

Endoscopic imaging in Barrett's esophagus: current practice and future applications

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Abstract

Barrett's esophagus (BE) is a condition that develops as a consequence of chronic gastro-esophageal reflux disease in which stratified squamous epithelium is replaced by metaplastic columnar epithelium which in turn predisposes to the development of adenocarcinoma of esophagus. In this review article, we discuss recent advances in the endoscopic imaging techniques for the detection of dysplasia and early carcinoma in BE. This will include some of the current available novel technologies as well as future applications specifically concentrating on high-resolution endoscopy, narrow band imaging, chromoendoscopy, confocal laser endomicroscopy and autofluorescence imaging.

Keywords Barrett's esophagus, autofluorescence imaging, chromoendoscopy, confocal laser endomicroscopy, high-resolution endoscopy, narrow band imaging, optical coherence tomography

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Introduction

Barrett's esophagus (BE) is a premalignant condition which develops as a consequence of gastro-esophageal reflux disease (GERD) [1-3]. In the United States, BE is defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and confirmed to have intestinal metaplasia (IM) by biopsies [4], whereas the British Society of Gastroenterology has excluded the need for IM. It is thought that BE progresses in a step wise manner from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally esophageal adenocarcinoma (EAC) [5] which has been attributed to DNA alterations in the mucosa [6].

Epidemiology

BE is usually seen in middle-aged and older adults whose mean age at the time of diagnosis by endoscopy is 55 years [7]. The male to female ratio is 2:1 [8]. Estimates of frequency

of BE in general population has varied widely ranging from 0.9-20% [9-12]. This may be partly explained by the different populations studied and definitions used.

Screening

In order to decrease mortality from EAC, endoscopic screening for BE in patients having GERD symptoms has been recommended by the American College of Gastroenterology (ACG) [13,14]. It is however unclear if screening patients with GERD symptoms has any impact on identifying individuals at increased risk of EAC as 40% of patients diagnosed with EAC have no history of heartburn [15]. This presents a major limitation in screening patients with GERD symptoms for BE and EAC [16,17]. Although highly controversial, screening may be recommended in patients with the following risk factors:

- Age 50 years or older
- Male sex and white race with chronic GERD symptoms
- Patients with evidence of a hiatal hernia
- Patients with an elevated body mass index and intra-abdominal distribution of body fat

The American Gastroenterology Association (AGA) recommends against screening the general population with GERD symptoms [18].

Surveillance

The annual rate of incidence of cancer in patients having BE has been estimated at ranging between 0.12-2.0% [19-27].

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Table 1 Dysplasia grade and surveillance interval, as per American College of Gastroenterology guidelines [4]

Dysplasia	Documentation	Follow-Up
None	Two EGDs with biopsy within 1 year	Endoscopy every 3 years
Low Grade	Highest grade on repeat EGD with biopsies within 6 months Expert pathologist confirmation	1-year interval until no dysplasia X 2
High Grade	Mucosal irregularity Repeat EGD with biopsies to rule out EAC within 3 months Expert pathologist confirmation	ER Continued 3 months surveillance or intervention based on results and patient

EGD, esophagogastroduodenoscopy; ER, endoscopic resection; EAC, esophageal adenocarcinoma

A recent large population based Danish study reported that the annual risk of EAC among patients with BE was 0.12%, or 1 case of EAC per 860 patient years [27]. This was similar to another large population based study from Northern Ireland in which incidence rate of EAC was reported to be 1.3 cases per 1000 patient years (excluding cases that were diagnosed during the first year) [26]. These studies have brought into question the cost effectiveness of current surveillance protocols.

Surveillance is performed by taking four quadrant biopsies every 1-2 cm, however only a very tiny fraction of Barrett's mucosa is sampled this way [28,29]. Lesions harboring dysplasia or EAC can be easily missed. Some studies suggest a risk of occult carcinoma in patients with HGD of around 40% [30-32]. The present recommended surveillance interval by the ACG is depicted in Table 1.

Endoscopic surveillance can potentially detect curable early neoplasia. Asymptomatic cancers found during surveillance are less advanced when compared with symptomatic cancer patients who have dysphagia and weight loss [33,34]. During the last decade, novel endoscopic techniques have enabled increased recognition of dysplasia and early cancers in BE. This review will discuss some of the advances in endoscopic imaging in BE.

Paris classification

Endoscopic appearance of lesions in BE may point towards the lesions' potential to invade the submucosa (hence endoscopically unresectable). The updated Paris classification categorizes superficial lesions in esophagus into: protruding pedunculated (type 0-Ip), protruding sessile (0-Is), slightly elevated (0-IIa), completely flat (0-IIb), slightly depressed (0-IIc), excavated (0-III), or a mixed pattern [35]. A Danish retrospective study of endoscopic resection in BE suggested that type 0-I and 0-IIc lesions have higher submucosal infiltration rates [36]. There is surgical literature for patients with HGD in BE suggesting that a visible lesion on white light examination (WLE) is associated with an increased risk of coexisting cancer [37,38].

WLE with high-resolution and magnification endoscopy

High-resolution endoscopes (HRE) are endoscopes equipped with high-density charged coupled device (CCD)

chips enabling improved optics and images to be displayed at up to 850,000 pixels [39] (Fig. 1A). Magnification endoscopy enables the images to be magnified by up to 115 times by optical magnification [39]. These are major advancements in technology allowing for better visualization of the mucosa. Magnification endoscopy is best used in conjunction with chromoendoscopy [40-43]. A study by Sharma et al demonstrated that magnification chromoendoscopy helped to identify areas with IM and HGD [44]. The issue with this modality of imaging has been the high interobserver variability [45]. A study by Mayinger et al suggested that one reason for this is the difficulty in differentiating gastric cardiac mucosa from non-dysplastic Barrett's mucosa [46].

Chromoendoscopy

Dyes can be used to better visualize the mucosal surface of the gastrointestinal tract. Methylene blue (MB) has been used to visualize the presence of IM/HGD, and cancer [47]. It is a vital stain that is actively absorbed by mucosa and is



Figure 1 (A) Overview with high-resolution white light endoscopy: nodule in Barrett's esophagus

taken up by IM, but not gastric or squamous mucosa. Multiple reports have however shown discrepant results [48-51]. A meta-analysis by Ngamruengphong et al of 450 patients with BE in 9 studies concluded that MB chromoendoscopy had a yield for detection of specialized IM comparable to conventional four-quadrant random biopsies [52]. There is also a theoretical risk of acceleration of carcinogenesis with MB [53]. Indigo carmine has been used to evaluate dysplasia or cancer [54]. Acetic acid is another stain which has been used. However its utility in detecting dysplasia is not yet established [45,55,56]. The limitations to chromoendoscopy include the high interobserver variability secondary to lack of standardization of pit pattern classification systems [45], lack in training of general endoscopists, and a significant increase in the time taken for the examination. Studies looking at the impact of chromoendoscopy on patient outcomes are required.

NBI

NBI was first described in 2004 [57]. It is a technique that uses filtered light where an increased contribution of the short wavelength blue light (440-460 nm) leads to better visualization of the mucosal surface pattern. The superficial capillary network is also highlighted as blue light has an increased affinity to and is better absorbed by hemoglobin in blood [58] (Fig. 1B/1C).

Different pit pattern classifications have been described with this technology in BE [58-60]. These classification systems are in itself a limitation in the use of NBI as they make reproducibility in the community a problem. It requires further validation in large randomized multicenter trials [61]. Sharma et al described NBI images with mucosal patterns (ridge/villous, circular, irregular) and vascular patterns (normal and

abnormal) [59]. They demonstrated that presence of irregular mucosal or vascular patterns had a high sensitivity, specificity and positive predictive value for the diagnosis of HGD and cancer [59]. A prospective cohort study of 109 patients with BE exhibited that the presence of villous/ridged/absent pit patterns were highly suggestive of specialized IM (SIM) [60]. In another study it was found that NBI with optical magnification was superior to WLE and optical magnification in the prediction of dysplastic tissue in BE ($p < 0.05$) [62], whereas in a randomized crossover study comparing WLE with NBI by Kara et al no difference was found in the detection of HGD/intramucosal cancer (IMC) [63]. In another study by Wolfsen et al, NBI was found to have a higher detection rate of dysplasia, compared with WLE (57% vs. 43%) [64]. However an important bias in this study was that NBI was used with a high-resolution system when compared with WLE which used standard resolution. A systematic review by Curvers et al found good sensitivity (77-100%), specificity (79-94%), and accuracy (88-96%) of NBI in differentiating gastric mucosa from IM [65].

The advantage of NBI is that both the mucosal and vascular pattern can be studied. It can easily be combined with other modalities for better mucosal examination. Some of the other advantages of NBI include its wide availability, ease of use and integration into standard endoscopy with no additional risks to the patient.

Autofluorescence imaging (AFI)

AFI takes advantage of the phenomenon in which tissue after exposure to light of a shorter wavelength emits fluorescent light with a longer wavelength. Examples of tissue fluorophores are collagen, amino acids, flavins, etc. This phenomenon is



Figure 1 (B) Nodule in Barrett's esophagus in Figure 1A seen with narrow band imaging: some overlying squamous mucosa clearly visible as well

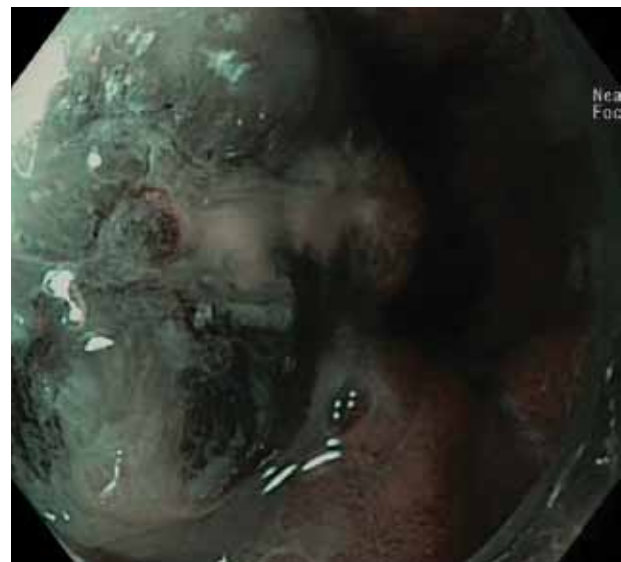


Figure 1 (C) Nodule on narrow band imaging with optical magnification: distorted pit pattern and vasculature in keeping with adenocarcinoma

called auto fluorescence [66,67] (Fig. 2A, 2B). Initial studies using point spectroscopy techniques demonstrated a difference between fluorescence pattern of Barrett's dysplasia/cancer and normal tissue [68-70]. Initial systems using fiber optic endoscopy with AFI were compared to WLE, and showed no difference in the number of patients detected with HGD/early stage cancer [71,72]. A plausible reason could be the substandard image quality of fiber optic endoscopy.

More recently endoscopic trimodal imaging (ETMI) system has been developed incorporating autofluorescence, HRE, and NBI. A prospective multi-center study in 4 tertiary referral centers demonstrated that AFI increases the detection rate of high grade intraepithelial neoplasia (HGIN), and early neoplasia (EN) from 53% to 90%. The problem with AFI is its false positive rate of 81%. In this study, the use of NBI reduced the false positive rate of AFI to 26% [73]. Another study using ETMI demonstrated that overall detection of patients with HGIN/EN was not statistically different from standard endoscopy (84% vs. 73%) [74]. In a recent multi-center, randomized, cross over study in a community practice setting, no significant difference in the overall histological yield between ETMI and standard video endoscopy was observed [75].

Confocal laser endomicroscopy (CLE)

CLE is a technique that allows the gastroenterologist to perform real-time histological assessment of the gastrointestinal lining. There are two systems available, endoscope based confocal system (eCLE) and a probe based system (pCLE). Both systems uses blue laser light which is focused on the

mucosa while an intra venous (IV) contrast agent (fluorescein sodium) is injected [76]. The microscopic images of the mucosa are magnified up to 1250-fold, up to 250 μm below the mucosal surface [77]. It is essential for the gastroenterologist performing CLE to have basic histopathology knowledge and ability to differentiate between normal and dysplastic mucosa [78]. Classification systems for BE have been described for both eCLE and pCLE [79,80].

Kiesslich et al reported an accuracy of 97.4%, sensitivity and specificity of 94.1% and 98.5% respectively for the prediction of BE associated neoplasia [79]. Dunbar et al in their single center, randomized, cross over study with eCLE reported that, when compared with standard endoscopy, eCLE increases the yield of unlocalized neoplasia from 17% to 34%. It was also reported that eCLE required fewer biopsies to achieve a comparable overall diagnosis [81]. Pohl et al, in a study using pCLE to distinguish dysplastic and non-dysplastic BE, demonstrated a very good negative predictive value of 98%, with good interobserver agreement ($k=0.6$) [80]. A blinded multi-center study by Wallace et al demonstrated a high sensitivity and specificity (91% and 100% respectively) and a very accurate interobserver agreement of ($k=0.83$) amongst endoscopists with prior pCLE experience for diagnosis of HGIN and cancer [82].

Optical coherence tomography (OCT)

OCT uses short coherence length broadband light for cross-sectional imaging of esophageal mucosa. It is similar to ultrasonography but uses light waves rather than acoustic waves [83]. There are several studies which have described



Figure 2 (A) Overview with white light of inconspicuous flat areas harboring dysplasia

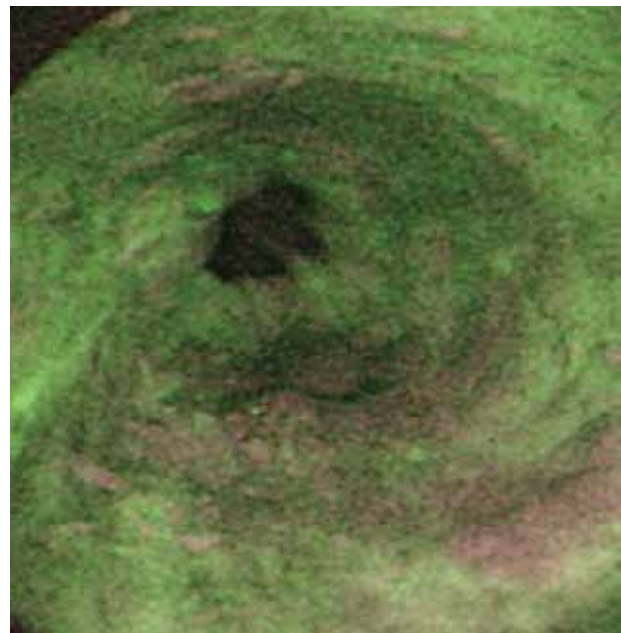


Figure 2 (B) Dysplastic areas on Figure 2A which clearly delineated by autofluorescence imaging as purplish patches

the normal and abnormal esophageal mucosa on OCT during endoscopy. In normal esophagus, the epithelium, lamina propria and muscularis mucosa are clearly identified [83,84]. One of the earliest prospective studies to establish the sensitivity and specificity of OCT for the diagnosis of SIM following a specific criterion found the sensitivity and specificity to be 97% and 92% respectively [85]. Qi et al, using a computer aided diagnostic algorithm with histology as a reference standard, reported the sensitivity, specificity, and accuracy of 82%, 74%, and 83% respectively [86]. Evans et al developed an algorithm for diagnosis of SIM using 2 blinded investigators [89]. They reported a sensitivity of 81% and a specificity of 66% for both OCT readers. The interobserver agreement was good ($k=0.53$) [87]. OCT however is not widely available currently [88].

Spectroscopy

Spectroscopy-based devices can assess the interaction between light and mucosal surface to provide information about the nuclear size, crowding, vascularity, and organization of glands. This technology can only examine potentially suspicious regions and is currently being investigated to differentiate between normal and abnormal tissue [88]. The different spectroscopic modalities are light scattering, reflectance, and Raman-based. Light scattering spectroscopy gives information about cell nuclei characteristics. Various studies have demonstrated dysplasia detection in BE using this technique [89-91]. Reflectance spectroscopy also assists in differentiating normal from neoplastic tissue [92,93]. A new system called Endoscopic Polarized Scanning Spectroscopy (EPSS) shows great promise in the detection of dysplasia in BE. Unlike other spectroscopic modalities, it scans the entire esophagus and combines polarized light scattering spectroscopy with diffuse reflectance spectroscopy in the same instrument [94]. Raman spectroscopy is used to study the different characteristics of molecular vibrations in cancerous and normal cells in BE thus differentiating one from the other [95]. A major drawback of Raman scattering is that the signal is typically very weak and the differences may be too small to be appreciated.

Conclusion

There has been great advancement in the imaging techniques used for the detection of dysplasia in BE. Most of these techniques have been studied in tertiary centers with investigators having special interest in BE. It would be interesting to see if these results could be reproduced in the hands of the general endoscopist. Ease of availability, cost, procedural time, and medico-legal issues associated with image interpretation are some of the concerns which need addressing. Currently, however, a detailed examination of the BE segment with WLE and random 4-quadrant biopsies is probably still the best approach, with other imaging modalities

used in addition to increase the yield of detecting dysplastic areas in BE.

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