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# Endoscopic Imaging in Barrett's Oesophagus: Applications in Routine Clinical Practice and Future Outlook

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The practice for endoscopic surveillance of Barrett's oesophagus has evolved from "blind" or random 4 quadrant biopsies (Seattle protocol) to a more "intelligent" targeted biopsy approach. This evolution has been possible due to the rapid advances in endoscopic imaging technology and expertise in the last decade. Previous endoscopes had relatively poor image resolution that often did not allow the subtle mucosal changes associated with dysplastic Barrett's mucosa to be identified. Newer endoscopic imaging techniques available today may allow endoscopists to identify areas of dysplasia or malignancy and target biopsies accordingly. These modalities which include narrow band imaging, chromoendoscopy, autofluorescence imaging, and confocal endomicroscopy as well as a few novel imaging modalities on the horizon will be discussed further.

**Key Words:** Barrett esophagus; Chromoendoscopy; Narrow band imaging; Autofluorescence imaging; Confocal endomicroscopy

## INTRODUCTION

Barrett's oesophagus (BE) occurs, according to British guidelines, when normal esophageal squamous mucosa is partially replaced by metaplastic columnar mucosa.[1] Gastroesophageal reflux disease is a major pathogenetic factor for the development of BE. BE in turn is the most important risk factor for development of oesophageal adenocarcinoma. This cancer has a rapidly rising incidence and earlier detection results in improved 5-year survival.[2] Endoscopic surveillance of BE is therefore recommended in order to detect treatable dysplasia or cancer at an early stage.

One of the limitations of current surveillance strategy is the difficulty in detecting early neoplastic lesions with conventional white light endoscopy (WLE). Random 4 quadrant biopsies are notorious at missing early neoplasia. Four biopsies in any given 2 cm BE segment using the Seattle protocol approach will only sample 3.5% of the surface of the segment. This can clearly miss any inconspicuous area harboring dysplasia or malignancy that may be present in the remaining 96.5% of the mucosa that is not sampled. The process can be laborious not only for the endoscopist but also the nursing staff and pathologist. This may partly explain its poor adherence in both the United Kingdom[3] (41%) and the United States[4] (44-56%).

A new paradigm involving targeted biopsies may enable the endoscopist to increase the yield of detecting dysplasia or malignancy. This approach involves spending time closely inspecting the mucosa utilizing some of the more novel advanced endoscopic imaging techniques which will be described in greater detail here.

## WHITE LIGHT ENDOSCOPY (WLE)

In order to understand advanced endoscopic imaging techniques it is important we grasp some of the basic tenets on conventional WLE. At the present moment, the Prague C&M criteria is the best available descriptor for grading the endoscopic extent of BE.[5] This criteria includes the assessment of the circumferential (C) and maximum (M) extent of the endoscopically visualized BE segment in centimeters from the upper end of the gastric folds. The Prague criteria have been shown to be reproducible and reliable in different patient populations.[6,7]

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There are a number of mucosal changes visible on WLE that can allow the endoscopist to target biopsies and increase the yield of finding neoplasia. Visible lumps in areas of high grade dysplasia (HGD) suggest a more advanced lesion where invasion may be present. Ulcers in Barrett's esophagus are a suspicious finding as they are associated with high rates of oesophageal adenocarcinoma. Ulcers that fail to heal with proton pump inhibitor therapy are particularly worrying, and should be monitored closely for carcinoma. Recently endoscopes with the capability of magnification of up to 115 times has been introduced to further enhance characterisation of the detected lesions.

## NARROW BAND IMAGING (NBI)

NBI enhances both the mucosal and the vascular patterns of the mucosa. It does this by illuminating the surface of the mucosa with 2 narrow wavelengths of light of 415 nm (blue) and 540 nm (green). NBI is based on the optical phenomenon that the wavelength of light determines the depth of light penetration into tissue and the amount of optical scattering. Blue light has a short wavelength and only superficially penetrates the mucosa illuminating the detail of the mucosal surface. By contrast, red light has a longer wavelength and penetrates a greater depth of the mucosa allowing visualization of deeper tissue components. In NBI, the relative intensity of blue light is increased and other wavelengths are reduced (green) or eliminated (red). This enhances visualization of the superficial mucosal structures and improves contrast of the vasculature.

There have been 2 studies looking at the utility of NBI without magnification in the detection of dysplasia in BE. Kara et al.[8] found no significant difference in the detection of HGD or intramucosal carcinoma (IMC) when high resolution WLE was compared to NBI in a randomised cross-over study. Although more areas of HGD were detected with NBI compared to WLE (4 additional lesions in 3 patients), this did not reach statistical significance, given there were only 28 patients enrolled in the study. A larger randomized cross-over study compared high resolution NBI with standard resolution WLE in 67 patients with BE.[9] NBI was found to be superior to standard WLE in the detection of dysplasia (57% vs. 43%). In addition, more biopsies were taken using standard WLE and random four quadrant biopsies compared with NBI-targeted biopsies (mean, 8.5 vs. 4.7; $p<0.001$). The difficulty with this study is that the endoscopes with NBI provided higher resolution images (180 series endoscopes) than the standard WLE (160 series endoscopes) which may account for some of the improved detection rate in the NBI group. In the recently concluded 'DON'T BIOPCE' trial by Sharma and colleagues, patients with BE were assessed with WLE, NBI and the probe-based CLE system. The investigators found that the addition of NBI to WLE improved the sensitivity of dysplasia detection from 85% to 92%.[10]

A study by Singh et al.[11] comparing still mucosal images with histology, found that NBI with optical magnification (NBI-Z) was superior to WLE and optical magnification in the prediction of dysplastic tissue in BE. However this study did not look at the real time benefit of NBI-Z in predicting which areas of Barrett's mucosa to biopsy.

## CHROMOENDOSCOPY

Chromoendoscopy involves the topical application of dyes at endoscopy to enhance visualization of the mucosal surface architecture. The three most commonly used dyes are acetic acid, methylene blue, and indigo carmine.

Acetic acid causes reversible acetylation of nuclear proteins when it is applied to Barrett's mucosa. This results in transient whitening of the tissue with vascular congestion allowing better visualisation of the surface mucosal patterns. The whitening effect is lost in dysplastic areas earlier than in the surrounding mucosa, helping the endoscopist further differentiate between the two tissues. This effect is transient; lasting 2 to 3 minutes, so repeated applications of acetic acid may be required. Acetic acid-assisted chromoendoscopy has been shown to increase the diagnostic yield of finding dysplasia over standard WLE in 2 studies.[12,13] The larger study[13] consisted of 190 procedures with acetic acid. There was a correlation between the lesions predicted to be neoplastic by acetic acid and those diagnosed by histological analysis. There was also a significant improvement in the detection of neoplasia using acetic acid compared with WLE. Dysplasia or cancer was identified with acetic acid with a sensitivity of 95.5% and a specificity of 80%.

Methylene blue is absorbed actively and homogeneously by normal mucosal cells and in a more uneven manner by neoplastic cells. The heterogeneous appearance of dysplastic or malignant tissue aids in its endoscopic identification.[14] Some early trials showed promising results, however a meta-analysis comparing detection rates of neoplasia in BE with methylene blue staining verses random 4 quadrant biopsies showed no significant increased yield for the detection of HGD and early cancer.[15] For this reason as well as the potential of toxicity from oxidative DNA damage to Barrett's mucosa,[16] methylene blue chromoendoscopy has gone out of favour in many centres.

Indigo carmine is a tissue stain that highlights superficial mucosal irregularities by pooling in crevices and depressions in and around a lesion. A study of 80 patients with suspicion of BE showed that biopsies guided by indigo carmine and magnification endoscopy were able to detect HGD and carcinoma in 100% of cases. However, this technique was not able to reliably

distinguish low grade dysplasia from non-dysplastic intestinal metaplasia.[17]

Chromoendoscopy is not widely used in the routine assessment of patients with BE. This is primarily due to the patchy evidence as well as practical limitations. These include the extra time required both in preparing for and performing the procedure. The procedure itself can be messy and some of the dyes have safety and toxicity concerns. The outcomes are dependent on the experience and expertise of the individual endoscopist. This tends to limit its usefulness outside of tertiary/academic referral centers.

## AUTOFLUORESCENCE IMAGING (AFI)

Autofluorescence is the natural emission of light by biological substances called fluorophores. When tissues are exposed to short wavelength blue or ultraviolet light, fluorophores are excited and emit longer wavelength fluorescent light. Examples of common fluorophores are collagen, flavins, aromatic amino acids and porphyrins. Normal, metaplastic and dysplastic tissues have different concentrations and types of fluorophores which in turn emit characteristic patterns of light that can help distinguish between tissue types.

AFI has been shown to be useful in detecting dysplasia[18,19] in a number of controlled studies. The technology has also shown to aid in the endoscopic resection in BE.[20] Two randomised controlled trails have shown a modest improvement in the yield using AFI in addition to random 4 quadrant biopsies.[21,22] However others have shown no benefit of AFI over WLE for the detection of dysplasia.[23]

One of the major limitations of AFI is the high false positive rate of up to 80%.[24] Attempts have been made to address this issue by adding NBI to endoscopes with AFI and high resolution white light capability (trimodal imaging). The false positive rate was reduced from 81% to 26% with Trimodal imaging.[24] Another study[22] found that trimodal imaging significantly increased the number of HGD or malignancies detected. However the false positive rates were high at 71% and when NBI was added 11 HGD lesions were misclassified as not suspicious. A community based randomized controlled trial in the Netherlands of trimodal imaging did not improve the overall detection of dysplasia compared with standard video endoscopy. The diagnosis of dysplasia was still being made in a significant number of patients by random biopsies.[25] This once again demonstrates the difficulty of applying modalities such as AFI outside large tertiary referral centres.

## CONFOCAL ENDOMICROSCOPY (CLE)

CLE is an endoscopic modality that allows microscopic examination of tissues during endoscopy. It provides a similar magnification to traditional histology facilitating in vivo assessment of cellular structures. CLE is based on tissue excitation and fluorescence after it is exposed to a low-power blue laser light. The laser light is focused at a selected depth in the tissue of interest and reflected light is then refocused onto the detection system by the same lens. This light passes through a small aperture that allows a huge increase in the spatial resolution of the image. The technique is able to generate a real time black and white image from a thin tissue plane. Use of an exogenous fluorescent dye is required to create the contrast necessary for adequate visualization. The most common contrast agent is intravenous fluorescein sodium however topical contrast agents can also be used.[26] Intravenous fluorescein has been used for decades by ophthalmologists for imaging the retinal vasculature and adverse events are rare.[27] Intravenous fluorescein highlights the vessels, intra cellular spaces and lamina propria but does not stain nuclei. Goblet cell in BE appear dark on CLE.

There are two types of confocal endoscopic systems available. The Pentax system (eCLE; Pentax Co., Tokyo, Japan) uses a confocal fluorescence microscope integrated into the distal tip of a conventional upper endoscope. The Cellvizio system (pCLE; Mauna Kea Technologies, Paris, France) is probe based and is inserted through the accessory channel of a traditional endoscope. The integrated system allows variable depth of tissue plane visualization up to 250 μm, while the probe system allows fixed-depth tissue plane visualization between 70 and 130 μm for standard probes and 55 and 65 μm for high definition probes.[28] The lateral resolution of the probes varies such that the probes with the highest resolution (1 μm) have a smaller field of view and the lower resolution probes (3.5 μm) have a larger field of view. Confocal probes have a limited number of uses, which increases cost.

Kiesslich et al.[29] first reported the application of eCLE in BE and described the endomicroscopic features of normal squamous oesophageal mucosa, BE, BE with dysplasia and cancer. Using histopathology as the gold standard, the classification system predicted the final diagnosis of BE with a sensitivity of 98%, specificity of 94% and accuracy of 97.5%.[29] A blinded, randomized crossover trial for eCLE in BE[30] looked at 23 patients undergoing surveillance and 16 patients with non-localized neoplasia. They underwent eCLE and standard endoscopy with random biopsies according to the Seattle protocol, in a randomized order. During eCLE, microscopic images were acquired, but only targeted mucosal biopsies were taken if the CLE imaging suggested neoplasia. Compared with standard endoscopy, eCLE with targeted mucosal biopsies increased the yield in subjects with unlocalized neoplasia from 17% to 34%. eCLE also led to 59% fewer biopsies to

achieve a comparable overall diagnosis. In subjects undergoing routine endoscopic surveillance, there were significantly less biopsies taken during CLE. This was highlighted by the observation that 65% of subjects undergoing surveillance had normal CLE imaging and so no mucosal biopsies were taken. In another study, eCLE has been shown to assist in allowing targeted EMR in subjects with unlocalized neoplasia in Barrett's mucosa.[31]

One of the first studies of probe based endomicroscopy (pCLE) looked at images from 23 subjects using pCLE to distinguish between dysplastic and nondysplastic BE.[32] The in vivo sensitivity for detecting BE neoplasia was 75% with a specificity of 89% to 91%. The positive predictive value for BE neoplasia was 44% and the negative predictive value was 98% using pCLE. A more recent study[33] involved 63 patients who had an overall prevalence of HGD or cancer of 83% which was thought to be more representative of general gastroenterological practice. In this setting the sensitivity was poor at only 12% with a specificity 95%. The pCLE appears to have a lower sensitivity in detecting HGD and malignancy in BE compared to eCLE. This may be because the probe based system can have a lower resolution, smaller field of view and more motion artifact depending on the probe used.

CLE has shown promise as a tool that may help endoscopist to target biopsies in BE. It is not yet clear at this stage whether it can replace biopsies. The technology is expensive and procedure itself can also be time consuming. CLE requires endoscopists expert in the technical skills to obtain the images and with the knowledge to interpret them.

## FUTURE OUTLOOK: OTHER TECHNOLOGIES

There are a number of other technologies being developed for the detection of neoplasia in patients with BE.

Several biomarkers of oesophageal adenocarcinoma risk are currently under investigation. Loss of heterozygosity of specific genes and nuclear DNA abnormalities (aneuploidy and tetraploidy) have been the mostly widely investigated.[34] Methylation of the genes p16, HPP1, and RUNX3 have been shown to predict future malignant transformation in patients with BE.[35,36] These and other biomarkers could possibly be used in the future to stratify the patients with BE into groups at particular risk of neoplasia who may benefit most from surveillance. None of the biomarkers have been validated for clinical use at this time, however.

Optical coherence tomography (OCT) uses a coherent short wavelength of light to provide real time cross sectional imaging of the oesophageal mucosa. It can identify pit patterns and glandular architecture. OCT has been shown to detect HGD or IMC with a sensitivity of 83% and specificity of 75%.[37] It is however not widely available and is limited by its inability to assess large surface areas.

Spectroscopic modalities use the interaction between light and tissue to provide information about the nanoscale architecture of the oesophageal epithelium.[38] Light scattering spectroscopy can elicit information about a cell nuclei and quantify differences between dysplastic and non-dysplastic tissue in BE.[39]

A much lower cost screening tool for BE is being developed called the capsule sponge oesophageal cytology. This consists of a cytology sponge that is compressed within a gelatin capsule attached to a string. The capsule is swallowed and expands in the stomach prior to being pulled back up the oesophagus by the string. The sponge collects oesophageal mucosal cells that then undergo molecular biological identification. Trefoil factor 3 is strongly expressed in Barrett's mucosa. A pilot study found this screening test to have a sensitivity of 78% and a specificity of 94% for BE.[40] In the future molecular markers may become available to screen for dysplasia or malignancy.

## CONCLUSIONS

The aim of endoscopic surveillance in patients with BE is to identify neoplastic lesions that can be targeted with biopsy and excised with endoscopic resection techniques. This approach can avoid the need for oesophagectomy which can have significant morbidity and mortality. A detailed clinical assessment, followed by a careful endoscopic examination of the oesophagus with high resolution WLE and targeted biopsies followed by random 4 quadrant biopsies still remains the standard of care for patients with BE. The examination however can be enhanced by the addition of more advanced imaging modalities such as NBI, AFI, and chromoendoscopy. These techniques have shown promise to help delineate lesions found at WLE and to increase the yield of detecting neoplasia.

There are a number of factors that may limit the widespread uptake of some of these advanced endoscopic technologies. The ease of use, learning curve, availability and cost are barriers at present to some of these modalities. Most studies of these techniques have been performed in expert tertiary referral centers with expert endoscopists in the use of a particular modality. The results of these trials may not be applicable to routine community practice in many instances.

Oesophageal adenocarcinoma has a bleak prognosis. Surveillance of its precursor lesion, BE, has many limitations at present. However, advances in endoscopic imaging have the potential to improve the yield and efficiency of BE surveillance with the ultimate aim of reducing the incidence and mortality and curb the rising trend of oesophageal adenocarcinoma in our patients.

## Conflicts of Interest

The authors have no financial conflicts of interest.

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