Endoscopic imaging of Barrett's esophagus

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Abstract

The incidence of esophageal adenocarcinoma (EAC) has dramatically increased in the United States as well as Western European countries. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small mucosal abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

Key words: Esophageal adenocarcinoma; Barrett's esophagus; Dysplasia; Intestinal metaplasia; Advanced endoscopic imaging; Narrow band imaging; Confocal laser endomicroscopy

Core tip: The majority of esophageal adenocarcinomas (EAC) arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

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INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has been steadily rising over the last three decades, with population-based cohort studies suggestive of a 300%-500% increase during this time[1]. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion which progresses through several stages of dysplasia to cancer. The prevalence and incidence of BE have increased over time, parallel to the increase in frequency of EAC[2]. There are various estimates (ranging from 0.1%-2.0%) of the annual rate of progression from BE to cancer, with higher rates of progression to cancer reported for patients with low grade dysplasia (0.54% to 1.8% per year) and high grade dysplasia (6.6% per year)[3-6]. Because of the increased risk of EAC, GI society guidelines recommend that patients with BE undergo endoscopic surveillance[7-10]. The aim of endoscopic surveillance is to identify areas of dysplasia which can subsequently be treated with endoscopic eradication therapy before progression to cancer. In patients with BE undergoing surveillance, biopsies are collected from areas with visible mucosal abnormalities and at random in four quadrants every 1-2 cm along the BE segment[11]. This protocol, however, is labor intensive and can still miss neoplasia despite multiple biopsies.

The emphasis on early detection of pre-cancerous lesions has led to the development of advanced imaging technologies to improve care of patients with BE. These techniques have the potential to improve mucosal visualization and detection of abnormal tissue, such as with high-definition white light endoscopy (HD-WLE), while other techniques such as dye-based or electronic chromoendoscopy enhance and adjust the color of the endoscopic images to improve lesion detection and tissue characterization. There are also techniques that allow histological evaluation such as confocal laser endoscopy (CLE). This review summarizes the currently available advanced imaging technologies used in evaluation of BE.

CONVENTIONAL (WHITE LIGHT) ENDOSCOPY

HD-WLE

Over the past decade, high resolution endoscopes using high definition (HD) systems have largely replaced the original low-resolution or standard definition (SD) white light video-endoscopes in most if not all endoscopic units. Capable of producing images with higher magnification and an image resolution of more than 1 million pixels (compared to the 100000-400000 pixels of standard-definition endoscopes), HD-WLE has enhanced the endoscopists' ability to inspect and visualize subtle mucosal abnormalities[12,13]. Many research studies using HD-WLE combine it with another advanced endoscopic imaging technique, such as narrow band imaging (NBI) or chromoendoscopy[14,15]. There are few studies comparing standard endoscopy with HD-WLE, but one study did show improved detection of dysplasia using HD-WLE[16]. In some studies, addition of additional imaging techniques does not significantly improve detection of BE and neoplasia above HD-WLE alone on a per-patient basis, although additional lesions may be detected and fewer biopsies may be acquired[17-19]. Though high resolution endoscopes have higher sensitivity for detection of neoplasia than standard endoscopes, targeted biopsies using high resolution endoscopy (HRE) alone may still miss dysplasia that is found using random biopsies[15].

Magnification endoscopy

Magnifying or zoom endoscopes permit better visualization of mucosal details by enabling the images to be magnified from 1.5 times to 150 times without loss of resolution[20]. While magnification endoscopy alone allows for visualization of mucosal surface patterns and vessels, this technique has most often been studied in combination with chromoendoscopy. In one study, magnification chromoendoscopy improved the detection of intestinal metaplasia (IM) and HGD in patients BE compared to standard endoscopy[21]. Magnification endoscopy is not widely used for patients with BE and some studies have shown a high level of inter-observer variability in identifying dysplastic lesions[22].

ENHANCING COLOR DURING ENDOSCOPY

Chromoendoscopy

Chromoendoscopy involves endoscopic evaluation of gastrointestinal mucosa following the topical application of dyes or contrast agents. The goal of chromoendoscopy is to improve the detection and characterization of abnormalities and facilitate targeted biopsy sampling of suspicious areas. While it can be used with standard endoscopy, chromoendoscopy is most often performed with another advanced imaging modality, such as HD-WLE, magnification endoscopy, or confocal endomicroscopy. There are several types of chromoendoscopy agents, some of which are absorbed by cells, while others highlight the mucosal surface. Absorptive stains, such as methylene blue (MB) and Lugol's iodine, are absorbed across cell membranes while contrast agents such as indigo carmine are not absorbed by the mucosa but highlight the surface topography and mucosal irregularities.

Methylene blue has been used in several studies of patients undergoing chromoendoscopy for evaluation of BE and BE-associated neoplasia. Several studies suggested that MB could discern areas of IM

and dysplasia with high accuracy and with fewer biopsies compared to traditional surveillance techniques[23-26]. However, other studies have found that chromoendoscopy was not better than conventional four quadrant random biopsies for detection of BE and neoplasia[27,28]. Further limiting the widespread use of methylene blue chromoendoscopy is the potential risk of DNA damage and carcinogenesis[29].

Indigo carmine has been used in conjunction with magnification endoscopy to identify the mucosal pit patterns within segments of BE[21,30]. The presence of villiform pit patterns and irregular mucosal patterns have been shown to correlate with presence of IM and dysplasia[30].

Acetic acid chromoendoscopy has been used in several recent studies for evaluation of patients with BE. Targeted biopsies following staining with acetic acid has been associated with increased yield for detecting BE as well as dysplasia and early cancer within an area of BE[31]. One retrospective cohort study evaluated the yield for neoplasia in patients with BE, comparing acetic acid chromoendoscopy and a standard random biopsy protocol. Acetic acid chromoendoscopy detected more neoplasia than conventional protocol-guided mapping biopsies and required significantly fewer biopsies per neoplasia detected[32]. Another randomized crossover study of acetic acid magnification endoscopy found a higher yield for detection of BE (78%) compared to standard endoscopy with biopsy (57%)[33].

In comparison to other endoscopic imaging modalities, chromoendoscopy is relatively inexpensive, requiring only a spray catheter and contrast agent, many of which are readily available. On the other hand, chromoendoscopy can be cumbersome requiring a significant increase in endoscopy time and image interpretation is operator dependent, with high inter-observer variability reported in some studies[22]. These factors and the mixed results of research studies have limited the widespread use of chromoendoscopy in patients with BE.

Electronic chromoendoscopy: Narrow band imaging
First described in 2004 by Gono *et al*[34], NBI enhances the resolution of the mucosal surface and is the most-investigated image-enhanced endoscopy technique[34,35]. NBI restricts the wavelengths of light used for endoscopic imaging. Shorter wavelength blue light (440-460 nm) highlights the superficial capillary network, while longer wavelength green light (540 nm) highlights the sub-epithelial vessels, allowing identification of subtle mucosal abnormalities. Furthermore, as blue light is absorbed by hemoglobin, the alterations in vascular patterns associated with neoplasia may be detected.

NBI has shown promise in the detection of BE-associated dysplasia[36,37]. In a recent meta-analysis of eight studies including 446 patients and 2194 lesions, NBI demonstrated a pooled sensitivity and specificity of 95% and 65%, respectively, for the detection of BE. The sensitivity and specificity of NBI in detecting HGD was 96% and 94%[38]. Additional studies have demonstrated NBI's superiority in identifying higher grades of dysplasia in comparison to WLE using significantly fewer biopsies per patient[14,17,37]. However, not all studies have shown an improvement in detection of neoplasia using NBI. Kara *et al*[15] found no difference in the detection of HGD and intra-mucosal cancer (IMC) in a tandem study comparing HD-WLE and NBI, although NBI did detect additional lesions in some patients who had neoplasia identified by HD-WLE.

Several studies have focused on the specific mucosal patterns, or pit patterns, associated with BE and BE-associated neoplasia. Hamamoto *et al*[39] described the use of NBI and a pit pattern classification system in BE and reported superior results when magnifying endoscopy was combined with NBI. Several studies of NBI combined with magnification endoscopy have identified irregular microvascular and microstructural patterns with a high sensitivity, specificity and positive predictive value for identification of HGD and cancer[36,37,40]. Singh *et al*[41] demonstrated that presence of a villous or ridged with regular microvasculature was suggestive of IM, while a distorted pit pattern and irregular microvasculature was highly suggestive of dysplasia. A meta-analysis of the various NBI pit pattern classification schemes for BE found a high sensitivity (96%) and specificity (94%) for detection of BE neoplasia when irregular pit patterns and/or microvasculature were identified using NBI with magnification[38].

The advantages of NBI include the ability to study both mucosal and vascular patterns, the ease of use, and integration into standard endoscopic equipment. Limiting the widespread implementation of NBI-targeted biopsies has been the lack of a universal classification system for the mucosal and vascular patterns observed and some studies have shown only moderate interobserver agreement with interpretation of NBI images[40,42].

Electronic chromoendoscopy: Flexible intelligent chromoendoscopy and i-scan
Similar to the principle behind NBI, Flexible Intelligent Chromoendoscopy (FICE) and i-scan are electronic chromoendoscopy techniques that manipulate the red, green, and blue components of light to create an image that enhances the superficial mucosal and vascular structures. FICE has been used in several studies, including one that showed FICE was able to clearly demarcate the junction between Barrett's mucosa and gastric mucosa[43]. In one study comparing FICE and acetic acid chromoendoscopy, FICE was found to have comparable sensitivity to acetic acid chromoendoscopy for detection of BE neoplasia[44]. I-scan has also been used in patient with BE, most recently in a randomized trial comparing the efficacy of endoscopy with 4-quadrant random biopsies and targeted biopsies using i-scan or acetic acid chromoendoscopy[45]. Use of i-scan or acetic acid-guided biopsies produced a significantly

higher diagnostic yield for IM compared to endoscopy with random biopsies. Acetic acid and i-scan showed comparable results for diagnosis of BE.

Autofluorescence imaging

Endogenous tissue fluorophores are biological substances in mucosa that emit fluorescent light when exposed to a light of a shorter wavelength. Autofluorescence imaging (AFI) is based on the principle that different tissue types differ in their fluorescence emission, with normal mucosa appearing green under fluorescence excitation, while dysplasia and neoplasia appears magenta or purple[46]. Differences in fluorescence emission can be examined using a fluorescence-detecting endoscope and these differences in fluorescence can be used for lesion detection and characterization.

AFI is a sensitive but poorly specific tool for the detection HGD and early cancer in BE[47-49]. Studies comparing AFI to white light endoscopy (WLE) found that AFI increased the detection of HGD and IMC compared with WLE, but was associated with a high false positive rate[49]. Subsequent studies have attempted to reduce this false positive rate by combining AFI with NBI, with improvement in one study of patients with BE and suspected neoplasia from false positive rate of 40% to 10% using NBI[48]. The combination of high resolution WLE, AFI and NBI is known as endoscopic trimodal imaging (ETMI), and is not currently available in the United States. An international multicenter study by Curvers *et al*[50] compared ETMI with standard video endoscopy and demonstrated that addition of AFI to HRE increased detection rate of HGD and IMC compared to WLE alone (90% *vs* 53%), but did so at the expense of a high false-positive rate of 81%, which was reduced to 26% with the addition of NBI. Two subsequent large randomized studies from the same group comparing ETMI and WLE failed to show superiority of ETMI over endoscopy with a 4 quadrant random biopsy protocol[19,51]. Furthermore, in these studies random four quadrant biopsies with WLE identified more areas of high grade dysplasia (HGD) and EAC than targeted biopsies after ETMI inspection. The addition of NBI to AFI and HRE reduced the false positive rate in one of the studies, although 17% of dysplastic lesions were re-classified as being normal[51]. While AFI may be useful as an adjunctive technique to WLE, due to its decreased sensitivity and high false positive rate, AFI as a solo method of detection is not suitable to replace the standard BE surveillance biopsy protocol.

MICROSCOPIC ENDOSCOPY

Several advanced endoscopic imaging techniques are available for *in vivo* histological evaluation of the esophageal mucosa, and are used in conjunction with WLE and other advanced endoscopic imaging techniques to identify suspicious lesions that require

further evaluation.

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) magnifies the mucosa up to 1000-fold and up to 250 μm below the mucosal surface allowing for real-time histological assessment of the GI mucosa during endoscopy. When evaluating patients with BE, this level of magnification allows for visualization of the specialized IM and goblet cells. Two endomicroscopy platforms have been used for most of the CLE studies of BE, an endoscope based confocal system (eCLE) in which a confocal microscope is integrated into the tip of a standard endoscope and a probe-based system (pCLE), in which a probe is passed through the accessory channel of the endoscope. Both systems use blue laser light and require administration of either topical or intravenous fluorescent contrast agents.

The initial study of eCLE found that BE and BE-associated neoplasia could be identified with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively[52]. A subsequent prospective randomized controlled crossover trial of eCLE found that CLE with targeted biopsies almost doubled the diagnostic yield for neoplasia compared to a standard biopsy protocol for BE (33% *vs* 17%), with a significant reduction in the number of mucosal biopsies needed for diagnosis. Two thirds of patients in this study undergoing routine surveillance of BE were able to avoid any mucosal biopsies during their CLE procedures[53]. In a subsequent multicenter randomized, controlled trial of eCLE, 192 patients with BE were randomized to either HD-WLE with random biopsies or HD-WLE and CLE with targeted biopsies. In this study, CLE with targeted biopsies outperformed HD-WLE with standard biopsies for detection of neoplasia (22% *vs* 6%) and impacted clinical decision-making (such as the decision to perform endoscopic mucosal resection) in almost 1/3 of patients[54]. Multiple studies have evaluated use of pCLE in patients with BE with promising results. Bertani *et al*[55] found the use of pCLE in addition to WLE enhanced the detection of dysplasia compared with WLE alone (28% *vs* 10%). A multi-center study of 101 patients found the addition of pCLE to HD-WLE improved the diagnostic yield and detection of neoplasia[56]. This study examined the pCLE for *in vivo* prediction of HGD and EAC and found that the addition of pCLE to WLE and NBI increased sensitivity for neoplasia from 45% to 76% and allowed for a reduction in number of biopsies needed for diagnosis[56]. The advantages of CLE, such as the potential for real-time histological diagnosis during an endoscopic procedure, may be offset by the increased procedure length, equipment costs, and the training necessary to interpret the images.

Endocytoscopy

Endocytoscopy allows for real time microscopic imaging of the mucosa using white light and special lenses for

magnification. Images are acquired on the surface of the mucosa after application of a contrast agent, most commonly methylene blue. Surface magnification during endocytoscopy is up to 1400-fold, depending on the endocytoscopy system used and has been used in several studies of squamous esophageal cancer and squamous dysplasia[57]. Studies have reported variable accuracy of endocytoscopy for the detection of neoplasia in a backdrop of BE and the technique has been limited in BE patients by inadequate image quality. In one study evaluating patients undergoing surveillance for BE, image quality was found to be inadequate in 49% of sites imaged at 450-fold magnification and inadequate in 22% of images using 1125-fold magnification[58]. Another study has examined *ex vivo* EMR specimens with endocytoscopy to develop a classification system which showed good accuracy and interobserver agreement. At this time, endocytoscopy is not widely used in management of patients with BE[59].

OTHER LIGHT-BASED TEHCNIQUES

Optical coherence tomography
Optical coherence tomography (OCT) is similar to ultrasound in acquiring tissue images but uses light waves rather than acoustic waves to generate cross-sectional images of epithelial and sub-epithelial tissues based on differences in optical scattering of the tissue structures. OCT does not require tissue contact and images are obtained *via* a catheter introduced through a standard endoscope. One prospective clinical study assessed the presence of dysplasia in BE in 55 patients using 177 biopsy correlated images and found that OCT could detect HGD and EAC with 83% sensitivity and 75% specificity[60]. Several other studies have evaluated a variety of OCT systems and found variable sensitivity, specificity, and accuracy for detection of dysplasia in Barrett's esophagus[61-63].

Optical frequency domain imaging and volumetric laser endomicroscopy
Optical frequency domain imaging (OFDI), also known as volumetric laser endomicroscopy (VLE), allows for high resolution, high-speed acquisition of larger areas of the luminal surface than standard OCT. Preliminary studies with both OFDI/VLE have suggested that differences between normal squamous mucosa, BE, and BE neoplasia can be identified using this technique[64,65]. Recent studies of VLE have focused on interobserver agreement with image interpretation and correlation of VLE images with histology findings[66,67].

Spectroscopy
Spectroscopy uses variation in scattered light across a full spectrum to obtain information about nuclear size, crowding, vascularity and tissue structure and organization. Several types of spectroscopy have been used to study BE, including light-scattering, reflectance and Raman spectroscopy. Light-scattering spectroscopy

provides information about cell nuclei characteristics and has demonstrated the ability to detect dysplasia in patients with BE[68,69]. Reflectance spectroscopy measures the color and intensity of reflected light after tissue illumination to help differentiate normal from neoplastic tissue and has also been used in studies of BE[70,71]. Raman spectroscopy detects scattered light that has been changed in wavelength (termed inelastic scattering) and results in characteristic peaks and bands that are correspond with normal *vs* abnormal mucosa. One study reported an accuracy of 96% when using Raman spectroscopy for detecting EAC[72]. In a large study of 373 BE patients, Raman spectroscopy was used for real-time detection of BE and neoplasia with good success[73]. At this time, spectroscopy remains an interesting research technique for patients with BE.

CONCLUSION

In the last decade there have been many advances in the field of endoscopic imaging for the detection of early dysplastic changes and neoplasia in patients with BE. While many of these modalities have demonstrated high sensitivity and specificity in detecting dysplasia and EAC, some limitations to widespread adoption exist. The need for training in image interpretation, inter-observer variability in image interpretation, expensive equipment, and potential increases in procedure length have limited use of these technologies. Technological improvements could make several of these novel endoscopic imaging techniques easier to use, and in time endoscopists may become more comfortable with advanced endoscopic imaging options. In the future, advanced endoscopic imaging techniques could improve care for patients with BE and BE-associated neoplasia by providing more accurate detection of dysplasia and providing real-time histology.

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