New Trends in Endoscopic Imaging

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Our understanding of the gastrointestinal (GI) tract has improved appreciably over the past 50 years, as we have begun to realize the full potential of new imaging technologies. Because of developments in optical and image sensor technologies, we are able to visualize the surface structures of the GI tract more clearly than ever before.

As the technology evolves, the ability to identify new mucosal patterns that predict histology increases. Furthermore, the development of in vivo microscopy has the potential to obviate the need for biopsy. Akin to the revolutionary discoveries that radio, infrared, and gamma-ray telescopes have contributed to the field of astronomy by helping astronomers see objects previously undetectable in the visible spectrum, we now stand at the threshold of a plethora of novel technologies capable of enabling endoscopists to see the “unseeable.”

The introduction of flexible fiber-optic endoscopy in 1961 revolutionized the diagnosis and management of patients with GI pathology. In the 1990s, the newer charged coupled device (CCD) replaced this technology. Developments in video chip technology and miniaturization of the image sensor further enhanced endoscopic optical capabilities. More recently, the emergence of newer imaging technologies, such as narrow band imaging (NBI), autofluorescence imaging (AFI), and confocal laser endomicroscopy (CLE) has further enabled the endoscopist to visualize the minute and finer details of the GI mucosal surface and subsurface structures.

With these developments, the field of endoscopy is evolving from detection to diagnosis in real time. Another windfall of these technologies is that they are enhancing our understanding of the in vivo pathophysiology by
helping researchers study mechanisms and microarchitectural changes at a histological level. Thus, we now are able to appreciate tissue function as opposed to morphology alone. The affect of many of these newer technologies on overall patient outcomes remains to be seen.

Wide-field Macroscopic Imaging Techniques

**White-Light Endoscopy**

White-light endoscopy (WLE) currently is the standard of care in modern endoscopic centers. WLE uses the visible spectrum of light to form an image, thereby producing images similar to inspection of the mucosa with the naked eye. The resolution of the endoscope is dependent on pixel density, which is the number of pixels per unit of area. A pixel is an individual photosensitive unit that converts visual input into an electrical signal. The signals generated by thousands of pixels located at the tip of an endoscope are synthesized to form an image. This process takes place approximately 30 times per minute to produce a final motion picture video of the mucosa that is displayed on a screen. With improvements in pixel density, high-resolution endoscopes (HRE) produce exceptionally high-quality images that make it possible to discern the smallest mucosal changes. Furthermore, magnification endoscopy also is possible via a user-controlled optical zoom or an electronic zoom system. Optical zoom generally is superior, with magnifications ranging from 1.5- to 150-fold magnification.

WLE is the standard of care for any GI endoscopic procedure. All other technologies are compared with WLE in order to show any added clinical benefit. Current research comparing newer technologies with WLE will be presented in the following sections.

**Chromoendoscopy**

Chromoendoscopy is a modification of endoscopy whereby a white-light endoscope is used to visualize the mucosa after the topical application of stains or dyes. A fine mist of a dye is delivered to the mucosa using a spray catheter that is passed through the working channel of the endoscope. The contrast agent (eg, dye or stain) provides enhanced visualization of the mucosal characteristics. Chromoendoscopy aids in the detection of subtle mucosal changes, however, it does not enable the endoscopist to visualize submucosal or vascular changes.

Various dyes are available commercially for clinical use. Lugol’s solution is actively absorbed by the mucosa and therefore is not recommended for routine clinical use because of the difficulty in achieving complete, even coating of the mucosal surface with the dye and also the inability of the dye to reveal subsurface vascular pooling in crevices and pits of the GI tract, thereby enhancing subtle areas of depression or elevation. It is used in the detection of neoplastic colonic polyps, dysplasia in patients with ulcerative colitis, and intestinal metaplasia and dysplasia in patients with Barrett’s esophagus (BE).

**Esophageal squamous cell cancer** Chromoendoscopy with Lugol’s solution and toluidine blue has been studied in high-risk patients with SCC of the esophagus. In a study of 225 Chinese patients, chromoendoscopy with Lugol’s solution improved sensitivity (from 62% to 96%) compared with WLE in the detection of high-grade dysplasia (HGD) and cancer. Additionally, Lugol’s solution offers better visualization of the lateral margins of lesions compared with standard WLE alone. A prospective study of 1,095 patients concluded that Lugol’s solution significantly improved detection of HGD and cancer in high-risk patients.

Toluidine blue also has been studied for the detection of dysplasia and cancer in high-risk populations. Toluidine blue used in combination with Lugol’s solution is useful before endoscopic mucosal resection of early esophageal SCC.

**Barrett’s esophagus** Methylene blue is the most studied chromoendoscopic technique in patients with BE. Studies have shown varying results with respect to sensitivity (32%-98%) and specificity (23%-100%) in the diagnosis of BE. Several large studies have shown higher detection rates of intestinal metaplasia when methylene blue is used compared with random biopsies. However, these results were not replicated in other smaller studies. Methylene blue also has been studied for surveillance of BE. A recent meta-analysis of 450 patients in 9 studies showed no significant incremental yield with methylene blue when compared with conventional random biopsies for the detection of intestinal metaplasia, dysplasia, HGD, and EC. Of note, there have been some safety concerns regarding possible DNA damage when methylene blue is used in combination with white-light illumination.

Indigo carmine staining has been studied for the detection of intestinal metaplasia in patients with BE. Sharma et al examined 80 patients with suspected BE with indigo carmine and magnification endoscopy; this technique allowed for detection of 97% of intestinal metaplasia and 100% of HGD and EC.

Although some evidence exists for the use of chromoendoscopy, it is not recommended for routine clinical use because of the difficulty in achieving complete, even coating of the mucosal surface with the dye and also the inability of the dye to reveal subsurface vascular changes. The affect of many of these newer technologies on overall patient outcomes remains to be seen.
Colon polyps and colon cancer

Uncontrolled studies have shown indigo carmine chromoendoscopy to be useful for the detection of small, flat, depressed, or non-polyoid colonic lesions not detectable with standard WLE.\textsuperscript{36-38} A randomized controlled trial (RCT) comparing pancolonic indigo carmine chromoendoscopy versus standard colonoscopy showed a higher detection rate of adenomas smaller than 5 mm in diameter with chromoendoscopy.\textsuperscript{39} Another RCT that compared high-resolution chromoendoscopy with magnification colonoscopy showed a higher detection rate of flat adenomas and hyperplastic polyps in with chromoendoscopy.\textsuperscript{40} Finally, another study showed that pancolonic indigo carmine allowed for the detection of more adenomas less than 4 mm in diameter, flat polyps in the right colon, and hyperplastic polyps in the left colon compared with targeted chromoendoscopy.\textsuperscript{41} However, procedure duration increased 2- to 3-fold,\textsuperscript{39,40} thereby making this technique impractical for routine use.\textsuperscript{42} In 2 back-to-back studies, indigo carmine increased the detection rate of adenomas—including flat adenomas—in patients with hereditary nonpolyposis colorectal cancer (CRC) syndrome.\textsuperscript{43,44}

Indigo carmine chromoendoscopy enhances patterns seen in colonic lesions. The kudo pit pattern classification is helpful for identification of hyperplastic polyps (eg, round, stellar pits) and adenomatous polyps (eg, tubular, gyrus-like, irregular pits).\textsuperscript{45} Indigo carmine was shown to have good sensitivity (82%-95%) and specificity (64%-95%) for the prediction of polyp histology.\textsuperscript{46-50} Magnification chromoendoscopy showed a further improvement in prediction capability, with an improvement in accuracy from 84% to 96%.\textsuperscript{51} Additionally, interobserver agreement of prediction of polyp histology using pit patterns has been reported to be good.\textsuperscript{52} However, despite its accuracy and good interobserver agreement, chromoendoscopy has not replaced histology in the evaluation of colon polyps.\textsuperscript{42}

Inflammatory bowel disease (IBD)

Prospective and randomized trials have shown indigo carmine and methylene blue to be useful in the detection of dysplasia in patients with chronic ulcerative colitis (UC). The technique is included in recommendations on surveillance of patients with IBD.\textsuperscript{53-58} A German study of 165 patients showed that chromoendoscopy with methylene blue staining was associated with a significantly higher correlation between disease activity and extent compared with endoscopy.\textsuperscript{53} Furthermore, chromoendoscopy was associated with significantly higher detection rates of flat neoplasia compared with standard colonoscopy.\textsuperscript{53} Another study of 117 patients with chronic UC revealed that chromoendoscopy with indigo carmine had significantly higher sensitivity and specificity for detection of low-grade dysplasia and HGD.\textsuperscript{55}

Autofluorescence imaging

Autofluorescence imaging (AFI) involves illumination of excitable components of human tissues—called fluorophores—with short wavelength light. This energy is absorbed by the fluorophores then emitted in the form of longer wavelength fluorescence. Each tissue emits a specific wavelength of light that is dependent on the type of fluorophores contained in the cells. The most common fluorophores are collagen, porphyrins, aromatic amino acids, flavins, and reduced nicotinamide adenine dinucleotide.\textsuperscript{59} This technology relies on the fact that abnormal (metaplastic and dysplastic) cells emit a different wavelength of light than normal cells because of differences in concentrations of endogenous fluorophores. The technology is called autofluorescence endoscopy because it relies on the emitted fluorescence of the tissue of interest. The first endoscopes equipped with AFI technology were based on fiber-optic systems, but AFI now is available in HREs.\textsuperscript{50}

AFI has the potential to be used in diseases where large areas of mucosa are at risk for harboring dysplasia in very small and patchy areas. Therefore, it has been considered to be helpful as a broad-field technique to obtain targeted biopsies of high-risk mucosa.

Barrett's esophagus

AFI has been studied in the detection of dysplasia in patients with BE. Initial studies with the fiber-optic system yielded mixed results. In a study of 34 patients with BE, AFI detected more patients with HGD compared with WLE (7 vs 1). However, a subsequent study revealed poor sensitivity (34%) of the technology.\textsuperscript{29} A randomized crossover trial by Kara et al concluded that AFI did not improve detection of HGD and EC in patients with BE.\textsuperscript{61}

Studies of AFI in the context of HREs also are inconclusive to support its routine usage. In a study of 60 patients with BE, AFI improved the detection of HGD and cancer compared with WLE (33% vs 23%); however, AFI was associated with a high false-positive rate (35%).\textsuperscript{62} Poor image quality, lack of visualization of sub-surface changes, high false-positive rates, and unstable color tone have limited the clinical usefulness of AFI.\textsuperscript{59}

An initial feasibility study of multimodality imaging including AFI in 84 patients demonstrated improvement in the detection of early neoplasia in patients with BE. The false-positive rate of AFI decreased from 81% to 26% after detailed inspection with NBI. In another study, promising results were seen in the targeted detection of HGD and cancer in patients with BE when compared with standard endoscopy.\textsuperscript{63}

Colon polyps

In a pilot study of 167 patients, AFI assisted in the detection of 100 polyps compared with 73 polyps detected with WLE. Furthermore, the miss rate was significantly lower with AFI compared with WLE (30% vs 49%).\textsuperscript{64} The study authors concluded that
AFI was capable of detecting more right-sided polyps than WLE. Another study examining the role of AFI in differentiating adenomatous and hyperplastic polyps reported good sensitivity (89%) and specificity (81%). Given the limited studies that have evaluated the role of AFI in colon, its role in colon cancer screening is unclear at this time.

**Inflammatory bowel disease** A small study published in 2007 showed that AFI could be used for the detection of dysplasia in patients with chronic UC. A randomized trial of tandem colonoscopies in 50 patients showed that neoplasia miss rates were significantly lower for AFI compared with WLE (0% vs 50%). Another prospective study (N=48) that compared AFI with histology found that protruding lesions were associated more often with dysplasia than with flat lesions (31% vs 3.3%).

**NBI and Other Electronic Chromoendoscopy Techniques**

NBI uses a narrow bandwidth of projected light of blue (415 nm) and green (540 nm) to construct an image of the mucosa. Because of the shorter wavelength and higher energy associated with blue light, it has the ability to superficially penetrate the mucosa. This wavelength of light also is absorbed by hemoglobin. As a result, superficial mucosal vessels appear brownish, whereas deeper vessels appear greenish.

NBI endoscopes are constructed using a red–green–blue (RGB) sequential illumination type (when black-and-white CCDs are used) or the color CCD type. In systems using the RGB sequential illumination system, the CCD input from blue and green light are video-processed and undergo color transformation to produce pseudo-color images. However, in the color CCD system, only the electrical signals transduced by the blue and green pixels are processed; this undergoes color transformation to produce a pseudo-color image. Newer endoscopes, such as i-scan and FUJI Intelligent Chromo Endoscopy, use an advanced post-image acquisition algorithm to convert white-light images to show surface and subsurface vascular patterns.

**Barrett’s esophagus** Using NBI, different mucosal (eg, regular, round, oval, villous, irregular, abnormal) and vascular (normal, regular, irregular, abnormal) patterns can be recognized within the BE segment. These patterns can be used to predict histology. A recent meta-analysis that included 3 studies and 580 biopsies revealed good sensitivity (77%-100%), specificity (79%-94%), and accuracy (88%-96%) of NBI in differentiating gastric mucosa from intestinal metaplasia. A pooled analysis of 5 studies and 756 biopsies showed that NBI had a sensitivity of 97% (95% confidence interval [CI], 89%-99%), a specificity of 94% (95% CI, 60%-99%), and an overall accuracy of 96% (95% CI, 72%-99%) for the differentiation of dysplastic and nondysplastic BE.

Only a few RCTs have evaluated the efficacy of NBI compared with WLE or chromoendoscopy. One trial by Kara et al compared chromoendoscopy and NBI in the detection of HGD or EC in 28 patients with BE. In this RCT, indigo carmine chromoendoscopy and NBI were comparable for the detection of HGD and EC. However, this study was likely underpowered to detect such a difference. A multicenter, crossover RCT by Sharma et al comparing high-definition WLE with NBI in 116 patients found no difference in the detection of intestinal metaplasia (85% vs 86%). However, this study found that patients in the NBI group required significantly fewer biopsies (3.7 vs 8 per patient). Wolfsen and colleagues evaluated 65 patients in a prospective, blinded, tandem endoscopy study comparing NBI with WLE. In this study, NBI identified more patients with dysplasia (57% vs 43%) and was associated with significantly fewer biopsies per patient (4.7 vs 8) compared with WLE. Based on these findings, it is likely that NBI may improve the detection of dysplasia, or at the least decrease the number of biopsies necessary, when used in conjunction with WLE.

**Colon polyps and cancer** Three RCTs have been reported comparing NBI with WLE for the detection of adenomas in screening and surveillance colonoscopies. A significant improvement in the number of adenomas detected per patient was noted in only one of these studies (0.84 vs 0.55). In the other 2 studies (Rex and Helbig, N=434; Adler et al, N=401), no difference in adenoma detection rates with NBI was observed. Additionally, 2 cross-tandem studies have been performed. Both studies examined patients who had undergone WLE colonoscopy with a second-pass NBI. East et al performed their study in patients with hereditary nonpolyposis CRC syndrome, whereas Rastogi et al included patients undergoing CRC screening. In these studies, the polyp miss rates were 41% (29 of 70) and 46% (21 of 46), respectively, when an additional inspection was performed with NBI.

Using mucosal and vascular pit patterns seen on electronic chromoendoscopy, several post hoc image studies evaluated the differentiation of neoplastic from non-neoplastic colon polyps. In a recent meta-analysis of 6 studies including 358 neoplastic and 158 non-neoplastic lesions, NBI predicted histology with high sensitivity (83%-97%), specificity (64%-100%), and overall accuracy (77%-93%). Also, there was good interobserver agreement in the prediction of histology. This could eventually lead to a resect-and-discard technique, especially for distal, diminutive polyps.

**Inflammatory bowel disease** A prospective RCT including 42 patients with chronic UC found no statistical difference between NBI and WLE for the detection of neoplasia. A prospective study that evaluated 296 sites (protruding and flat areas) examined the ability of NBI to predict histology based on mucosal pit patterns in patients with chronic UC. The study showed that NBI could predict dysplasia better in protruding lesions rather than flat lesions. Recently, there has been growing interest in using NBI as a tool for assessing active inflammation in IBD. Using 157 colorectal segments from 30 patients with chronic UC, it has been shown that NBI may have some value in determining the grade of inflammation.
Microscopic Imaging Techniques

**ENDOMICROSCOPY**

Confocal laser endomicroscopy (CLE) is a novel endoluminal imaging technique that uses the principles of confocal imaging to visualize in vivo histology in real time. Unlike light microscopy, confocal microscopy provides high-quality images by preventing light scattering. This is achieved by using a single distal lens as a condenser for the purpose of focusing the laser on to the tissue of interest, as well as the objective lens to transmit the light emitted by the tissue. This generates highly focused images from a thin focal plane, and the technology therefore is believed to have “optical slicing capability.” There are 2 main types of CLE: an endoscope-based CLE (eCLE) in which the confocal imaging system is integrated into the endoscope; and a probe-based CLE (pCLE), which can be passed through the accessory channel of most endoscopes. Both types of CLE require contrast agents for imaging. pCLE involves a blue laser that causes excitation of tissue after it has been exposed to IV fluorescein dye. The light emitted by the tissue is transmitted through the probe to a laser-scanning unit by means of numerous optic fibers. The laser-scanning unit then generates black-and-white “sliced” images of the tissue in real time.

**Barrett’s esophagus** CLE has yielded promising results in the characterization of HGD and EC in BE. An initial study of 63 patients undergoing BE surveillance and those referred for endoscopic therapy showed that eCLE was capable of predicting neoplasia with good sensitivity (92.9%), specificity (98.4%), and accuracy (97.4%). The study also found high interobserver (κ=0.84) and intraobserver agreement (κ=0.89). A randomized double-blind crossover study of 39 patients showed that eCLE with target biopsies significantly improved the diagnostic yield of endoscopically apparent BE neoplasia compared with standard endoscopy 4-quadrant random biopsies (33% vs 17%). The study also found that eCLE reduced the number of biopsies needed per patient compared with standard endoscopy random 4-quadrant biopsy (9.8 vs 23.8).

Pohl et al performed a prospective cohort study in which 296 biopsies were taken from 38 patients with BE. They found high sensitivity (80%), specificity (94%), and overall accuracy (93%) for the detection of HGD and EC. Additionally, interobserver agreement was good (κ=0.6). Another interobserver agreement study of 11 BE experts using 20 high-quality video sequences found an overall accuracy of 92% for the diagnosis of HGD and EC with pCLE. The overall agreement in this study was 86%.

Recently, Sharma et al evaluated the role of pCLE in combination with 2 broad-field macroscopic techniques—high-definition WLE and NBI—for the detection of HGD and EC. In 97 patients with BE, sensitivity increased from 45% to 76% when pCLE was used in combination with WLE, NBI, or both. The study also showed that 39% of biopsies could be avoided using this modality compared with standard 4-quadrant targeted biopsies. pCLE was thus capable of reducing the number of biopsies needed and improving detection when used in combination with multimodal imaging.

**Colon polyps** Kiesslich and colleagues published the first study evaluating the role of CLE in the diagnosis of intraepithelial neoplasia and CRC. A total of 13,020 confocal images from 390 locations in 42 patients were compared with histologic data. CLE was found to have high sensitivity (97%), specificity (99%), and accuracy (99%) in the prediction of histology. Another prospective study of 39 patients found comparable sensitivity (97%), specificity (97%), and overall accuracy (99%). More recently, a prospective study of 75 patients reported higher sensitivity of pCLE compared with virtual chromoendoscopy (91% vs 77%). Despite the high sensitivity and specificity of CLE in predicting histology in colon polyps, the role of CLE in colon cancer screening is unclear at this time.

**Inflammatory bowel disease** A feasibility study comparing CLE-generated features in patients with or without chronic UC concluded that CLE images were equivalent to conventional histology. The study found differences in the shape and size of crypts and microvascular structures between patients with and without chronic UC. Another recent study found that crypt architecture, microvascular alterations, and fluorescein leakage were markers for inflammatory activity in patients with chronic UC.

An initial study of 36 patients showed that CLE was capable of differentiating between adenoma-like masses and dysplasia-associated lesional masses in patients with chronic UC with a high degree of accuracy (97%). Thus, CLE may have a role in decreasing the number of biopsies required in patients with chronic UC undergoing surveillance.

**Newer Imaging Technologies**

Numerous other new imaging technologies are now being tested for clinical use. Light-scattering spectroscopy, Raman spectroscopy, and laser-induced spectroscopy have been shown to have a role in colon cancer screening. Optical coherence tomography (OCT) has been said to be similar to ultrasound, however, it uses light in place of sound. Optical frequency domain imaging, a recent advance in OCT, may be capable of high-speed microscopic screening of distal esophagus for EC. Newer molecular imaging techniques are being explored. A CLE visualization of labeled vascular endothelial growth factor has shown promising results in animal studies. Digital image analysis may be available soon to help interpret findings with a high degree of accuracy. These “new” imaging techniques currently are undergoing rigorous preclinical and early clinical testing and will need to be evaluated in large clinical trials before becoming available for routine clinical use.
Conclusions

This article describes the advances in endoscopic imaging techniques and their clinical implications. The goal of advanced imaging is to identify subtle changes in the GI mucosa and to provide real-time characterization of lesions so that neoplastic tissue can be identified early and perhaps removed, thereby improving patient outcomes. Other benefits of these imaging techniques include helping the endoscopist obtain targeted biopsies of high-risk lesions, making in vivo, real-time diagnoses, and decreasing overall procedural costs by decreasing the number of necessary biopsies.

Despite technologic advancements, certain challenges remain, such as interobserver variability and increased procedure duration. Furthermore, after a technology has been shown to be clinically useful, the extent to which it is adopted into clinical practice relies on many other issues, such as cost, reimbursement, ease of use, availability of training, interobserver agreement, and procedure duration.

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