REVIEW

Barrett's Esophagus: Diagnosis, Screening, Surveillance, and Controversies

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Barrett's esophagus (BE) is a frequent complication of gastroesophageal reflux disease, an acquired condition resulting from persistent mucosal injury to the esophagus. The incidence of Barrett's metaplasia and Barrett's adenocarcinoma has been increasing, but the prognosis of Barrett's adenocarcinoma is worse because individuals present at a late stage. Attempts have been made to intervene at early stage using surveillance programmes, although proof of efficacy of endoscopic surveillance is lacking. There is much to be learned about BE. Whether adequate control of gastroesophageal reflux early in the disease alters the natural history of Barrett's change once it has developed remains unanswered. Thus there is great need for carefully designed large randomised controlled trials to address these issues in order to determine how best to manage patients with BE. The AsPECT and BOSS clinical trials provide this basis. (*Gut and Liver* 2007;1:93-100)

Key Words: Barrett's esophagus; Gastroesophageal reflux

INTRODUCTION

Barrett's esophagus (BE) is an acquired condition resulting from persistent mucosal injury to the esophagus. New British Society of Gastroenterology (BSG) guidelines have defined BE as an endoscopically apparent area above the esophagogastric junction that is suggestive of BE and which is supported by a histology finding of a columnar lined esophagus, with the presence of areas of intestinal metaplasia (IM) not being a requirement for the diagnosis.¹ This differs from guidelines from several other soci-

eties that emphasize endoscopy and a pathological diagnosis of IM.² While it is recognized that esophageal adenocarcinoma arises from a segment containing IM, the BSG's rationale is that a patient with BE on endoscopy but with only columnar epithelium without IM in biopsies might be overlooked by a surveillance program purely due to sampling error. This controversy is likely to remain until further data are obtained. However, it remains important for the endoscopist to identify BE and its associated landmarks of a diaphragmatic pinch, gastroesophageal junction, and squamocolumnar junction. This has been standardized with the Prague Classification, which also takes into account the circumferential and maximal extent of Barrett's segment.³

NATURAL HISTORY OF BARRETT'S ESOPHAGUS

Although the natural history of dysplasia in BE is poorly understood, it is still accepted as the best available marker for cancer risk. A phenotypic sequential progression from IM to low grade dysplasia (LGD) then high grade (HGD) and finally adenocarcinoma (AC) has been postulated albeit the time course being highly variable. Skacel and colleagues followed 25 patients with LGD for 26 months and found that 12% had persistent LGD, 62% regressed and 28% went on to develop HGD or AC.⁴ Another similar study by Weston et al with slightly higher number of patients (n=48) and longer follow up (41 months) showed that 25% had persistent LGD, while 65% regressed and 10% progressed.⁵ One must take into consideration though whether the areas which harboured LGD were actually the areas which were biopsied on fol-

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low up hence whether sampling errors could have over or underestimated the progression or regression. Moreover pathologists often have difficulties differentiating LGD from regenerating non neoplastic tissue or inflammation and the agreement amongst even experienced pathologists has been graded as poor to fair.⁶ It can be surmised though that there is marked variability in the natural history of LGD. Nevertheless in view of the risk of progression to HGD/AC, a patient diagnosed with LGD should not be taken lightly.

The case with HGD is not too indifferent. Buttar's group found that 38% and 56% of patients with diffuse disease developed AC at 1 and 3 years after HGD was diagnosed.⁷ The figures for focal HGD were 7% and 14% respectively. In another similar study by Reid and colleagues, almost 6 out of 10 patients had AC after a mean follow up period of 5 years (n=76).⁸ Schnell et al followed 79 patients for a mean of 7 years out of which 1/5th developed cancer.⁹ As HGD in BE can arise from endoscopically inconspicuous areas, it must be questioned again whether sampling error on follow up biopsies could have resulted in the marked variability in these studies. However, expert pathologists seem to agree more with HGD/AC exhibiting a higher interobserver agreement compared to LGD.

SCREENING

Screening is done to identify individuals with cancer or those with high risk of cancer. The incidence of AC has increased rapidly over the last 2 decades.¹⁰ It is well known that AC has a dismal 5 year survival rate ranging from 5-10%.

Gastroesophageal Reflux Diseases (GERD) is present in about 10-20% of the general population. About 40% of patients with GERD will go on to develop erosive oesophagitis, out of which 10-15% will have BE. These patients can subsequently develop AC with an incidence of 0.5-1%/year. GERD therefore is a risk factor for developing BE/AC and screening endoscopies have been advocated to detect BE. A case controlled study done by Lagergen et al showed that the odds of developing AC increased by 7.7 times in patients with GERD.¹¹ The study also showed that as the duration of symptoms increased, the odds of AC increased. If a patient had reflux symptoms for more than 20 years, the odds of developing AC increased by 16.4 fold.

However the prevalence of BE in patients with no reflux symptoms ranges from 6-9.8%, which is not too different from the prevalence in the GERD group which is 10-15%. The majority of patients with BE are not diag-

nosed because they are asymptomatic. In a study by Cameron et al, BE was detected mostly at autopsies compared to endoscopy (>20 fold prevalence).¹² It is also well known that almost 40% of patients with AC do not have reflux symptoms and these patients would certainly be missed if only patients with chronic GERD are screened.¹¹ Cost issues and the invasiveness of the current screening tool has also limited the effectiveness of screening for BE. Furthermore less than 5% of ACs are detected as a result of screening and subsequent surveillance. Until better criteria is established for more targeted screening and perhaps newer methods, screening endoscopy for BE is still largely contentious, not evidence based and not widely practiced yet.

SURVEILLANCE

Surveillance is a continued investigation of patients who are at a higher risk for development of cancer. Surveillance endoscopy is commonly practiced in the hope that patients with dysplasia or cancer can be detected early and hence treatment initiated. Several studies have showed that surveillance endoscopy increased survival in patients with BE compared to no surveillance. These are however small retrospective studies.^{13,14}

1. Present recommendations, follow up and treatment strategies (Fig. 1)

The recognition of BE as the pre-malignant precursor to AC has led to recommendations regarding surveillance endoscopy.¹⁵⁻¹⁷ The end-point for surveillance is the detection of HGD or invasive carcinoma. In some patients occurrence of other significant co-morbidities during follow-up may preclude the need for continued surveillance. Hence it has to be stressed that surveillance endoscopy is only appropriate for patients without significant co-morbidities and fit to undergo therapy, be it surgery or endoscopic mucosal resection/ablation.

When BE is identified, multiple systematic biopsy specimens should be obtained. Biopsies of any macroscopic lesions in particular should also be performed. The recommended approach is to obtain 4 quadrant biopsy specimens every 2 cm.^{18,19} For patients with established BE of any length and with no dysplasia, an acceptable interval for surveillance is every 2 years as long as enough biopsies are taken (minimum of 8).²⁰

LGD should be managed firstly by extensive re-biopsy after intensive acid suppression for 8-12 weeks. If persisting, surveillance should be six monthly for as long as it remains stable. If apparent regression occurs on two consecutive examinations, surveillance intervals may be in-

creased to two yearly.

HGD is associated with a focus of invasive AC in 30-40% of patients. For this reason, esophagectomy is traditionally recommended in patients considered fit for surgery.²¹ On the other hand it has been shown that up to 40% of patients diagnosed with HGD are found to have no dysplasia on follow-up endoscopies.⁹ With recent developments in endoscopic imaging technology and resection techniques, it is now possible to accurately stage the disease and diagnose invasive cancer pre-operatively. It has been suggested that patients with HGD should have a thorough work-up in a tertiary referral centre that see high volume cases with multi-disciplinary expertise.²² In patients who are unfit or decline surgical treatment, endoscopic mucosal resection or ablation should be considered. Some patients may opt for a wait and watch policy and defer any intervention until definite cancer is detected. In these cases, surveillance should be done every 3 months with an extensive biopsy protocol and additional biopsies of macroscopic abnormalities.²⁰ If no dysplasia is found on 2 consecutive endoscopies, the interval

may be lengthened to every 6 months for 1 year and then yearly as long as no dysplasia is reencountered. Patients who have undergone endoscopic therapy should continue to have surveillance at intervals appropriate to the highest grade of dysplasia pre-treatment.

If the presence of dysplasia is indeterminate and/or if there is evidence of acute inflammation due to gastro-esophageal acid reflux, repeat biopsy should be performed after 8 weeks of effective acid-suppression therapy. There are however numerous limitations in routine endoscopic surveillance.

2. Limitations and controversies

The surface area of a given 2 cm segment of BE is roughly equivalent to 13 cm². Quadrantic biopsies would equate to a total surface area of 0.5 cm² and this would represent only 3.5% of the area which would be sampled in a 2 cm BE segment.²³ Random biopsies would hence lead to a very poor yield. Other than making the pathologist uncomfortable, the patient too is generally subjected to a prolonged procedure. This is perhaps why current

Fig. 1. Recommended strategy for surveillance in Barrett's esophagus.

practice guidelines are not generally adhered to.²⁴ The case against surveillance is further strengthened when we look at the absolute risk of developing AC in patients with BE which is very low at 0.5%/year. Van der Burgh et al reported that after a mean follow up of almost 10 years in 166 patients with BE undergoing surveillance, only 2.5% died from AC.²⁵ Most of the patients died from other causes. The cost issue once again crops up in surveillance for BE and various models have suggested that to be cost effective the prevalence of AC per year should be higher than 0.4-0.5%.²⁶

Despite these shortcomings, surveillance endoscopy is still the recommended by most societies in BE. In order for BE surveillance to be optimized though, two distinct areas have received widespread interest lately:

- 1) Improvements in imaging techniques which would allow sampling or targeting BE 'intelligently'.
- 2) Identification of better (bio) markers for disease progression thereby allowing efforts to be concentrated on individuals at greatest risk.

3. Potential strategies to enhance surveillance

1) Advance Imaging techniques

Over the last few years, improvements in endoscopic imaging technology have enabled identification of dysplasia and early cancer in BE. In order to be effective and efficient when a novel imaging technology is assessed, various issues need to be taken into consideration. This includes the technique itself having high sensitivity and specificities, good interobserver agreement, it being affordable as well as having the capability of imaging a wide area in real time whilst enabling the endoscopist to specifically target dysplastic areas for biopsies. A multitude of techniques have been assessed to further improve the detection of dysplasia:

- i) White Light Endoscopy with High Resolution Magnification Endoscopy and Chromoendoscopy.
- ii) Optical Endoscopy comprising of Autofluorescence Imaging, Narrow Band Imaging and Optical Coherence Tomography.
- iii) Endomicroscopy which encompasses Confocal Endomicroscopy and Endocytoscopy
- iv) Optical Spectroscopy comprising of Raman, Fluorescence and Elastic spectroscopy.

The latter two techniques are still in the preliminary stages of investigation and will not be discussed further in this review.

(1) White Light Endoscopy: Standard video endoscopes are tailored to view the mucosa from a focal distance of 1-2 cm from the endoscope tip. With a pixel density of

200,000, detailed inspection is limited especially if the tip of the scope is advanced closer to the area of interest. The focused area tends to exhibit a blurred view. Coupled with low resolution monitors, the quality of images obtained in real time can be compromised. As technology improves, the pixel density and resolution of monitors has increased tremendously and this has resulted in improved image quality with high resolution (>850,000 pixel density) and high magnification (115X) systems. This phenomenon is especially crucial in BE surveillance as early, subtle lesions harbouring dysplasia or cancer should not be missed.

① **Chromoendoscopy;** Chromoendoscopy involves topical application of various dyes during endoscopy which improves the visualisation of mucosal surfaces. The stains can be divided into three main classes: contrast, absorptive, and reactive. Contrast stains, for example indigo carmine,^{27,28} accumulates in the mucosal fissures thereby accentuating surface topology. Absorptive stains such as lugol's iodine,²⁹ crystal violet³⁰ and methylene blue³¹⁻³⁶ on the contrary are absorbed into components of the cellular structure in the mucosa. Differences in the uptake of these stains can therefore be used to elucidate different types of mucosa. Reactive stains such as Congo red and Phenol red are not used routinely in the esophagus.

Methylene Blue (MB), an absorptive dye is probably the most investigated stain for evaluation of BE and also the most controversial. It is a vital stain taken up by actively absorbing epithelial cells after topical application at a concentration of 0.5-1.0%.³¹⁻³³ The dye is absorbed by goblet cells present in IM epithelium. Initial work done by Canto's group revealed that MB can distinguish IM and dysplasia in BE with high precision.³¹ However these results were not reproducible. The main contention with MB in BE is that dysplastic areas do not stain but the problem with it is that even areas which do not harbour IM does not absorb the dye. This makes it difficult for the endoscopist to decide on which areas to target the biopsies during the procedure. There were also some issues with the uniformity of the dye and recently even toxicity with MB. It has been examined in long and short segment BE^{31,34,35} with conflicting results. Two patterns of staining have been documented - diffuse and focal. Canto et al³¹ found that most patients with long segment BE exhibited diffuse staining whereas Wo and colleagues³⁶ observed focal staining in their cohort of patients with long segment BE. As a result of all these controversies and confusion, MB has hence not really gained widespread acceptance in the GI fraternity.

Though chromoendoscopy has been available for more than 20 years, the lack of standardisation of the techni-

que, the dearth of well controlled studies that determine its clinical utility, cost efficacy issues, patient tolerability in terms of the additional time needed are amongst the reasons why it has not truly caught on.

② **High Resolution Magnification Endoscopy;** Recent advancements in endoscopic technology have produced high resolution magnification endoscopes (HRME) with electronically moveable lenses which allow real time visualisation of mucosal morphology in greater detail. Magnification enlarges the endoscopic image while better resolution improves the ability to discriminate detail by enabling two closely approximated points to be better appreciated. The clinical utility of this modality had been limited by the size of the endoscope in the past. However, improvement in the design of the charged-couple device, an electronic light sensing apparatus located at the tip of the endoscope has given rise to less bulky and more manageable instruments.

Stevens et al used indigo carmine as a contrast stain to assess BE using magnification endoscopy and noted a villiform appearance correlated with the histological finding of IM.³⁷ Endo and colleagues characterised the pit pattern of BE using magnification endoscopy and MB staining and found that IM was detected in patients who exhibited a tubular/villous pattern in their BE segment.³⁸ Similarly, Sharma's group found 97% of their cohort of patients with a ridged/ villous pattern on magnification chromoendoscopy using IC had IM and 100% with an irregular and distorted pattern exhibited HGD.²⁷ Fortun et al reported that enhanced magnification endoscopy with acetic acid allows clear visualisation of the epithelial pit patterns within BE, and targeted biopsy resulted in a high yield of IM and dysplasia.³⁹ However, despite the increas-

ing availability of this technique, there is a lack of a standardised classification criterion for magnified endoscopic images.

(2) Optical Endoscopy

① **Autofluorescence Imaging;** When tissues are exposed to short wave length light, endogenous biological substances (ie fluorophores) are excited, leading to emission of fluorescent light of a longer wavelength. This phenomenon is known as autofluorescence.⁴⁰

Autofluorescence Imaging (AFI) is a technique that can potentially differentiate tissue types based on their differences in fluorescence emission. Normal and neoplastic tissue have different autofluorescence spectra which may enable their distinction. This is due to the various different compositions of the endogenous fluorophores which includes collagen, NADH, aromatic amino acids and porphyrins in these tissues. Until recently AFI has been restricted to either autofluorescence spectroscopy or autofluorescence endoscopy using the older generation fibre optic endoscopes.⁴¹⁻⁴³ The main limitation of AFI using this modality is that the quality of the images produced was inferior. Recently, video AFI which incorporates high resolution endoscopy has been evaluated.⁴⁴ In this uncontrolled feasibility study, AFI led to the detection of a significant number of patients with HGD/early cancer in BE. There was however a very high false positive rate (51%) using this modality.

② **Narrow Band Imaging;** The quest for a simpler technique which would obviate the complexity of chromoendoscopy led to the development of Narrow Band Imaging (NBI). Termed 'Electronic Chromoendoscopy' by some quarters, this unique technology was first described

Fig. 2. An example of trimodal imaging. (A) A subtle type IIa-c lesion in the distal esophagus is vaguely visible with high resolution magnification endoscope in Barrett's esophagus. (B) The lesion 'lights up' on autofluorescence imaging at the 3-4 o'clock position. (C) Detailed examination of the lesion with narrow band imaging and magnification reveals distorted pit patterns and irregular microvasculature, biopsies of which are in keeping with high grade dysplasia.

by Gono et al.⁴⁵ Standard white light endoscopy consists of 3 light waves blue, green and red. The principals behind NBI technology is that the bandwidth of blue (440-460 nm) and green (540-560 nm) wave light is narrowed and the contribution of the red wave light is totally negated out of the emitted light. This is achieved by placing a special filter which is electronically activated once the endoscopist presses a switch on the endoscope. The whole process takes less than 1 second and is practical during any endoscopy procedure provided the system is equipped with NBI. The narrowed bandwidth green and blue light lead to superficial penetration of the mucosa accentuating the microvasculature pattern as hemoglobin has a peak absorption spectrum towards both these wave lengths. The quality of the surface pit pattern morphology is also clearly enhanced by this technology. It enables the endoscopist to switch between conventional white light and NBI views easily and quickly during the procedure thus making the procedure itself less messy and cumbersome compared to chromoendoscopy. By depressing a lever on the endoscope, the focal distance of the lens at the tip of the endoscope can be adjusted electronically thus enabling the endoscopist to achieve a maximal magnification of 115X in real time. NBI has been evaluated in the BE with very promising early results.⁴⁶⁻⁴⁹

③ **Trimodal Imaging:** With various new technologies available, it was inevitable that combining them into a single system was the next step forward, hence the introduction of the novel concept of 'trimodal imaging'. This modality incorporates three advanced endoscopy imaging techniques into a single endoscope: HRME, NBI and AFI thereby enabling the endoscopist to use all 3 modalities during a single procedure (Fig. 2). Promising early results have been reported in a recently concluded multicenter feasibility study.⁵⁰

2) Biomarkers of Increased Risk

Although several biomarkers such as p53 mutation, p16 loss of heterozygosity and aneuploidy are associated with increased risk of progression, they have not been tested adequately for clinical criteria guidelines (REMARK).⁵¹ As a consequence detailed histological mapping is still the best approach.⁵²

(1) **Future Trends:** With the rapid development of various novel technologies, it seems that the ideal endoscopy system could very well be in the horizon. It would incorporate a 'red flag' technique similar to the AFI system but with hopefully a lower rate of false positives followed by a detailed inspection of the suspicious area with either NBI or a confocal probe to obtain 'optical biopsies' thus enabling the endoscopist to ascertain histopathological di-

agnosis in real time. It is hoped that risk stratification using a panel of affordable biomarkers could potentially lengthen the surveillance period for low risk patients and have the converse effect for the higher risk patients.

CONCLUSIONS

There are numerous unresolved issues in BE and many questions still unanswered. Will the diagnosis be standardised? What is the true natural history of dysplasia in BE? Is there a select patient group who will benefit from screening? Is there an alternative strategy to surveillance endoscopy? If so, would it be financially viable and acceptable to patients and physicians alike? Could the classification of various novel imaging modalities be standardised? If that is the case, given that these 'fancy' systems are validated in high volume large tertiary centres, would it be practical to the general gastroenterologist? Answers to these questions and many more are eagerly awaited in future studies.

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