Barrett's oesophagus: diagnosis, surveillance and treatment

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Barrett's oesophagus is a premalignant condition with rising incidence in the UK. The technological progress in the area of endoscopic imaging and the rapid development of endoscopic treatment modalities for early neoplastic lesions have altered patient management in recent years and highlighted the need for more structured screening and surveillance schemes and the introduction of novel, cost-effective approaches to identifying high risk patients.

Epidemiological background and risk factors

According to the 2005 Montreal classification, Barrett's oesophagus is defined as metaplastic columnar lined epithelium (with or without goblet cells) that extends clearly proximal of the gastro-oesophageal junction (Vakil et al, 2006). However, only the combination of the endoscopic appearance and the histopathological confirmation of columnar epithelium legitimates the diagnosis 'Barrett's oesophagus' (Vakil et al, 2006). This is in keeping with the UK Barrett's guidelines which have been revised in 2013 (Fitzgerald et al, 2013). Patients with Barrett's oesophagus show an increased risk of developing oesophageal adenocarcinoma, although the annual rate of malignant progression is lower than previously thought, probably as a result of publication bias. A meta-analysis of 57 studies comprising 11 434 patients (58 547 patient years) reported an incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's metaplasia of 0.33% (95% confidence interval 0.28–0.38%) (Desai et al, 2012). The individual risk of development of dysplastic changes or invasive cancer correlates with the length of the metaplastic segment.

Established risk factors for Barrett's oesophagus are male gender, increasing age, smoking history and a history of reflux symptoms (Lagergren et al, 1999). Obesity has also been shown to further increase the risk of Barrett's oesophagus as well as further malignant progression towards oesophageal adenocarcinoma, with waist to hip ratio and abdominal circumference being more highly correlated with cancer risk than body mass index (Eusebi et al, 2012). There is a two-fold increase in risk of malignant progression of Barrett's oesophagus towards invasive adenocarcinoma in smokers compared to non-smokers (Coleman et al, 2011).

Over the past two to three decades, there has been a consistent increase in the annual incidence of oesophageal adenocarcinoma in western countries, with the incidence of oesophageal adenocarcinoma exceeding that of squamous cell cancer. There is an annual increase in the incidence rate for oesophageal adenocarcinoma in England and Wales of 7.9% in males and 7.5% in females (Lepage et al, 2008). Owing to the non-specific symptoms the majority of patients present at a late stage and hence the 5-year survival rate for oesophageal adenocarcinoma is <20%.

Thus, there is strong need to establish protocols for early detection of both Barrett's oesophagus and oesophageal adenocarcinoma, as well as surveillance of individuals at high risk of malignant progression of metaplastic changes (*Figure 1*).

Diagnosing Barrett's oesophagus

Owing to the current reliance on endoscopy for diagnosing Barrett's oesophagus which is relatively invasive and expensive, screening for Barrett's oesophagus should not be undertaken in an unselected population but rather in preselected individuals at high risk. Although Barrett's oesophagus can occur in the absence of symptoms, from a practical point of view the main indication for endo-scopy is the presence of a history of reflux symptoms. Further factors including increased age (above 50 years), male gender, caucasian ethnicity and increased body weight should also be taken into consideration, as well as a positive family history of Barrett's oesophagus. In the past the National Institute for Health and Care Excellence dyspepsia guidelines discouraged referral for endoscopy but the recent guidelines of the British Society of Gastroenterology and emerging evidence on the propensity for late referrals with associated poorer outcome, are in favour of endoscoping patients with these risk factors in view of the importance of an early diagnosis of cancer (Fitzgerald et al, 2013; Shawihdi et al, 2013).

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There is an increasing number of diagnostic options but currently upper gastrointestinal endoscopy with histopathological evaluation of biopsies remains the gold standard. The endoscopic report for Barrett's oesophagus should include a description of the extent of the circumferential segment ('C-level') and the maximum length of the longest tongue of the metaplastic columnar epithelium ('M-level') according to the Prague C&M classification in order to facilitate communication between clinicians, especially when being considered for treatment. In order to accurately assess the extent of Barrett's oesophagus the diaphragmatic hiatal pinch and the proximal extent of the gastric folds should also be reported.

Targeted biopsies should be taken from visible lesions suspicious for dysplastic changes of the mucosa, as well as four 'random' quadrantic biopsies at 2 cm intervals over the entire extent of the Barrett's segment (Levine et al, 2000).

Endoscopy

The standard procedure is white light endoscopy. For the initial diagnostic procedure the use of thinner transnasal endoscopes which increase patient acceptability are a reasonable alternative to standard gastroscopy. However, for surveillance of Barrett's oesophagus to detect dysplasia a high resolution trans-oral gastroscope which also permits larger biopsies to be taken should be used.

Another emerging option for screening is the use of video capsule endoscopy. In a meta-analysis of nine studies including 618 patients, the pooled sensitivity for the detection of Barrett's oesophagus was 77%, with a specificity of 86%, which are both inferior to traditional white light endoscopy (Bhardwaj et al, 2009).

The quality of traditional white light endoscopy can by enhanced by chromoendoscopic techniques (e.g. staining with methylene blue or indigocarmine) or application of acetic acid. By application of these dyes, the surface pattern of the metaplastic mucosa can be enhanced and thus highlight dysplastic changes which show an irregular and distorted pattern. Whether the diagnostic yield of targeted biopsies can be improved by classical chromoendoscopy is still under debate. Overall, the data currently available on these methodologies do not suggest that any of them are superior to white light resolution endoscopy in routine surveillance practice.

Technologies that allow virtual chromoendoscopy by the use of optical filter systems have also been advancing as an alternative to the application of intraluminal dye. The combination with optical magnification of the mucosal surface pattern further increases the diagnostic accuracy and is discussed below.

Narrow band imaging

Narrow band imaging filters the wavelengths at 415 nm and 540 nm such that red structures like blood vessels or inflamed areas are enhanced, resulting in a sensitivity and specificity for the detection of Barrett's oesophagus above 90% (Sharma et al, 2013). In research studies the detection rate for dysplastic areas is significantly improved compared to white light endoscopy because there is an irregular mucosal or vascular pattern (Sharma et al, 2013). Compared with histopathology reports, the sensitivity, specificity and area under the curve for narrow band imaging-based diagnosis of high grade dysplasia is 96%, 94% and 0.99 respectively (Mannath et al, 2010). Modern endoscopes are equipped with both optical filter systems and high resolution processors that also allow real time magnification of the mucosal structures. The outcome of diagnostic procedures is at least comparable to chromoendoscopy concerning the detection of high grade dysplasia or early cancer.

There are ongoing efforts to develop a universal classification system for the distinction of malignant from non-malignant tissue, which also includes preneoplastic conditions and different patterns of inflammation.

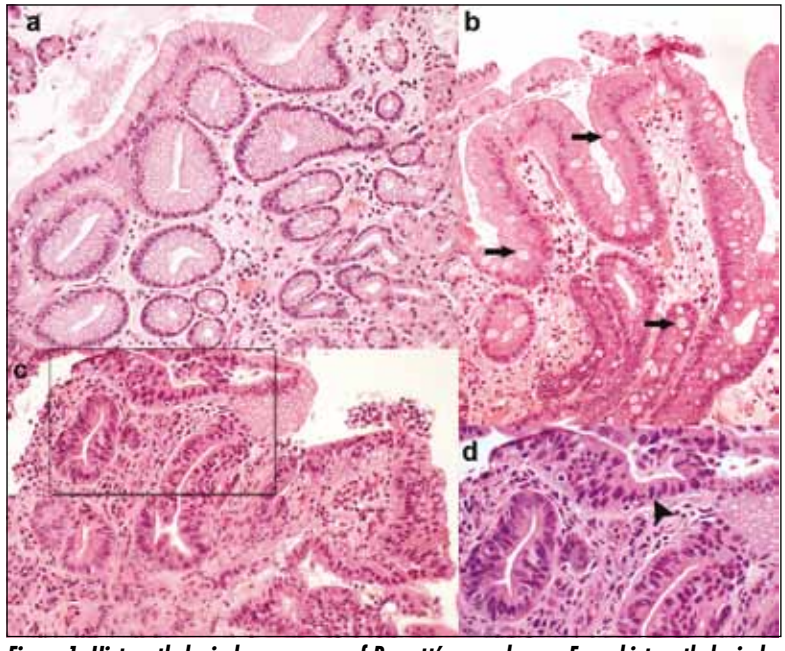


Figure 1. Histopathological appearance of Barrett's oesophagus. For a histopathological confirmation of Barrett's oesophagus, the squamous epithelium of the distal oesophagus has be replaced either by (a) gastric type columnar epithelium or by (b) intestinal type columnar epithelium including goblet cells (arrows indicating examples). Barrett's metaplasia carries a high risk of progression towards high grade dysplasia (c: 200x, d: 400x, arrowhead indicating mitosis figure).

Autofluorescence imaging and trimodal imaging endoscopy

One problem with narrow band imaging is the narrow field of view and this technique therefore needs to be combined with a 'red flag' technique to highlight areas to then image with narrow band imaging. Autofluorescence imaging exploits endogenous fluorophores that are excited by light of short wavelengths. Despite a generally lower resolution than white light endoscopy, the different

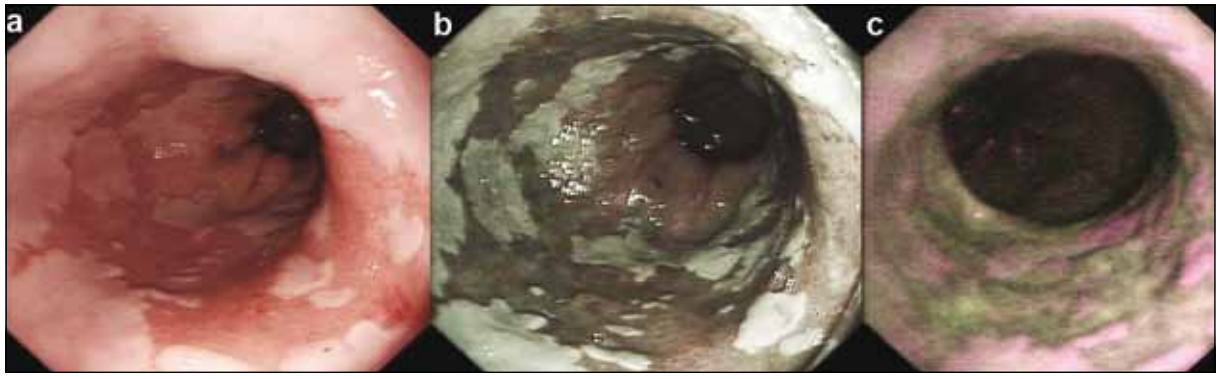


Figure 2. Trimodal imaging endoscopy. Short segment (C0 M3) Barrett's oesophagus with several islands of squamous epithelium scattered between the columnar lined oesophagus. Endoscopic image (a) with traditional white light, (b) narrow band imaging and (c) autofluorescent imaging.

autofluorescent patterns in metaplastic or dysplastic lesions increase the diagnostic yield of targeted biopsies. However, this technique has been plagued by a high false positive rate. In view of the potential complementarity of autofluorescence imaging and narrow band imaging these filter systems have been combined into a single endoscope called trimodal imaging endoscopy (*Figure 2*). Using this approach, autofluorescence imaging positive lesions can be directly assessed by narrow band imaging including a magnifying zoom technique to increase the sensitivity, specificity and accuracy of endoscopic diagnostic procedures. This also reduces the false positivity rate of single autofluorescence imaging use (Giacchino et al, 2013).

The diagnostic value of targeted biopsies using trimodal imaging endoscopy needs to be evaluated further in appropriately powered prospective trials (Curvers et al, 2011).

Flexible spectral imaging colour enhancement

Flexible spectral imaging colour enhancement endoscopy is a similar approach to narrow band imaging, which offers up to eight digital optical filter channels which can be switched on easily during the investigation. Besides the assessment of surface and microvascular patterns, the high contrast enhancement allows a better definition of the lateral demarcation line of metaplastic or dysplastic lesions compared with other approaches. This can be particularly helpful when delineating an area for endoscopic resection (Osawa et al, 2009). The diagnostic yield can also be increased further by application of relief dyes such as acetic acid (Camus et al, 2012).

Confocal laser endomicroscopy

Another recent technique is confocal laser endomicroscopy that enables an in-vivo real-time assessment of the histopathological alterations present in the mucosa at the gastro-oesophageal junction. This high-end magnification technique allows the detection of goblet cells and of the brush border present in the absorptive intestinalized epithelium characteristic of intestinal metaplasia as well as the detection of dysplastic changes. A recent meta-analysis on eight studies including 709 patients demonstrated a pooled sensitivity for the detection of early neoplastic lesions of 89% and a specificity of 75%, with an area under the curve of 0.947 (Wu et al, 2013). A further approach is the labelling of dysplastic cells with molecular markers such as fluorescent peptides that enrich the diagnostic yield of confocal laser endomicroscopy (Hsiung et al, 2008).

Confocal laser endomicroscopy has also been assessed for the detection of residual lesions and thence surveillance following endoscopic treatment, but the applicability of this technique in this indication is still under debate and needs further assessment (Wallace et al, 2012).

For confocal laser endomicroscopy, the diagnostic accuracy and detection rate is significantly higher for experienced compared to inexperienced examiners since the investigation is time-consuming and demands high concentration and patience.

Molecular biomarkers

There is increasing interest in inclusion of molecular biomarkers in the diagnostic algorithms, either applied to biopsy specimens or as part of an in-vivo imaging modality. p53 is starting to be used in routine histopathology laboratories since it significantly increases the inter-observer agreement of pathologists for dysplastic lesions (Kastelein et al, 2012). Abnormal staining for p53 (increased or loss of expression of the protein following mutation of p53) is further associated with an increased risk of neoplastic progression of the lesion. There have been efforts to describe a marker panel that can be applied to formalin-fixed sections allowing distinction of individuals at increased risk of future progression (Bird-Lieberman et al, 2012a).

There are efforts to develop less invasive devices that would sample the entire Barrett's oesophagus without recourse to endoscopy and random biopsies. An interesting approach is a retractable Cytosponge for the detec-

tion of Barrett's oesophagus and assessment of putative dysplastic changes. This densely folded sponge is packed in a capsule that rapidly dissolves when in the gastric cardia and can then be retracted by a string attached to it. During reverse passage through the oesophagus surface cells of the oesophageal mucosa stick to the sponge and can thereafter be assessed for biomarkers such as TFF3 which is diagnostic of Barrett's oesophagus. This technique has been demonstrated to be well tolerated, cost-effective and yields a good sensitivity (73.3% for Barrett's oesophagus segments ≥1 cm, 90.0% for segments ≥2 cm), and a specificity of 93.5–93.8% (Kadri et al, 2010).

For surveillance there is interest in molecular probes that can be viewed in real time and might provide an alternative red flag technique to autofluorescence imaging. One such approach takes advantage of the altered glycosylation patterns in the progression towards cancer which can be imaged with a fluorescent lectin (Bird-Lieberman et al, 2012b). In vivo data on the use of this technique are awaited.

In summary, despite exciting technological developments, white light endoscopy with systematic biopsy sampling remains the current gold standard for diagnosis and surveillance of Barrett's oesophagus. In the view of cost-effectiveness of a surveillance regimen, the new British Society of Gastroenterology guidelines are stricter concerning clinical risk stratification of the individual patient. Patients with short segment Barrett's oesophagus (<3 cm) and gastric metaplasia only should be considered for discharge from surveillance programmes since they carry a low risk of malignant progression of the lesion (Fitzgerald et al, 2013).

Therapy of Barrett's oesophagus and associated lesions

Radical surgery, i.e. oesophagectomy, is still the treatment of choice for an early adenocarcinoma that invades the submucosa, since there is a high risk of lymphatic spread that cannot be managed by endoscopic treatment modalities (Dunbar and Spechler, 2012). There are no data that confirm one surgical approach as superior to another.

For high grade dysplasia and any adenocarcinoma confined to the mucosa, endoscopic treatment should be preferred to oesophagectomy. In properly selected patients the outcome of endoscopic treatment results in excellent response rates comparable to surgical treatment with lower risks of complications and fewer sequelae on quality of life (Pech et al, 2011). A prospective case series on 349 patients treated endoscopically for high grade dysplasia and early oesophageal cancer revealed a complete response in 96.6% and a 5-year survival of 84% with no cancer-related deaths (Pech et al, 2008). Patients undergoing surgery present with significantly higher complication rates as well as a higher treatment-related mortality. In a systematic review including studies of oesophagectomy as well as eight different endoscopic treatment techniques, the pooled mortality rate was 1.2% for patients treated with surgery and 0.04% for the endoscopic approach (Menon et al, 2010).

Adverse events in the surgery groups including anastomotic leakage (9.4%), wound infections (4.1%) and pulmonary complications (4.1%). The main complications in the endoscopic group were bleeding (0.1%) and stricture formation, especially after photofrin-based photodynamic therapy. Strictures are much less problematic following radiofrequency ablation compared with photodynamic therapy and bleeding can be dealt with endoscopically. Radiofrequency ablation is now recommended by the National Institute for Health and Care Excellence for the treatment of high grade dysplasia and intramucosal cancer (Fitzgerald et al, 2013).

In cases of low grade dysplasia, there is significant intra- and inter-observer variability in the diagnosis with a substantial impact on the likelihood of progression when a consensus histopathological opinion is reached (Curvers et al, 2011). Therefore it is imperative that all cases of dysplasia should be confirmed by at least two independent pathologists with gastrointestinal experience and cases of confirmed low grade dysplasia reviewed endoscopically at 6 months (Fitzgerald et al, 2013). In the case of a visible lesion, the Paris classification should be applied for risk stratification since this will have implications for the likelihood of invasion and hence the recommended treatment (Endoscopic Classification Review Group, 2005). All patients with suspected high grade dysplasia or early cancer should be discussed by a multidisciplinary team comprising a therapeutic endoscopist, upper gastrointestinal surgeon, pathologist and radiologist (*Figure 3*).

Endoscopic resection

The two major techniques in use for endoscopic resection of early neoplastic lesions in the oesophagus are the 'cap and snare' technique with prior submucosal injection to lift the lesion, and the 'band ligation' technique using suction of the lesion that is then fixed by a detachable rubber band to generate a resectable pseudopolyp. Both approaches show similar efficacy and a comparable safety profile (Pouw et al, 2011). However, the procedure time is significantly shorter for the cap resection which can also be performed with lower costs than the band ligation technique. Submucosal dissection is more complex and risky and there are no data currently to show that this is superior to endoscopic resection (Inoue et al, 2010).

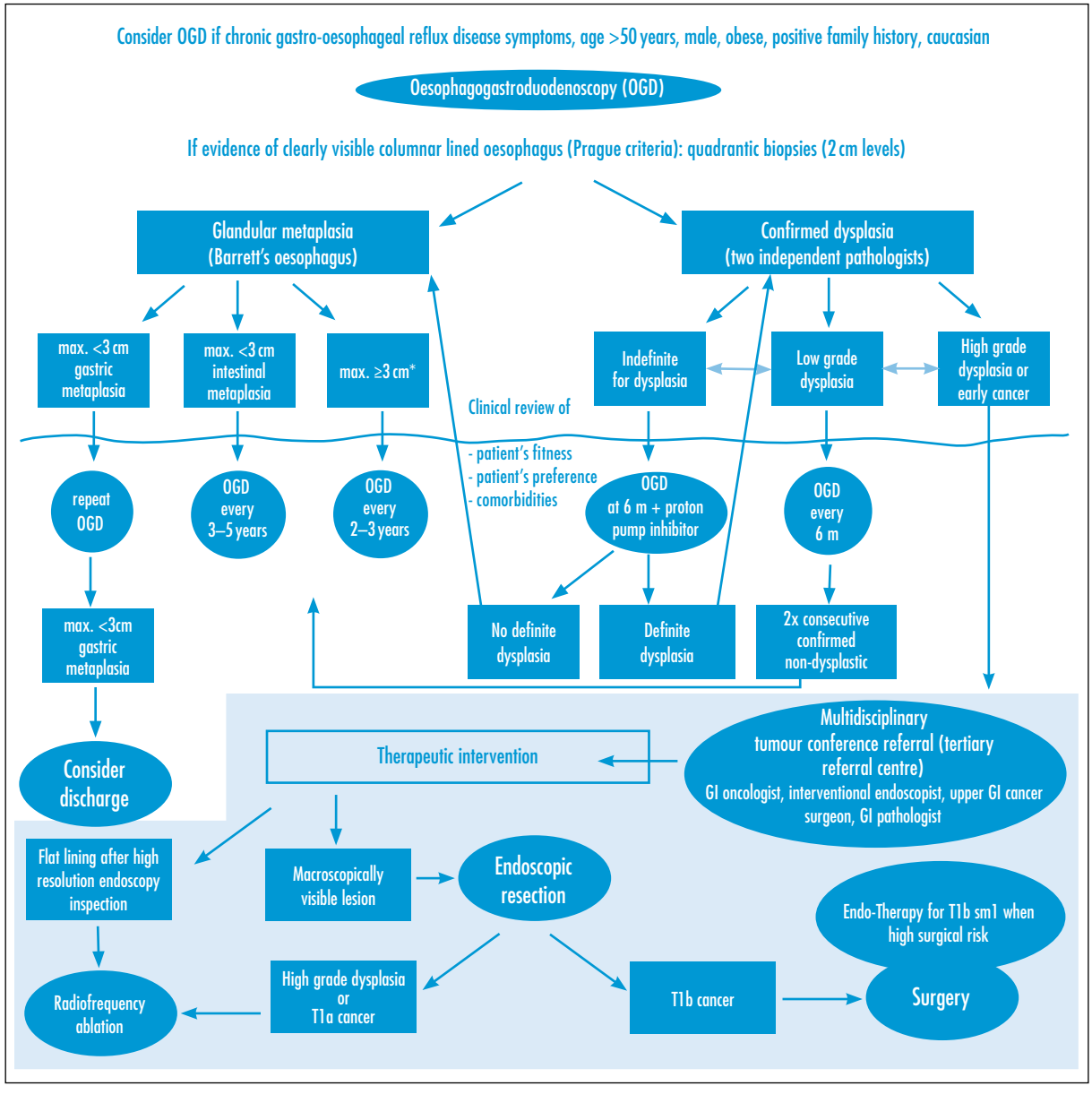
Radiofrequency ablation

Shaheen et al (2009) performed a prospective, randomized, sham-controlled multicentre trial on the effectiveness of radiofrequency ablation in patients with dysplastic Barrett's oesophagus. The complete eradication

rate in the intention to treat analysis was higher in the treatment compared to the sham group for both low grade dysplasia (90.5% *vs* 22.7%; *P*<0.001) and high grade dysplasia (81% *vs* 19%; *P*<0.001). There was also a lower rate of disease progression and cancer incidence (1.2% *vs* 9.3%; *P*=0.045) in patients after ablation. The main complication was a 6.0% stricture rate. Long-term outcome after radiofrequency ablation reveals an ongoing complete response concerning eradication of high grade dysplasia in >90% of patients (Shaheen et al, 2011). A meta-analysis of 24 studies including 4342 patients reporting efficacy and durability of treatment response showed complete eradication of dysplasia in 91% and complete eradication of intestinal metaplasia in 78% (Orman et al, 2013). Recurrence of intestinal metaplasia was noted in 13%, progression to cancer in 0.2% and oesophageal strictures developed in 5%. Data from the UK registry on radiofrequency ablation treatment confirm that radiofrequency ablation is not inferior to endoscopic resection alone (Haidry et al, 2013). Endoscopic resection as a single technique was compared to endoscopic resection followed by repeated radiofrequency ablation interventions in 3-monthly intervals until complete ablation was achieved. After a mean of 2.5 procedures at 12 months follow-up, eradication of high grade dysplasia was achieved in 86%, and of Barrett's oesophagus in 62%.

Most patients will require removal of a visible lesion by endoscopic resection followed by radiofrequency ablation to eradicate the remaining Barrett's oesophagus segment;

Figure 3. Diagnostic and therapeutic algorithm for Barrett's surveillance. Combined algorithm for Barrett's oesophagus surveillance including regimens for diagnosis, follow-up and therapeutic intervention according to the new British Society of Gastroenterology guidelines (Fitzgerald et al, 2013). GI = gastrointestinal; OGD = oesophagogastroduodenoscopy. * independent of the type of metaplasia.



this was shown to be both safe and effective. Radiofrequency ablation treatment can also be applied in ultra-long segments of Barrett's oesophagus (>8 cm) (Dulai et al, 2013), but the increasing length of the segment is associated with lower response rates as well as a higher degree of stricture formation (Haidry et al, 2013). Since the procedure is time consuming in long segments of Barrett's oesophagus, requiring high expertise as well as adequate sedation, there is a rationale for simplification of the process (i.e. two applications of thermal energy with intermediate cleaning of the device and the ablation zone). Introduction of through the scope ablation catheters may further simplify the procedure, reducing the need for repeated intubations.

Photodynamic therapy

Photodynamic therapy is based on the intravenous application of a non-toxic photo-sensitizer that can be activated by light of specific wavelength locally distributed via the endoscope. The two major compounds in use are 5-aminolaevulinic acid (ALA-photodynamic therapy) and porfimer sodium (PFS-photodynamic therapy) (Qumseya et al, 2013). In most comparisons effectiveness is similar between the two substances. However, PFS-photodynamic therapy results in significantly higher stricture rates and has been shown to be less cost-effective (Menon et al, 2010). The eradication rates of high grade dysplasia treated with ALA-photodynamic therapy are comparable to radiofrequency ablation treatment, and the approach can also be used for patients with low grade dysplasia or for eradication of non-dysplastic Barrett's oesophagus. With the advent of radiofrequency ablation which does not require photosensitization this technique is becoming much less commonly used for early lesions; however, work is ongoing in the context of more advanced cancer including the potential to molecularly target the photodynamic therapy.

Other ablative techniques

Argon plasma coagulation is a useful, low-cost additive technique for example to eliminate small remnants of Barrett's oesophagus persisting after radiofrequency ablation. As a single modality approach it seems to be similarly effective as photodynamic therapy, but it is less expensive than photo-ablation (Ragunath et al, 2005).

Although not in widespread use, spray cryo-ablation with topical application of low-pressure liquid nitrogen is a further alternative showing adequate effectiveness concerning the eradication rates of high grade dysplasia (Shaheen et al, 2010).

Conclusions

Virtual chromoendoscopy by optical filter systems increases the diagnostic yield for detection of dysplastic or early neoplastic lesions by experts in research settings. However, thorough assessment of the mucosa by traditional high resolution white light endoscopy including systematic biopsy sampling and review by an experienced histopathologist remains the gold standard for diagnosis and surveillance of Barrett's oesophagus.

Approaches to treatment of high grade dysplasia and early cancer have improved rapidly with the advance in endoscopic therapies. The most commonly used approach is now endoscopic resection for visible lesions combined with radiofrequency ablation for flat mucosa. Whichever technique is preferred it is essential that units delivering the therapy have the required training and expertise coupled with surgical back-up and that patients are properly selected so that more advanced lesions are referred for definitive surgery to ensure oncological clearance. There are now guidelines on the recommended training and throughput of cases (Fitzgerald et al, 2013).

Clinical and molecular risk stratification algorithms are likely to be recommended increasingly in routine clinical practice during surveillance and after treatment with important benefits in terms of clinical efficacy, quality of life and cost-effectiveness (*Figure 3*). It is of pivotal importance that any algorithms are easily applicable for general use in the basic health-care system to enable an equal chance of adequate assessment and early diagnosis of neoplastic lesions for each patient, otherwise we need to consider centralization of services (Shawihdi et al, 2013). BJHM

KEY POINTS

- One in three hundred patients with Barrett's oesophagus is at risk of developing oesophageal adenocarcinoma per year.
- The risk is 30–50-fold higher in cases with Barrett's-associated high grade dysplasia. Screening for Barrett's oesophagus should be considered in patients with symptomatic reflux, especially when further risk factors (e.g. male gender, advanced age, obesity, history of smoking) are present and in those with a family history of Barrett's or oesophageal adenocarcinoma.
- Modern endoscopic imaging techniques can help to identify individuals at high risk of cancer development who need early intervention.
- High grade dysplasia and early cancer confined to the mucosa should be managed endoscopically.
- Endoscopic resection of visible lesions and radiofrequency ablation of metaplastic or dysplastic areas are the methods of choice for treatment of high grade dysplasia or early cancer.
- Patients with Barrett's oesophagus without high grade dysplasia or neoplastic tissue formation who are fit for endoscopy should undergo endoscopic surveillance.

Conflict of interest: Professor RC Fitzgerald developed the Cytosponge and associated assay technology which has been licensed by the Medical Research Council to Covidien; Dr J Bornschein: none.

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