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Endoscopic Detection and Eradication of Dysplastic Barrett's Oesophagus

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1. Introduction

Over the past four decades the incidence of oesophageal cancer has increased more rapidly than that of any other solid tumour in the Western World. This rise reflects the emergence of oesophageal adenocarcinoma as the most common pathological type. Despite this growing incidence, progress towards early detection and treatment has been slow and mortality figures have remained dismal – Cancer Research UK quotes overall one and five year survival rates of just 28% and 8% respectively.(CrUK, 2010) As a result, oesophageal cancer repreasents a real and growing public health problem and urgent action is required to improve detection and facilitate early intervention, ideally at a pre-malignant stage.

Most oesophageal adenocarcinoma develops following a well recognised series of cellular changes secondary to a multifactorial aetiology. In the classically described pathway there is initially a metaplastic change in the epithelial lining of the oesophagus (Barrett's oesophagus) which then progresses to 'low-grade' and then 'high-grade' dysplasia. As many as 30% of patients newly diagnosed with high-grade dysplasia may already have a coexistent invasive cancer, and between 5-60% of patients will develop cancer during surveillance over 1-7 years.

To date there is no early diagnostic test which can enable instantaneous accurate diagnosis of dysplasia. Clinicians are advised to take random biopsies from areas of Barrett's oesophagus in order to identify dysplasia, but even histological assessment of dysplasia is subjective and can be unreliable. As a result, significant dysplastic change (or even intramucosal cancer) may be missed. In addition, as dysplasia (the premalignant lesion) is difficult to identify, screening for early oesophageal cancer / high-grade dysplasia cannot currently be recommended, and as a consequence, oesophageal tumours present late and so have a poor prognosis.

The early recognition of high-grade dysplasia is paramount to enabling a successful treatment strategy. Surgery is one option for patients with confimred HGD, however the emergence of multiple endotherapies over the past 20 years have demonstrated the ability to cure focal high-grade dysplasia, thus preventing progression to invasive malignancy. In this chapter we will discuss the accuracy of endoscopic and histological diagnosis of dysplasia and will consider novel endoscopic adjuncts which may improve endoscopic sensitivity. We will then discuss the endoscopic therapeutic options that are available for management of dysplastic Barrett's oesophagus and will propose a endotherapy algorithm for use in specialist Barrett's surveillance centres.

2. Endoscopic detection of Barrett's oesophagus

Barrett's oesophagus is most often identified incidentally in patients who are undergoing an upper endoscopy for investigation of reflux symptoms. Barrett's oesophagus has a classical endoscopic appearance of 'salmon pink' columnar mucosa arising proximally from the oesophago-gastric junction (OGJ), often with characteristic 'tongue' extensions. There may also be readily identifiable islands of columnar mucosa. Following endoscopic recognition, the extent of proximal extension above the OGJ should be measured and documented, taking care to accurately identify any sliding hiatus hernia which may confuse this measurement. The diagnosis must then be confirmed / corroborated histologically by multiple pinch biopsies of the affected segment. When biopsies are obtained it is crucial that they originate from the oesophagus and that their site is recorded as accurately as possible.

The 'Prague C and M criteria', defined by an International Working Group on Barrett's oesophagus, offers a validated method of classifying Barrett's based on its endoscopic appearance. (Sharma et al., 2006b) The extent of circumferential involvement in centimetres from the OGJ should be recorded, as should the maximum length of the Barrett's segment (including tongues of Barrett's but excluding isolated 'islands').

Difficulties arise in diagnosis particularly in 'ultra-short' segment Barrett's oesophagus. The original description of Barrett's oesophagus was of columnar metaplasia extending for at least 3cm from the OGJ. Although the risk of malignant progression is greater in long Barrett's segments (>8cm), it is now recognised that shorter lengths, even below 3cm have malignant potential. (Hirota et al., 1999; Schnell et al., 1992; Sharma et al., 1997; May et al., 2002) However, what appears endoscopically to be a short segment of Barrett's oesophagus in the distal oesophagus or an irregular z-line may in fact represent intestinal metaplasia of the gastric cardia known as cardia intestinal metaplasia (CIM). (BSG Working Party, 2005) This can lead to misclassification of CIM as short segment Barrett's. For this reason, the endoscopist has a crucial role in defining the exact position from which biopsies are taken to prevent misdiagnosis.

3. Definition and clinical significance of Barrett's dysplasia

Dysplasia is defined as "an unequivocal neoplastic alteration of epithelium which has the potential to progress to invasive malignancy but remains confined within the basement membrane of the epithelium within which it arose." (Shaheen and Ransohoff, 2002; Riddell et al., 1983) Dysplasia is classified as either low grade (LGD), or high grade (HGD) (often also termed high-grade intraepithelial neoplasia HGIN)), based on its histological appearances. As already described, HGD has a higher malignant potential than LGD and malignant transformation classically occurs through a stepwise progression of pathology from metaplastic Barrett's oesophagus, to LGD, then HGD, and finally invasive adenocarcinoma.

Understanding the pathogenesis and natural history of Barrett's oesophagus is key to understanding the malignant potential and clinical significance of the various dysplastic stages. Surveillance studies have shown that the risk of developing adenocarcinoma varies between 0.4% and 1% per year (in the US and UK respectively). However, it is clear from cohort studies that not all Barrett's oesophagus progresses to dysplasia. In fact, in most long-term studies fewer than 10% of patients show evidence of progressive disease. (Schnell et al., 2001a) Patients with Barrett's oesophagus are thought to have a lifetime risk of developing oesophageal adenocarcinoma of 3-14% (approximately 0.5-1% per year following diagnosis).

(Shaheen et al., 2000; Drewitz et al., 1997) (Jankowski et al., 2000; Spechler et al., 2010; Shaheen and Richter, 2009; Jankowski et al., 2002) This represents an increased risk of 30-100 fold compared to the general population. However, cancer rates in excess of 10% per year have been described in patients with HGD. (Shaheen and Richter, 2009)

Several studies have also noted regression of disease in patients treated with acid suppression, and even complete resolution has been described. Similarly there is some data suggesting that anti-reflux surgery can improve the histological appearance of Barrett's oesophagus, although it is not currently recommended for this purpose. (BSG Working Party, 2005).

4. Endoscopic recognition of dysplasia

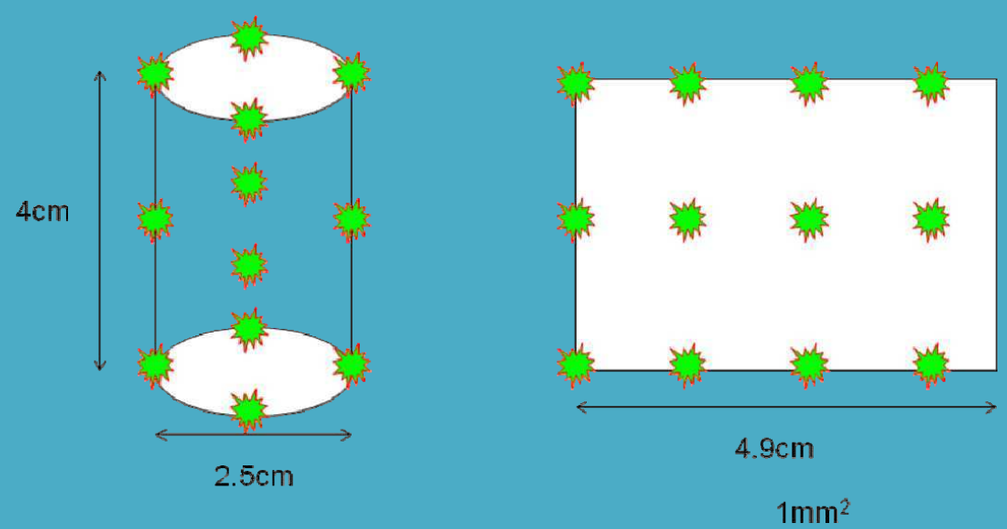
Endoscopic recognition of dysplasia within Barrett's oesophagus is difficult and unreliable, even for skilled endoscopists. A rigorous biopsy protocal such as that recommended by the British Society of Gastroenterologists (Box 1) is therefore necessary to identify any dysplastic change so that apropriate surveillance / endotherapy / surgery can be considered. Sites of biospy must be accurately recorded and when possible macroscopic lesions should be classified using the Paris classification (Box 2).

Box 1. Biopsying Barrett's oesophagus

Dysplasia is often macroscopically invisible. In patients with Barrett's oesophagus, endoscopists are therefore advised to follow a rigorous biopsy protocol. The British Society of Gastroenterologists recommends the following:

- Quadrantic biopsies for every 2cm of columnar lined oesophagus
- Additional biopsies of macroscopically suspicious areas

NB/ Even with strict adherence to this policy <5% of oesophageal mucosa is sampled.



Relative sampling volume = 0.05%

Endoscopic recognition of gross mucosal abnormalities such as ulceration, nodularity, and erythema is relatively straightforward. The problem is that early neoplastic lesions are frequently flat and often have little or no visible mucosal abnormality. Only 50-70% of HGD can be identified by experienced endoscopists using white light endoscopy. This figure is lower for non-specialists and is considerably lower for the detection of LGD. In addition, more than 20% of intramucosal cancers may be missed endoscopically, even in specialist units. This is particularly concerning when it is considered that routine biopsy protocols used for Barrett's surveillance have been shown to miss up to 57% of early neoplastic lesions. (Vieth et al., 2004)

As early neoplasia in Barrett's oesophagus is a relatively rare finding, the lack of familiarity of most endoscopists with its typical appearances is a significant limiting factor in its detection. Knowledge of the appearance of these early lesions is therefore key to their early recognition. Figure 1 illustrates a range of mucosal abnormalities within segments of Barrett's oesophagus which are consistent with early neoplastic change.

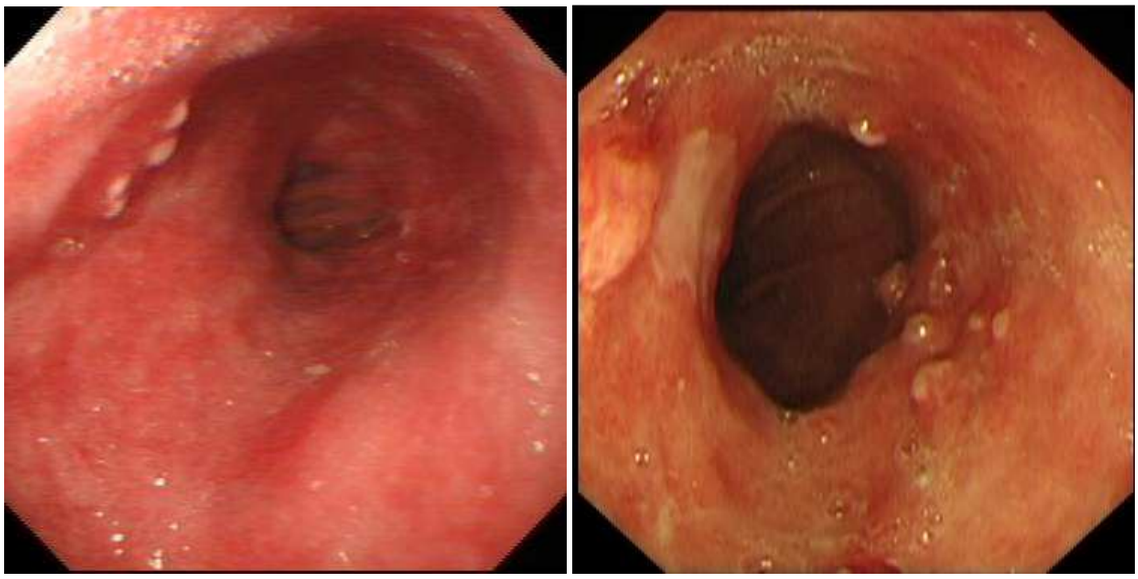


Fig. 1a (left) illustrates a nodular area of what proved to be HGD in a tongue of Barrett's oesophagus. 1b (right) illustrates multifocal nodular Barrett's neoplasia. In this example clinicians must have a very high level of suspicion for the presence of invasive malignancy

Another factor critical to endoscopic detection of dysplastic Barrett's oesohagus is a systematic approach to mucosal inspection. The oesophagus may be cleaned using water or 1% acetylcysteine to remove saliva and gastric refluxate and the oesophagus must be adequately distended by inflation. Special care must be taken in patients with a hiatus hernia as in these cases the distal extent of the Barrett's segments can be difficult to identify meaning dysplasia at the oesophagogastric junction can be missed. In addition, clinicains should be aware that the majority of neoplastic lesions are located between 12 and 6 o'clock in the endoscopists view. (Curvers et al., 2008b) Importantly clinicians should also commit to investing considerable time to endoscopic inspection (as well as the time required for multiple biopsies), and endoscopy lists should be planned accordingly when patients with known Barrett's oesophagus are attending for surveillance.

Biopsies should be taken (as per the BSG guidelines described in Box 1) and should start distally and work proximally to minimise any obstruction to the endoscopic view caused by bleeding. A description of the Barrett's segment should then be recorded using the Prague C&M classification (see section 2) and positions of random biopsies and suspicious areas recorded meticulously. Where possible, visible macroscopic neoplasia should also be classified according to the Paris classification (Box 2).

Box 2. Classification of visible early Barrett's neoplasia

Visible macroscopic early neoplastic lesions in Barrett's oesophagus are classified using the Paris classification. A description of the superficial (0) lesions is detailed below.

0	**Superficial lesions**	
0-I		Protruding / polypoid lesions
	0-Ip	Pedunculated
	0-Is	Sessile lesions
0-II		Non-protruding / non-excavated lesions
	0-IIa	Slightly elevated
	0-IIb	Completely flat
	0-IIc	Slightly depressed
0-III		Excavated / ulcerated lesions

Most dysplastic Barrett's lesions are of superficial type (0-II).

Several techniques have been developed to improve endoscopic recognition of dysplasia and intramucosal carcinoma in Barrett's oesophagus. These aim to minimise sampling randomness and also facilitate targetted endoscopic resection in patients with histologically confirmed HGD / IMC. In addition, they aim to improve assessment of disease extent and minimise the incidence of missed synchronous tumours.

4.1 High resolution endoscopy by expert endoscopists

Modern high resolution endoscopes which generate up to one million pixel images (compared to the 300,000 pixel images of traditional scopes) have been shown to have a higher sensitivity for the detection of early Barrett's neoplasia provided they are used by expert endoscopists.(Kara et al., 2005a; Kara et al., 2005c) These high definition endoscopes should be used in conjunction with a high definition television to further enhance the projected image quality and enable projection onto a larger screen without loss of image resolution.

Studies have shown that up to 80% of patients referred to specialist units with biopsy proven HGD without visible abnormality will be found to have 1 or more visible abnormalities when endoscopy is repeated by an expert endoscopist using a high resolution endoscope. (10,12 from endoscopic work-up) (Kara et al., 2005a; Curvers et al., 2008d)

4.2 Chromoendoscopy

Chromoendoscopy utilises stains which bind selectively to different oesophageal mucosa and so can enable discrimination between non-dysplastic Barrett's oesophagus and HGD /

adenocarcinoma. Staining and lesion defining agents utilised include methylene blue, indigo carmine, and acetic acid. Results from studies utilising this technique have been mixed citing problems such as an inability to uniformly coat the oesophageal mucosa with the stain, and excessive time necessary for stain spraying as particular concerns.(Shaheen and Richter, 2009; Lim et al., 2006; Ragunath et al., 2003) None of these techniques has been shown to consistently out-perform high resolution endoscopy in the detection of early neoplastic lesions.(Curvers et al., 2008c) Chromoendoscopy is often both labour-intensive and operator-dependent and therefore although it may have a role when used in specialist centres by expert users, it is unlikely to develop a wider role in routine clinical practice.

4.3 Narrow band imaging (NBI)

NBI filters white light into blue and green wavelengths (at the push of a button) giving more accurate images of the mucosal and vascular patterns in the oesophageal lining. This increased superficial imaging of the oesophagus (without the need for staining) can be used to identify dysplastic lesions within Barrett's segments.(Kara et al., 2006a) In the hands of experienced users the technique has shown promise however, results have been mixed.(Sharma et al., 2006a; Curvers et al., 2008a) A recent trial from Holland shows no diagnostic benefit from either NBI or chromoendoscopy.(Curvers et al., 2008a) However, data on the accuracy of NBI is still inconclusive and results of ongoing mulitcentre randomised controlled trials are awaited.

4.4 Autofluorescence imaging (AFI)

Following excitation with short wavelengths of light many endogenous tissues emit fluorescence radiation which can be measured using fluorescence spectroscopy. Metaplastic and dysplastic Barrett's oesohagus have been shown to emit slightly different fluorescence spectra enabling the technique to be used as a mechanism to discriminate between the two pathologies. AFI appears to improve the detection of early Barrett's neoplasia when used in combination with high resolution endoscopy, although the false positive rate is relatively high.(Curvers et al., 2008b; Kara et al., 2005b; Kara et al., 2006b) Further studies are clearly indicated to truely assess the potential long-term role for AFI.

4.5 Optical coherence tomography (OTC)

OCT is analogous to ultrasound but can produce higher quality images as it relies on scattering of near infrared light as opposed to reflection of sound waves. OCT can obtain cellular images of sub-epithelial tissue through differences in their light scattering properties and avoids the need for exogenous contrast material.

In a study of 55 patients with Barrett`s oesophagus, OCT was shown to delineate between HGD and oesophageal adenocarcinoma with a sensitivity of 83% and a specificity of 75%.(Evans et al., 2006) Similarly, a study of 33 patients demonstrated a diagnostic accuracy of 78% for the identification of dysplastic Barrett's oesophagus but with considerable user discrepency (56% to 98%). (Isenberg et al., 2005) Further clinical evaluation is required to fully assess the performance of OCT and assess the feasibility of introducing this promising diagnostic tool into routine clinical practice.

4.6 Confocal microscopy (CM)

CM magnifies the mucosa by more than 1000 fold producing images with 1-2 μm spatial resolution and allowing real time visualisation of cellular structures. Kiesslich et al studied

63 patients with Barrett`s oesophagus using white light endoscopy and confocal microscopy. Intravenous fluorescein was administered to generate vascular contrast and at sites of neoplasia could be seen to disperse within the lamina propria due to irregular neovascularisation. Accuracy of CM was found to be 97.4% (sensitivity 93%, specificity 98%). (Kiesslich et al., 2006) In another study by Dunbar et al, CM was shown to help target biopsies to areas of neoplasia, doubling diagnostic yield per biopsy taken, and avoiding the need for biopsy in two thirds of patients undergoing surveillance. However, no overall increase in neoplasia was identified when CM targetted biopsying was compared to random quadrantic random biopsies every 2cm.

Confocal microscopy is an expensive technique and requires the use of exogenous contrast. It has already demonstrated potential in early diagnosis of Barrett`s neoplasia although the excellent results reported by some studies have not been universally matched. (Pohl et al., 2008) Further studies are required before this technique can be reccommended for widespread use.

4.7 Labelling of biomarkers

Molcular biomarkers associated with neoplastic cells can be labelled using a specifically targetted probe molecule which has been tagged with a visual agent such as a fluoresecent dye. (Pierce et al., 2008) (Thekkek et al., 2011) The probe molecule selectively binds to the biomarker so that areas of neoplasia can be visualised with a high signal to noise ratio.

Lu et al identified a cell surface peptide specific to adenocarcinoma which they labelled using a fluorescein-tagged antibody delivered topically. The oesophagus was then washed to remove any unbound antibody and a fluorescence endoscope was used to visualise neoplastic disease. (Lu and Wang, 2008)

Other similar studies have used a range of potential biomarkers with similar effect. This is clearly a very promising technique for the detection of early neoplasia but further on-going work is necessary to identify novel molecular targets in order to improve sensitvity and specificity before widespread implementation of the technique can be contemplated.

4.8 Raman spectroscopy

Raman spectroscopy is an optical diagnostic technique which has shown considerable potential for early diagnosis of a variety of malignant disease states including oesophageal neoplasia. Raman spectroscopy measures the molecular-specific, inelastic scattering of laser light within tissue in order to generate a unique molecular 'fingerprint'. Normal, dysplastic and cancerous tissues have differing biochemical cellular components leading to characteristic spectral differences which can be analysed. Laboratory based Raman spectrometers are capable of discriminating between eight pathological groups in the distal oesophagus (including Barrett's metaplasia, HGD and adenocarcinoma) with sensitivities between 73% and 100%. (Kendall et al., 2003) Several groups are currently investigating the potential for endoscopic Raman spectroscopy using a fibre-optic Raman probe. Fibre-optic Raman sectroscopy has already demonstrated encouraging results following in vivo trials in the stomach, bladder and cervix. Although some way off clinical implementation in the oesohagus, in vivo and ex vivo results are promissing and this technique may become widely available in the short to medium term to enable instant endoscopic diagnosis of dyslasia (without the need for biopsy) and to facilitate immediate, targetted endotherapy.

5. Barrett's oesophagus surveillance

As endoscopic recognition of dysplasia remains limited at present, a policy of regular endoscopic surveillance, in conjunction with a rigourous biopsy regimen, is recommeded. The frequency of surveillance endoscopy depends predominantly on the presence and degree of dysplasia identified, and also to a lesser extent on patient age, comorbidity and patient preference.

Several retrospective studies have demonstrated a survival benefit for patients with cancers detected by surveillance endoscopy rather than following symptom investigation. (Streitz et al., 1993; Peters et al., 1994; van Sandick et al., 1998; Fountoulakis et al., 2004; Corley et al., 2002) However, many other studies have failed to show this. (Wong et al., 2010) The Barrett's Oesophagus Surveillance Study (BOSS) is a multi-centre randomised control trial currently recruiting patients throughout the UK. In this study patients are randomised to either 'endoscopy at need' (no routine surveillance), or repeat OGD combined with BSG biopsy regimen every two years for a total of ten years. The study aims to define the objective value of endoscopic surveillance and the most appropriate surveillance protocol.

Despite the current lack of high level evidence, most clinicians elect to follow up patients with Barrett's oesophagus provided the pros and cons of surveillance have been fully discussed with the patient and they subsequently wish to proceed with surveillance endoscopy. Clearly, this approach is not suitable for all-comers, and management should therefore be individualised appropriately. For example, long-term follow-up of elderly patients who are unfit for intervention is not usually recommended.

Where surveillance is deemed appropriate BSG guidelines recommend 2-yearly endoscopy using a comprehensive biopsy protocol. (BSG Working Party, 2005) Quadrantic biopsies are recommended every 2cm of Barrett's oesophagus, with more targeted biopsies of any raised or suspicious looking areas (Box 1). Patients should have their reflux treated with a proton pump inhibitor so that the presence of oesophagitis does not complicate the histological identification of dysplasia. Patients with Barrett's oesophagus who are not enrolled in endoscopic surveillance should also receive proton pump inhibitor (PPI) therapy The effectiveness and dosage of PPI therapy with and without aspirin for the prevention of progression of Barrett's oesophagus is being addressed in the Aspirin Esomeprazole Chemotherapy Trial (ASPECT) in the united Kingdom.

For those patients undergoing routine endoscopic surveillance, the risk of developing adenocarcinoma is approximately 1% a year in the UK, and about half this figure in the US. (Jankowski et al., 2002) Critcially when dysplasia has been identified on endoscopy every effort must be made to ensure that the correct diagnosis has been reached and an appropriate management strategy should then be formulated.

6. Importance of histological / radiological assessment

Accurate histological diagnosis is essential when assigning treatment strategies for Barrett's dysplasia and early Barrett's malignancies. Histopathologists can have difficulty differentitating HGD from LGD, and also HGD from early invasive (T1) carcinoma based on point biopsy appearances alone. In recent years endoscopic resection (ER) has become recognised as not only a potentially curative therapy, but also a vital diagnostic technique (section 7.1.1). The role of 'diagnostic' ER is expanding as pathologists realise the importance of accurate assessment and grading of early tumours.

The current BSG guidelines from 2005 do not recognise the diagnostic role of ER. However, new guidelines are currently being formulated by an international consensus group the 'Barrett's Dysplasia and Cancer Taskforce' (BAD CAT). These will stress the need for extremely accurate assessment of the presence and depth of invasive cancer and will recommend confirmation using ER, as well as (when indicated) further staging using endoscopic ultrasound (EUS) (which is known to be poor at differentiating between T1a and T1b tumours but is sensitive for lymph node metastases), and possibly PET-CT.

Recent studies have demonstrated the importance of accurate staging of early (T1) tumours. T1a lesions (confined to the mucosa) have a very low incidence of lymphatic invasion (<5%) whereas, invasion into the submucosa (T1b) is associated with lymphatic spread in 20-45% of cases. New evidence has suggested that the distinction between $T1sm_1$ and $T1sm_2$ (i.e. between the upper 1/3 and lower 2/3 of the submucosa) may be particularly significant as the risk of lymphatic spread appears to significantly increase in $T1sm_2$ tumours. This distinction is vital as surgical oesophagectomy and lymphadenectomy provide the only chance of cure for patients with lymphatic spread, whereas endoscopic therapy is potentially curative in those without lymphatic invasion.

As histopathological diagnosis and grading of dysplasia is difficult and subjective, any suggestion of dysplasia should be reviewed by expert pathologists at an MDT prior to initiation of a management plan. In cases where exact histopathological diagnosis proves difficult clinicians should have a low threshold for 'diagnostic' endoscopic resection to aid histological classification. This may be of particular benefit in distinguishing between HGD and early invasive (T1) carcinoma, and in accurately T-staging these early cancers.

7. Endoscopic therapies for HGD and IMC

Once an accurate diagnosis has been made and corroborated by consensus opinion in an MDT, a management plan can be formulated. All patients should be commenced on high dose PPI therapy. Subsequent management is currently subject to significant debate but is largely dependent on the degree of dysplasia, patient comorbidity and patient preference.

Recent developments have led to potentially curative endoscopic treatments for HGD and early mucosal cancer. Many of these techniques are relatively novel and are not supported by highest level evidence (RCTs). BSG and American College of Gastroenterology (ACG) guidelines from 2005 and 2008 respectively are now somewhat out-of-date when considering the management of advanced dysplasia / early cancer. However, the management of LGD has not altered in recent years as a simple 'number needed to treat' analysis confirms that the limited risks posed by LDG (in isolation), do not warrant the cost and morbidity imposed by endoscopic therapies.

The management of HGD and intramucosal cancer (T1a) is currently hotly debated and new guidelines are awaited (BAD CAT consensus). It is clear that management policies must be individualised according to the nature and severity of disease and the age and comorbidity of the patient being treated, and all management decisions must be discussed at a specialist cancer MDT.

There are two main forms of endoscopic therapy available to treat HGD and intramucosal tumours – endoscopic resection and endoscopic ablation. These techniques aim to destroy the lining of the oesophagus and promote regenerative re-growth of normal squamous mucosa. In order for this to occur, (as opposed to columnar re-growth) some of the superficial squamous lined ducts must survive the process. Techniques for mucosal ablation include photodynamic therapy, thermal ablation, radiofrequency ablation and argon plasma coagulation.

8. Endoscopic resection

Endoscopic mucosal resection (EMR) describes any technique which removes a complete area of mucosa. However, the term is somewhat misleading and many authors recommend a switch to the term 'endoscopic resection' (ER), as the aim of EMR should involve complete excision of the mucosal and submucosal layers down to the muscularis propria.
The technique involves raising an area of mucosa using suction or by submucosal injection, and then snaring it off (in a similar manner to a colonic polyp). It is a useful technique for removing focal areas of HGD or early cancer, and as well as being therapeutic, can provide important diagnostic information.

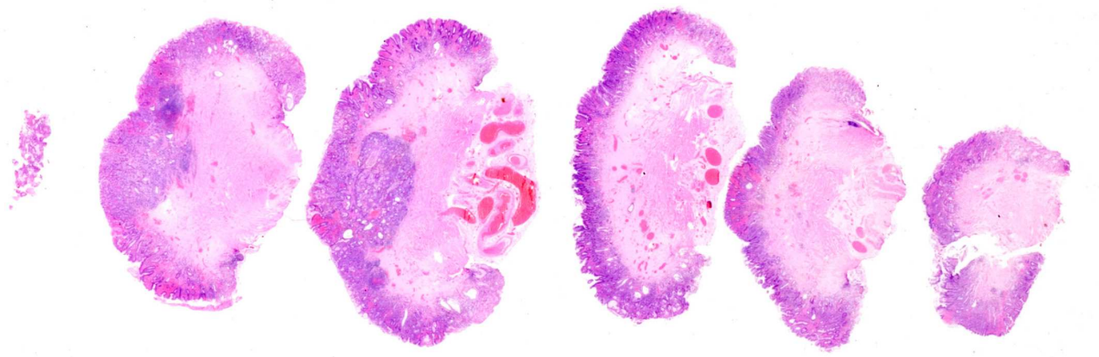


Fig. 2. Endoscopic resection of an early invasive cancer

8.1 Diagnostic endoscopic resection

Although not yet recognised by BSG guidelines, ER has now become an important diagnostic technique in patients with HGD / early cancer. ER preserves tissue architecture so that a full histopathological assessment can be made. (Odze and Lauwers, 2008) An ER specimen can be more easily orientated than a mucosal point biopsy and should contain a significant portion of submucosa allowing accurate assessment of the depth of invasion of IMC. A retrospective study of 150 EMR specimens (focal lesions) found that following analysis of EMR specimens, initial diagnoses (based on point mucosal biopsies) where changed in 49% of cases, leading to a change in management plan in 30%. (Peters et al., 2008) Mino-Kenudson et al recently demonstrated that interobserver reporting agreement between pathologists was improved when reporting EMR specimens rather than point biopsies, particularly when differentiating between intramucosal and submucosal carcinoma – a key distinction when planning a treatment strategy. (Mandal et al., 2009) ER specimens also enable improved assessment of other important prognostic factors such as the grade of cellular differentiation and the presence of lymphovascular invasion. ER has been shown to be the best technique for assessment of visible mucosal abnormalities within Barrett's oesophagus. However, the technique does have complications, and these must be considered when performing an ER for diagnostic purposes.

8.1.1 Therapeutic ER

As a therapeutic technique, oesophageal ER has been assessed in a number of large studies, although no randomised controlled trials currently exist. Its first description in HGD and

early mucosal cancers in Barrett's oesophagus was published in 2000, although ER was described for early oesophageal SCC as far back as the early 1990s.
A recent study reported that ER achieved remission in 82.5% of patients with HGD. However, over a 12 month period of follow-up, metachronous lesions or disease recurrence were identified in 14% of patients, necessitating re-treatment. A further study using ER, photodynamic therapy (PDT) or a combination, showed overall complete disease remission in 98% of patients, but metachronous cancer was identified in 31% over a 34 month post treatment surveillance period. (Pech et al., 2007)
Extensive, multifocal disease is more difficult to manage endoscopically using ER. Several studies have described circumferential ER of extensive Barrett's segments but, despite experienced hands, these extensive resections have been associated with significant complication rates (bleeding 33%, strictures 17-26% and perforation 3%) and large studies with prolonged follow-up have not been conducted. (Pech et al., 2007; Seewald et al., 2003)In addition, significant recurrence rates have been reported and in up to 25% of cases, complete resection of the Barrett's segment was impossible despite several staged attempts at treatment. (Pech et al., 2007)
As discussed previously, oesophageal lesions that invade into the lamina propria but are confined to it (do not invade the submucosa) T1m1-3 (T1a) lesions have a 5% chance or less of nodal involvement. Recent data have suggested that shallow mucosal invasion $T1_{sm1}$ also has a significantly lower risk of nodal metastases than other grades of submucosal invasion. (Prasad et al., 2007; Gondrie et al., 2008) Whereas deeper invasion into the submucosa (T1sm2-3) sees this risk rise to 20-45%. (Peyre et al., 2008) In early cancers with a low risk of lymphatic spread, ER offers a curative, minimally invasive treatment option, which may be particularly appropriate in older patients at higher risk of operative morbidity / mortality. Average 3-year survival rates of more than 80% have been reported for IMC treated by ER.
In recent years there has been a move towards combination therapy in an attempt to reduce recurrence rates. Areas of focal dysplasia (or IMC) could be treated with ER, followed by complete ablation of the entire Barrett's segment using APC, PDT, or RFA.

8.2 Mucosal ablation therapy

Ablation techniques aim to destroy the lining of the oesophagus and promote regenerative growth of normal squamous mucosa. Techniques for mucosal ablation include photodynamic therapy, thermal ablation, radiofrequency ablation and argon plasma coagulation, all of which must be used in combination with acid suppression.
There are so far no randomised trials comparing these treatments against each other. In addition, the natural history of regenerated squamous epithelium is not fully known, (although there certainly appears to be a substantial reduction in malignant potential) so further long-term studies are still awaited. (Overholt et al., 2005)

8.2.1 Radiofrequency ablation

RFA is a relatively new technique which can be used to ablate circumferential ($HALO^{360}$) or focal ($HALO^{90}$) Barrett's oesophagus. Circumferential ablation is performed using a balloon to apply radiofrequency energy evenly to the oesophageal lining.
The length of the Barrett's segment is first measured endoscopically. N-acetylcysteine is then used to wash saliva, mucus and gastric juice from the oesophagus and a guidewire is placed into the gastric antrum. The endoscope is removed and a sizing balloon is inserted

over the guide wire and inflated once in the distal oesophagus. In long segment Barrett's oesophagus several measurements are taken and subsequently, an appropriately sized ablation catheter is selected (based on the smallest oesophageal diameter measurement). The catheter is then passed over the guide wire and positioned at the proximal extent of the Barrett's segment. The endoscope is re-passed to ensure correct positioning of the catheter and the balloon is then inflated and a standardised dose of energy is delivered (which has a power density sufficient to ablate down to the muscularis mucosae, 700-1000μm deep). After a short period of treatment (<5s) the catheter is passed distally to the next portion of the oesophagus to be treated, trying to minimise overlap between zones by endoscopic visualisation. Once the entire Barrett's segment has been ablated the catheter is removed and the endoscope is reinserted in order to debride the ablated mucosa. The procedure is then repeated so that the whole Barrett's segment receives two treatments.

Complications are rare but include significant bleeding (1-2%), stricture formation (6%) and perforation (very rare). (Shaheen et al., 2009) Repeat OGD is recommended after 2 – 3 months and any residual focal Barrett's oesophagus can then be treated using HALO^{90} RFA.

The only RCT, by Shaheen et al in 2009, demonstrated successful resolution of dysplastic Barrett's oesophagus following treatment with RFA.(Shaheen et al., 2009) Complete eradication of LGD was seen in 90.5% (ablation group) compared to 22.7% (control group) ($P<0.001$). Complete eradication of HGD occurred in 81.0% (ablation group) versus 19.0% (control group) ($P<0.001$). RFA also decreased the likelihood of disease progression (3.6% vs. 16.3%, $P=0.03$) and cancer (1.2% vs. 9.3%, $P=0.045$).

Recent NICE guidelines (June 2010) recommend that clinicians in the UK consider endoscopic ablation therapy (preferentially RFA) along with EMR, for treatment of HGD and IMC, particularly in patients not suitable for oesophagectomy.

8.2.2 Photodynamic therapy

Porfimer sodium photodynamic therapy (PDT) has been approved by the US Food and Drug Administration (FDA) and (provisionally) by NICE for treatment of HGD in Barrett's oesophagus.

The procedure involves systemic (intravenous) administration of a photosensitising agent (porfimer sodium) which is retained selectively by dysplastic cells. After about 48 hours the patient undergoes an upper endoscopy and a laser is used to excite a cytotoxic reaction in dysplastic Barrett's cells, leading to their destruction. There is now strong evidence that PDT can prevent the progression of disease in patients with Barrett's HGD. (Overholt et al., 2007) A five year randomised multicentre trial by Overholt et al demonstrated that PDT was significantly more effective at eradicating HGD than omeprazole only (odds ratio 2±0.7). It also significantly lengthened the time taken to progress to malignancy and reduced the overall risk of malignant progression by half. (Overholt et al., 2007) Following PDT, patients are required to continue life-long surveillance, and repeat ablation may become necessary.

Side-effects of PDT include nausea and chest pain in the first day or two after treatment. In the longer term, oesophageal strictures may occur in up to a quarter of patients. Oesophageal perforation has also been described (very rarely). In addition, due to the photosensitising affect of porfimer sodium, patients are required to minimise light exposure to their skin for up to 4-6 weeks after the treatment.

Several trials in Europe have used 5-ALA as the photosensitising agent in an effort to reduce skin sensitivity and oesophageal strictures. However, additional blood pressure and cardiac

complications have been reported with 5-ALA and further work is therefore required to clarify the most effective drug with the least side-effects.

8.2.3 Argon plasma coagulation

APC (the most commonly used form of thermal ablation) uses a jet of ionized argon gas (plasma) directed through an endoscopic probe to ablate short segments of Barrett's or areas of persistent disease following other ablative treatment. A trial by Pech et al retrospectively assessed disease recurrence in patients treated by EMR with or without subsequent APC ablation of the residual Barrett's segment. Rates of recurrence fell from 33.3% to 17.6% with the inclusion of APC ablation. Other studies support these results and confirm low complication rates.

9. Buried glands

In some cases following ablative therapy for Barrett's oesophagus, a normal squamous epithelium may re-grow over a portion of Barrett's tissue. Endoscopically this appears normal, but these buried Barrett's glands may retain malignant potential. Endoscopists must be aware of this when surveying patients who have previously undergone ablative endotherapy and for this reason life-long endoscopic surveillance is recommended for these patients, even in the absence of residual Barrett's oesophagus.

10. Oesophagectomy

HGD is associated with early invasive malignancy in up to 30% of cases, and carries a significant long-term chance of malignant progression. In addition, recurrence rates following ablative therapies are significant and endoscopic surveillance must be lifelong. For these reasons, surgical excision of the entire Barrett's segment must still be considered the 'gold standard' treatment for young, fit patients with multifocal HGD.

Oesophagectomy is the only potentially curative treatment once lymph nodes are involved. It also aims to remove the entire Barrett's segment minimising the chance of recurrence or missed metachronous lesions. Recent centralisation of cancer services has improved operative mortality to 5% or less in most specialist units. However, for patients without proven invasive cancer, this still remains a considerable risk. In addition, morbidity following oesophagectomy remains considerable although minimally invasive and vagal sparing surgery aims to minimise this and improve long-term functional outcomes. (Ell et al., 2007)

11. Management of low-grade dysplasia

Patients with LGD should undergo repeat endoscopy with adherence to a 'gold standard' biopsy regimen 8-12 weeks after the commencement of PPI therapy. A repeat endoscopy should then be performed at 6 months, and if LGD persists, endoscopy should be repeated 6-monthly unless regression to normal Barrett's or squamous epithelium occurs, at which time surveillance can be reduced to 2 yearly intervals. (BSG Working Party, 2005)

In some cases of multifocal, persistent LGD, endoscopic mucosal ablation therapy could be considered, particularly if there is a strong patient desire for intervention (BSG Working Party, 2005) (although evidence for this statement is limited and widespread treatment of LGD is not cost-effective and is not recommended).

12. Management of high-grade dysplasia / intramucosal cancer

Data from case series suggest that up to 10% of patients with Barrett's oesophagus develop HGD, and that HGD may be associated with a focus of adenocarcinoma in up to 30% of patients. Several studies also have described high rates of progression to malignancy – annual rates of progression of 2.2%, 4% and 11.8% have been described recently. (Schnell et al., 2001b; Buttar et al., 2001; Reid et al., 2000b) In addition, the average time to progression from HGD to cancer is known to be short, typically around 24 months, (ranging from 6-43 months), (although, in most cases, HGD remains stable without progression, or may even regress). (BSG Working Party, 2005)

In confirmed cases of IMC, clinicians must not only consider T-stage, but also other important prognostic indicators including the grade of cellular differentiation and the presence of lymphatic or vascular invasion, when formulating a management strategy.

It is now clear that ER has an important diagnostic role in the determining these important prognostic indicators. Endoscopic ultrasound (EUS) is also important in intramucosal cancer to assess for the presence of early nodal metastases. EUS has been shown to be substantially more accurate than CT for detecting nodal metastases and the role of CT in investigation of intramucosal tumours is probably limited. PET-CT is a more reliable means of assessing the presence of distant metastasis which would circumvent the need for surgery and necessitate palliative therapy.

EUS is known to be poor at distinguishing between T1a and T1b tumours (33-85% accuracy) and importantly, under-diagnosis of T1b lesions is common. (May et al., 2004; Zuccaro et al., 2005). ER assessment is much more reliable but may fail to completely excise the submucosa making exact distinction between $T1_{sm1}$ and $T1_{sm2}$ difficult. Frequently pathologists use the measured depth of invasion in micrometers to differentiate the two. However, there is a paucity of published data correlating measured depth of submucosal invasion with likelihood of lymph node metastasis. Currently the role of endoscopic submucosal dissection (ESD) in the oesophagus is unclear and further trials are awaited.

If endoscopic therapy is to be considered ahead of surgery for early oesophageal tumours and HGD, a number of important considerations should be satisfied (Box 3). Similarly, if surgery is to be considered in cases where there is no overt evidence of lymphatic spread, complication rates must be low. Many papers continue to quote historic rates of mortality following oesophagectomy. It is important when contemplating treatment options to compare up-to-date data which reflects recent improvements in operative outcomes (mortality and morbidity) since surgical centralisation took place.

Box 3. Important considerations when considering the role of endoscopic therapy.

- There must be no (or minimal) under-staging of disease.
- Practitioners must be adequately skilled.
- Recurrence must be identified early and there must be a means of treating it.
- Patients must understand that endoscopic therapy is less likely to provide a "cure" than surgical treatment.
- Patients must understand that they will require long-term surveillance, (unlike following surgery).
- Complication rates (morbidity and mortality) must be low.

12.1 Multifocal HGD

Patients with multifocal disease are at a significant risk (up to 30%) of an undetected metachronous cancer and therefore warrant definitive treatment. Surgical oesophagectomy should still be considered as the first line treatment option for patients with persistent HGD provided they are deemed low operative risk and have a long life expectancy. Surgery must be carried out in specialist centres where mortality rates do not exceed 5%.

Those patients with confirmed persistent multifocal HGD who are deemed unfit for an oesophagectomy should receive ER to visible areas of HGD and subsequent ablation of the entire Barrett's segment. Several ablative treatments (using different modalities) may be required to establish complete remission. Patients will subsequently require lifelong endoscopic surveillance.

12.2 Focal HGD

Patients should be initially managed by ER of the affected area to confirm the diagnosis and exclude early malignancy. Those with a limited area of histologically confirmed HGD should undergo subsequent mucosal ablation of the whole Barrett's segment. Young patients who are fit for major surgery should be considered for oesophagectomy.

Clinicians should have a high level of suspicion for cancer and if suspected appropriate investigations e.g. endoscopic ultrasound and PET-CT should be considered. Nodularity on endoscopy should particularly raise concern although occult intramucosal tumours can occur with no visible mucosal abnormality.

Patients with HGD should initially undergo three monthly endoscopy with quadrantic biopsies every 1cm – shown to half the chance of missing oesophageal adenocarcinoma compared to 2cm biopsies. (Reid et al., 2000a) Jumbo biopsies (using large capacity forceps) can also be taken in this setting.

12.3 Intramucosal carcinoma

All patients with confirmed oesophageal cancer should undergo formal tumour staging to establish the presence or absence of distant or locoregional metastases. Surgery should be regarded as the treatment of choice for patients deemed fit enough to tolerate oesophagectomy. Patients with high operative risk with T1a (and possibly $T1_{sm1}$) tumours confirmed on ER should be considered for endoscopic therapy (ER followed by ablation).

13. Summary

All treatment decisions should be discussed in a multidisciplinary team meeting once every effort has been made to ensure the correct diagnosis has been reached. Patients (and families) should be fully informed and involved in the decision making process. All surgical and endoscopic procedures should be performed by specialists in recognised cancer units.

ER should be used as a potentially curative treatment for IMC and focal HGD, and also has an emerging role in aiding histological diagnosis. Following ER the goal should be to ablate the entire Barrett's segment. Due to the technical difficulties and costs associated with PDT, its role is increasingly being superseded by that of RFA. Following initial ablative therapy, further treatments (using the same or different treatment modalities) should be given in an attempt to destroy any remaining metaplastic / dysplastic epithelium. The aim should be complete squamous regeneration, however even if successful, surveillance should be life-long as glands with malignant potential may persist burried beneathe the regenerated mucosa.

This combination of endoscopic resection and ablation of high-grade dysplasia and intramucosal cancer offers alternative therapeutic options to those unsuitable or unwilling to contemplate radical surgical excision. This combination endotherapy has been shown to provide long-term survival in patients with HGD and IMC and it is possible that this management strategy may soon become the treatment of choice for all patients with HGD.

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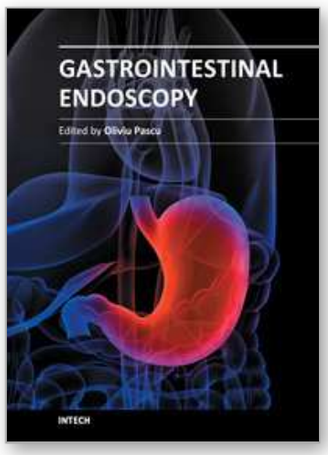

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Endoscopy has had a major impact in the development of modern gastroenterology. By using different data it provided a better understanding of pathogenic mechanisms, described new entities and changed diagnostic and therapeutic strategies. Meanwhile, taking advantage of many technical advances, endoscopy has had a developed spectacularly. Video-endoscopes, magnification, confocal and narrow-band imaging endoscopes, endoscopic ultrasounds and enteroscopes emerged. Moreover, endoscopy has surpassed its function as an examination tool and it became a rapid and efficient therapeutic tool of low invasiveness. InTech Open Access Publisher selected several known names from all continents and countries with different levels of development. Multiple specific points of view, with respect to different origins of the authors were presented together with various topics regarding diagnostic or therapeutic endoscopy. This book represents a valuable tool for formation and continuous medical education in endoscopy considering the performances or technical possibilities in different parts of the world.

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