by placing a rotating filter in front of the xenon arc lamp. This selectively filters light in order to limit the spectrum to blue light (390e470 nm) and green light (540e560 nm). At the tip of the scope are two CCDs, one used for WLE, whilst the other is dedicated to AFI. The AFI CCD contains in front of it a further light filter so that only reflected fluorescent and green light between 500 and 630 nm is detected (Song, 2011). The resultant image is composed of a mixture of green and purple hues, with dysplastic tissue represented by the latter. The presence of two CCDs means that switching between imaging modalities can occur at the press of a button, although in practice a delay of a few seconds is experienced.

Clinical applicability

The major limitations of this technique are the inferior quality images produced in AFI mode and a false positive rate that can be as high as 81% (Curvers, 2008). The specificity of this modality is enhanced when combined with WLE and NBI, which together form Endoscopic Tri-Modal Imaging (ETMI). As large mucosal surface areas can be visualized with AFI, this technique is ideal for highlighting potentially dysplastic regions within large areas of normal mucosa, which can then be further evaluated with close inspection with WLE and NBI. AFI has a high negative predictive value and so is considered to be a 'red flag' technique (Song, 2011). Its role in Barrett's esophagus is likely to be localizing and excluding lesions in high-risk patients. The data for AFI in improving adenoma detection rates is conflicting. Whilst one study of 167 patients undergoing tandem colonoscopies demonstrated a reduced the polyp miss rate from 49% to 30%, a similarly designed and powered trial was unable to reproduce these results. AFI is of noadditive benefit in the characterization of colorectal polyps and is of uncertain benefit in looking for early gastric lesions.

Confocal laser endomicroscopy

Technology: Confocal Laser Endomicroscopy (CLE) offers the most detailed level of endoscopic imaging currently available, with the images produced akin to histological sections. The tissue being visualized is illuminated with a focused blue laser light, the resultant reflected light is filtered through a pinhole that eliminates the detection of light from all other focal planes. The image is composed of a single color, with differences expressed in grey-scale. CLE is available in two different platforms. Endoscope based CLE (Pentax) uses fibre optics to deliver illumination, with the confocal microscope integrated at the tip of the endoscope. This leaves the accessory channel free for use. The large diameter of the endoscope means that this method cannot be used to interrogate the biliary tree. This system is no longer commercially available for clinical use. Probe based CLE (Mauna Kea Technologies) utilizes a reusable CLE catheter, measuring up to 2.8mm in diameter, which can be fed through the working channel of a standard endoscope. The probe consists of a fibre optic bundle that transmits light to the confocal microscope and scanning unit outside of the patient. There are three available probes, designed to work optimally in either the biliary tree, the upper or lower gastrointestinal tract.

Contrast agents

Whilst CLE is able to take advantage of tissue auto-fluorescence, relying solely on this results in lower solution images that limit clinical utility. The use of intravenous or topical fluorescent dyes significantly improves image contrast and resolution. The intravenous use of these dyes in the context of CLE is an off-label indication, with 2.5e5 mls of 10% fluorescein the most widely accepted preparation. Intravenously administered fluorescein penetrates the epithelium, staining the extracellular matrix. Optimal images are visible up to 8 minutes after administratio). In comparison topical fluorescein provides very superficial staining, with a predilection for the cell nuclei. It is worth considering that topical application of fluorescein is less practical with probe based CLE, given the catheter occupies the accessory channel of the endoscope. The side effect profile of intravenous fluorescein has been best studied in the context of retinal angiography, its most common indication. Here this has been proven to be generally safe, although rarely occurring adverse events, such as allergic reactions, have been observed. When the use of fluorescein for CLE was examined across in 16 centers, amongst 2272 patients there were no major adverse

Table 1. Table summarizing the characteristics of the imaging modalities

Imaging modality	Location Oesophagus	Stomach	Colon
High definition white light endoscopy	Standard of care. Helpful in the delineation of Barrett's Esophagus and dysplasia, however not sufficiently accurate to dispense with random biopsies	Standard of care. Can be a useful adjunct to improving visualization of gastric lesions.	Standard of care. Can be used to classify polyp characteristics, as per the NBI International Colorectal Endoscopic classification system. There is no evidence for improved ADR. Potential benefit in UC surveillance but insufficient evidence to advocate routine use.
FICE	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations
I-SCAN	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations	Insufficient evidence to advocate routine use. Use limited to experts, with use in high risk populations
Autoflourence imaging	Helpful in highlighting potentially dysplastic regions within Barrett's esophagus, however not sufficiently accurate to dispense with random biopsies. Most useful in high risk cases, to for example identify dysplastic regions when dysplasia has already been diagnosed in nontargeted biopsies.	Insufficient evidence to advocate routine use.	Insufficient evidence to advocate routine use.
Blue light laser imaging	Limited evidence for the detection of dysplasia within Barrett's Esophagus.	A small number of studies, predominantly in the Far East, suggest that this may be a promising technique for the detection of early gastric neoplasia. Experience in Western populations awaited. Use limited to experts, with use in high risk populations.	Limited evidence for adenoma detection or characterization. Insufficient evidence to advocate routine use.
Confocal laser endomicroscopy	Highly accurate in predicting both Barrett's Esophagus and dysplastic change. Use limited to experts, with use in high risk populations	Limited evidence for CLE assessment of gastric lesions at present. Use limited to experts, with use in High risk populations.	Highly accurate in the Prediction of polyp histology. Not an appropriate technique for improving polyp detection

events, with mild side effects such as nausea, vomiting and rash noted in 1.4% of patients. The use of fluorescently labelled probes targeted at disease specific biomarkers is likely to increase the relevance of CLE in future practice.

Clinical applicability: CLE is able to confirm Barrett's esophagus with an impressive sensitivity of 98.1% and detect associated early cancers at 94.1%. Due to the highly detailed images acquired, a broad field technique such as AFI or NBI are required to locate suspicious lesions that warrant evaluation (42). Using such an approach to target potentially dysplastic areas offers us an attractive alternative to quadranticbiopsies. Validations studies are required to test this strategy. The narrow field of vision obtained in CLE precludes its use as a method of adenoma detection in the colon. Its strength lies in confirming dysplasia in identified lesions, with probe based CLE having a 91% accuracy in diagnosing neoplastic polyps and a five time greater dysplasia detection rate in inflammatory bowel disease compared to WLE. The major limitation of this technique is the significantly increased procedural duration incurred by such detailed imaging. In addition to this there is a learning curve required to interpret the images that are vastly different from traditional endoscopic images. One study estimated an average learning curve of 35 cases required to interpret post-procedural CLE images with 93% accuracy. Case selection will be key in maximizing outcomes obtained from this modality.

Emerging technologies: Whilst existing technologies predominantly focus on enhancing macroscopic differences between early malignant lesions and normal background mucosa, newer techniques enable the detection of cellular abnormalities without the need for tissue sampling.

The below technologies are undergoing evaluation for more widespread use, but may in the future play an important role in advanced endoscopic imaging.

Optical coherence tomography

Optical Coherence Tomography (OCT) is an emerging imaging technique that uses similar principles to those used in B-mode ultrasongraphy. Instead of sound waves, this technology utilises near-infrared light. Comparable to ultrasound, which creates images based on the differential reflection of acoustic waves by different surfaces, OCT focuses light onto a tissue detecting light scatter to create a cross sectional image. The rapid speed of light reflection means that differences in echo-delay are miniscule. In order to overcome this low coherence interferometry is used, this divides the broadband light source into two separate beams, with one beam directed towards the desired target and the other onto amirror at a known distance. By detecting reflected light form both sources it is possible to infer the depth of light reflected from the various tissue layers. Using infrared light allows resolutions ten times that of traditional ultrasonography, enabling visualization of cellular structures. The trade off for such high resolutions is a lower depth of imaging, OCT can accurately image up to 2 mm below the mucosal surface. The OCT system consists of a scanning unit, within which the optical imaging equipment is contained. Images are obtained by the use of a reusable OCT probe fed through the accessory channel of a standard endoscope. This probe consists of a catheter containing a fibre optic bundle and a distal lens, with a diameter of 2.7 mm. No specific preparation of the mucosal surface is required. The OCT probe does not require tissue contact or a specific interface, however

in practice the probe is often placed on the target tissue in order to keep it stable and to minimize motion artifact.

Optical frequency domain imaging

An adjustment in image acquisition of OCT images has led to a new technology by the name of Optical Frequency Domain Imaging (OFDI) This uses the same image interpretation technology, but by using a rotating scanning laser, it is able to assess several areas of the mucosa simultaneously. This allows for rapid assessment of a large field of mucosa, shortening scanning time to several minutes.

Volumetric laser endomicroscopy

Using similar principles to OCT is a circumferential imaging technique called Volumetric Laser Endomicroscopy (VLE) developed by Ninepoint Medical. This is particularly useful in obtaining images within a fixed circumferential lumen, such as the esophagus. A balloon-containing probe is fed through the scope accessory channel, before being inflated within the oesophagus. An optical probe, based on OCT technology, can then be fed through the centre of this balloon. As the probe is pulled back through the balloon it rotates, enabling rapid 360scanning of the entire length of mucosa that is in contact with the balloon. The balloon is 6 cm in length, with the probe taking just 90 seconds to acquire images along the length, at a scanning depth of 3 mm. this technology offers the potential of rapid, highly detailed imaging of an entire length of Barrett's oesophagus. Feasibility and animal studies have confirmed its utility, with larger population based trials awaited.

Conclusion

The field of digestive endoscopy is undergoing rapid development, owing a parallel evolution in technological capabilities (Table 1). This offers us a unique opportunity to diagnose gastrointestinal malignancies at a point at which they are amenable to curative therapy. Studies to date have highlighted the advantages and weaknesses of novel imaging modalities; a greater body of evidence is required to understand their full potential. Before widespread use of new techniques is advocated, it must be proven that they can satisfy the standards as described in preservation and incorporation of valuable endoscopic innovations (PIVI) statements, in generalized populations and not just in enriched study populations. At present there is a paucity of data in such scenarios. However, universal in the published data is the recognition that training in both image acquisition and lesion recognition is an important factor in successful use. Whilst existing technologies predominantly focus of enhancing macroscopic differences between early malignant lesions and normal background mucosa, newer techniques enable us to detect cellular abnormalities without the need of tissue sampling.

Practice points

- HD WLE has become the standard of care in endoscopic imaging.
- Detection and treatment of premalignant lesions has been shown to reduce mortality, as exemplified by screening for colorectal polyps.
- At present there is insufficient data to recommend the routine use of advanced imaging techniques, however these are useful adjuncts for selected indications.
- Training in understanding the technology and lesion interpretation is a prerequisite for the effective use of advanced imaging modalities.
- The future of imaging is likely to combine broad-field techniques to localise suspicious lesions, followed by narrow field high resolution techniques identify precancerous change.

Research agenda

- A greater number of well-designed randomized controlled trials are required to assess the clinical effectiveness of new imaging modalities such as FICE, I-Scan, BLI and AFI, especially in every day clinical practice.
- The required training to be able to effectively acquire and interpret images using the new modalities needs to be established.
- The cost effectiveness of the use of these new technologies, compare to the current standard of care needs to be evaluated.

Conflicts of interest

Above mentioned all the equipment's will give their excellent service to diagnosis of abnormal pathology as well as normal structure of GI track mucosa and the raputitic advantage to cure it. DR. Taisir Shahriar, MBBS, MD (Gastroenterology) ,So no Hospital Ltd ,Court Para, Kushtia -7000, Bangladesh as well as also Zhongnan Hospital of Wuhan University (Dept of gastroenterology), Hubei, PRC.

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