Current Management of Barrett’s Oesophagus

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ABBREVIATIONS
BO – Barrett’s Oesophagus, GORD - Gastro-Oesophageal Reflux Disease, LSBO - Long Segment Barrett’s Oesophagus, HGD - High Grade Dysplasia, EMR – Endoscopic Mucosal Resection, 5-ALA - 5-AminoLevulinic Acid, PDT - PhotoDynamic Therapy

Introduction

Barrett’s Oesophagus (BO) describes a histological abnormality of the lower oesophagus widely accepted to be associated with gastro-oesophageal reflux disease (GORD). The nature of this disease has been a subject of debate since its description by Tileston in 1906 as peptic ulceration of the oesophagus. Barrett himself initially theorised that the abnormal oesophagus was in fact stomach that had been pulled into the chest by a congenitally short oesophagus (1). This idea was ultimately challenged as the area in question lacked a peritoneal covering, contained submucosal glands and muscularis propria characteristic of the oesophagus (2). In 1976, Paull et al. described a distinctive type of intestinal metaplasia the investigators called "specialised columnar epithelium". Specialised intestinal metaplasia is now widely accepted to be the hallmark of BO with its presence predisposing to dysplasia and cancer regardless of its location within the oesophagus (3).

Barrett’s Oesophagus, its identification and treatment continues to be an area of debate and interest. Although not sinister in itself, it is a known precursor to malignant disease and strongly associated with GORD. Barrett’s oesophagus is the most frequent predisposing risk factor for the progression to adenocarcinoma in the oesophagus. Sufferers have a 40 fold increased risk when compared to the general population (4). The progression of GORD to BO appears to be related to exposure of oesophageal tissue to the acidic contents of the stomach. It is therefore seen in hiatus hernia, lower oesophageal dysfunction, delayed oesophageal acid clearance and duodenogastric reflux. Furthermore, it is the duration and not frequency of exposure to acidity that dictates erosive damage to the oesophagus. Levels of acidity also contribute. The damage to cells incurred leads to inflammatory infiltration and cell necrosis with replacement of oesophageal epithelium by metaplastic columnar cells.

Assessing severity of BO relies partly on endoscopic visualisation techniques and length of oesophagus involved. Long segment Barrett’s oesophagus (LSBO) indicated a >3cm segment of involvement with short segment disease involving <3cm. LSBO carries a higher risk of progression to adenocarcinoma. Its development is associated with long term symptoms, severe combined patterns of reflux (both erect and supine) on 24 hour pH monitoring and reduced lower oesophageal sphincter pressures. Patients are less sensitive to direct acid exposure than those with short segment disease. The latter group also tend to have shorter duration of symptoms, normal sphincter pressures and only upright reflux on 24 hour pH monitoring (3).

The Prague C and M criteria is a recently developed classification system utilising the circumferential and maximal extent of oesophageal columnar tissue to assess disease severity endoscopically (5). Its accuracy is yet to be assessed clinically, however, it is believed to largely improve the overall assessment of Barrett’s (6). The further classification of disease severity is based on the degree of dysplasia, with high grade dysplasia carrying a higher risk of progression to malignancy.

Barrett’s oesophagus is predominantly seen in the age group 55-65, with males being affected twice as frequently as females. The disease is more prevalent in the white population. Obesity, smoking and alcohol intake being further risk factors. H.pylori may be protective against Barrett’s oesophagus with two mechanisms postulated. Namely, the induction of atrophic gastritis, which results in decreased acid production and the production of neutralising ammonia independent of gastric atrophy (7). The duration of symptoms...
of GORD but not necessarily symptom severity is also associated with increased risk of progression to BO. The exact pathogenesis is not clearly understood and is believed to be a culmination of both hereditary and environmental factors. For example, some studies report a greater incidence of BO amongst first degree relatives in comparison to their unrelated counterparts (8). Other reports associate environmental factors such as a high body mass index, with an increasing risk of GORD and progression to BO (9). Underlying mechanisms include the proposition that central obesity predisposes to hiatus hernia formation (10) and subsequent gastric acid reflux. However further research is required to unlock the key processes that lead to the formation of BO; as these pathways may hold novel therapeutic targets.

Prevalence of BO is difficult to ascertain due to the lack of population based studies. Studies from the United States involving patients aged over 40 years undergoing gastroscopy reported a prevalence of 6.8% in all patients (11). A Swedish study involving 1000 volunteers is the only available true population based study and found a prevalence of 1.6% (12).

Endoscopic surveillance

The most appropriate method for both diagnosis and surveillance of Barrett’s Oesophagus is endoscopy. Its sensitivity is higher than other comparative techniques, such as barium based studies or CT/MRI. Endoscopic screening programmes can be beneficial in both highlighting patients with BO from those with chronic GORD, as well as monitoring patients with established disease who are at risk of progressing to adenocarcinoma of the oesophagus. The American College of Gastroenterologists identify older patients with chronic GORD symptoms as the most likely to benefit from endoscopic surveillance techniques. Studies have also shown that five year survival rates are generally greater for patients who have had their adenocarcinoma identified by surveillance in comparison to those who have not (13). Importance also lies in the method of surveillance, for example shorter endoscopic interval analysis for surveillance in low grade dysplasia, are associated with higher rates of detection of adenocarcinoma (14).

Although screening for Barrett’s oesophagus relies largely on established endoscopic techniques, it remains an area of contention for several reasons. These include low prevalence and the invasiveness of endoscopy, as well as a lack of an easily identifiable demographic group. Alternative methods include the use of capsule endoscopy which offers increased acceptability of screening, is less invasive and carries an increased uptake rate in comparison (15). However a study involving 96 patients demonstrated only 67% sensitivity and 84% specificity for identifying the condition using this technique (16). A recent meta-analysis of nine studies comprising 618 patients offers the most up to date evaluation of this technique. The pooled sensitivity and specificity for diagnosing BO using this method was found to be 77% and 86% respectively. Studies using OGD as reference demonstrated sensitivity 78% and specificity 90%. With intestinal metaplasia as the reference standard, sensitivity 78% and specificity 73% was discovered although the latter figure was particularly affected by one study with very low values for this (17). Capsule endoscopy offers benefits in patient tolerance and morbidity as well as cost as the capsule can be swallowed in an office, potentially under nursing supervision. Despite this latter point, cost-benefit analysis of this technique have proved equivocal. There are also several drawbacks. Views achieved are no longer under operator control and anatomical landmarks are more difficult and potentially impossible to identify. Oesophageal transition time has been demonstrated to be as short as 1 second and biopsy is not possible regardless of this. This greatly limits the use of capsule endoscopy in BO surveillance which relies on biopsy. Ultimately, the use of capsule endoscopy in diagnosis or screening of BO is unsupported at this current time and is an area for future research.

Other methods include small calibre trans-nasal endoscopy, which involves inserting a small-calibre endoscope through the nose and oesophageal sphincter to visualise the oesophagus, stomach and duodenum. It has the advantage of not requiring any sedation, having a lower complication rate, requiring less nursing staff and being more cost effective in comparison to its more frequently performed counterpart. Capsule endoscopy, as described earlier, also has the advantage of lacking sedation, being less invasive and yielding lower complication rates. Other alternatives include narrow band imaging, which involves scanning large areas of mucosa for possible neoplasia and autofluorescence imaging in which dysplastic lesions are visualised by differences in colour. The usefulness of visualisation techniques including high-resolution magnification endoscopy and tissue staining with agents such as methylene blue or indigo carmine are still an area of debate. These techniques have been evaluated when used in combination and alone. Pit patterns identified using acetic acid chemoendoscopy were described in 2001 by Guerlud et al (18) and Sharma et al described differing mucosal patterns in BO (19). Numerous other agents and classification systems have been described. Currently the use of these techniques for diagnostic purposes has not been shown to offer superior results than the current gold standard of four quadrant biopsies. Comparison of biopsies taken with methylene blue directed biopsy versus conventional biopsy showed no significant benefit (20). The ability to identify areas of BO (particularly high-grade dysplasia) are not in question. However, low grade dysplasia may be missed and operator experience and skill must be greatly superior to utilise the benefits of these techniques. Staining techniques offer the additional complications and additional expense of carrying out the procedure. Methylene blue has been shown to induce
cellular DNA damage in vitro via the generation of singlet oxygen when photoexcited by light (21) thereby potentially 

being carcinogenic in itself. Evidence to support non-biopsy detection of BO is currently not sufficient to replace the current gold standard but is another area of current and future research.

The low prevalence of BO in the general population makes screening, with upper GI endoscopy, less viable on both a financial and logistic level. The general consensus is those individuals who suffer from chronic GORD are most susceptible to BO and would therefore benefit the most from upper GI endoscopy (22). However the factors involved in the progression of BO to dysplasia and subsequent adenocarcinoma remain unclear, and hence the value of endoscopic surveillance remains a point of discussion.

**Treatment options**

The treatment options for BO must also be taken into consideration when addressing surveillance and burden of the disease. The treatment options can broadly be divided into three groups, which include conservative management with surveillance endoscopy, endoscopic therapy and surgical oesophagectomy. The pathways of treatment are governed by patient-specific factors as well as the degree of oesophageal dysplasia. Surveillance endoscopy forms an integral part of the management of BO, and this is largely due to studies which have demonstrated a greater five year survival and an earlier stage of detection of oesophageal carcinomas detected by surveillance endoscopy (13, 23). Current recommendations target individuals at high risk of BO, for example those with chronic GORD symptoms. If no dysplasia is found on biopsies from two endoscopies, surveillance intervals of 3 years are recommended. However, patients with low-grade dysplasia on biopsy should have an immediate repeat endoscopy to confirm the diagnosis, and then yearly surveillance endoscopies until no dysplasia is observed. The management of patients with high-grade dysplasia is contentious and varies between centres. Recommendations include a repeat endoscopy to evaluate for cancerous progression, with some centres instituting regular three month surveillance with biopsies every 1-2cm of affected mucosa (6). Other centres, depending on the multi-focal extent of dysplasia recommend surgical intervention with oesophagectomy or endoscopic therapy; which includes mucosal resection, photodynamic therapy, argon plasma coagulation and endoscopic ablative techniques.

**Surgery**

Oesophagectomy is normally reserved for the management of high grade dysplasia with the potential for malignant transformation. The percentage of high grade dysplasia which progress to adenocarcinoma vary throughout the literature from 5% to 59% up to seven years from initial diagnosis (7). Although oesophagectomy provides potential for complete resolution, it also carries increased number of adverse effects which include strictures, infections and anastomotic leaks. Mortality rates may also exceed 18% in centres which perform smaller amounts of the procedure on average every year (24) in comparison to high volume centres where the mortality rates can be lower than 5% (25); making the procedure very operator-dependent. As a result less invasive therapeutic modalities are preferred in the management of lower grade oesophageal dysplasia.

**Endoscopic Therapy**

Endoscopic treatment of Barrett’s oesophagus is currently an area of great interest. Endoscopic resection alone, or in combination with other treatments, have been investigated thoroughly in the past; however studies including large populations based and long term standardised protocol are lacking. The interpretation of these results is therefore very difficult.

Endoscopic mucosal resection (EMR) for high grade dysplasia in BO was first reported in 2000 (26). The procedure involved initial identification of macroscopically visible or chemoendoscopically identifiable Barrett’s lesions. If the lesion showed no evidence of penetration into deeper tissue or metastasis, confirmed by ultrasound guidance, it would be open to resection (27). Ideal lesions include those easily identifiable by macroscopic techniques, limited in size and restricted to the mucosa. However, almost all reports realised the risk of incomplete treatment with recurrence of disease. Some authors advocated the use of circumferential endoscopic resection in order to minimise this risk (28). Endoscopic ultrasound has also been used, prior to treatment, to optimise therapy and has a degree of use in staging of oesophageal cancers (29). Post EMR data showed a low rate of complications with high rate of complete eradication of Barrett’s tissue in the short term. Larghi et al (30) investigated the long-term follow-up of patients undergoing EMR and complete Barrett’s eradication (CBE-EMR). This study involved 24 patients over a 3 year period. Histological eradication of Barrett’s oesophagus was achieved in 87.5% of patients. 3 patients suffered strictures which were endoscopically resolved. Other studies have shown similarly successful eradication with similar complications of bleeding and stricture formation (31, 32). Comparison with previous studies also demonstrated the need for long follow-up to identify potential disease recurrence. In order to minimise stricture formation, a maximum circumference of 50% could be resected during each therapy. A median of 2 sessions was required for complete eradication. 13 patients also received argon plasma photocoagulation in order to ablate isolated islands of a few centimetres of BO. These studies highlight the
use of mucosal resection either alone or in conjunction with other treatment modalities, such as argon plasma coagulation, in the treatment of BO. Other options are discussed below.

**Argon Plasma Coagulation**

This procedure involves the use of a high voltage current to ionise a jet of argon gas and treat the affected tissue. It is also used to treat bleeding lesions endoscopically hence the term coagulation. This procedure has been suggested to be of use in the treatment of BO (33, 34) and several studies have evaluated its efficacy (35-37). Conclusions have been mixed with some studies showing high rates of Barrett’s recurrence and others also suggesting poor rates of initial lesion ablation (37). Generally, rates of complete reversal of BO range in the region of 61-70% (38-42). Other studies have shown more successful results with complete ablation in 87-100% of patients (43-46). A later study evaluated these results as well as performing a further long-term follow-up of 66 patients with high-grade dysplasia undergoing APC with anti-reflux treatment. Histologically confirmed Barrett’s oesophagus was found in 12.1% of patients during further endoscopic surveillance. Patients were treated with anti-reflux therapy (both medical and surgical) and one repeat session of APC. No intraepithelial neoplasia or oesophageal adenocarcinoma was detected during the entire follow-up period of 51 months median (range 9-85) (35).

The available evidence in relation to APC still remains slightly difficult to interpret. Even the larger trials do not involve extensive samples of patients. Furthermore there is a variance between studies with regard to patient selection and exclusion criteria, anti-reflux strategies and the procedure itself. Other pitfalls include the difficulty in assessing the precise depth of the lesion and whether the penetration during treatment was successful enough to ablate the entire lesion. There is also no histological confirmation to help correct insufficient ablation and for this reason some studies have reported an increased risk of progression to cancer and metastasis if invasion past the muscularis occurs (47). Low rates of recurrence seem to be related to the use of higher power settings for ablation, up to 90W as demonstrated by Madisch et al (35). This group also demonstrated the potential role for high dose proton pump inhibitor therapy using a total of 120mg daily in three divided doses to suppress acid for the duration of treatment. Surgical anti-reflux procedures were also found to be associated with reduced recurrence rates. As mentioned above, this procedure may in itself provide a form of treatment for BO and further progression.

Although rare, complications of APC can be severe. Oesophageal perforation has been reported with 2 patient deaths as a consequence (40, 42). Mild oesophageal strictures amenable to endoscopic dilatation have been widely reported. Pleural effusions and bleeding ulcers have also been reported. Despite this, APC can be useful as an adjunct and also effective in the treatment of distinct groups of Barrett’s sufferers with amenable lesions.

**Photodynamic therapy**

Photodynamic therapy (PDT) involves the systemic administration of a photosensitising drug, followed by irradiation with a controlled light source via an endoscope. The light, in the presence of oxygen, activates the photosensitiser causing photochemically induced tissue destruction (48). Although technically this sounds a difficult procedure, in practice it is actually one of the simplest to perform. However, as with surgical oesophagectomy, it is operator dependent with complication rates increasing within the community in comparison to specialist centres.

The component parts of the photosensitisation process have also evolved with time. Several photosensitisers have undergone trial with varying results. Trials with Hematoporphyrin derivative as the photosensitising agent showed high rates of stenosis as well as prolonged sensitivity of the skin to light (49). More recently, 5-aminolevulinic acid (5-ALA) has shown promise with good therapeutic results and reduced side-effects in the short term (50-51). 5-ALA also has a reduced period of cutaneous photosensitivity of around one week, in comparison to previous photosensitisers such as sodium porfimer, in which patients would need to take precautions for thirty to ninety days (27). Several studies have demonstrated the effectiveness of photodynamic therapy in BO. The first randomised clinical trial looked at 485 patients with BO and high grade dysplasia (HGD) (52). 208 patients were accepted into the to-treat population, and received photodynamic therapy and omeprazole (PDT+OM); whilst 202 patients formed the control group and received omeprazole alone (OM). The study demonstrated a significant difference with 77% of the PDT+OM group, compared with 39% of the OM group, receiving complete ablation of HGD. The progression from HGD to adenocarcinoma was also significantly lower in the PDT+OM group (13% vs 28%). This study highlighted the effectiveness of photodynamic therapy in conjunction with medical antacid therapy, in ablating high grade dysplasia and reducing the incidence of oesophageal adenocarcinoma.

Pitfalls of PDT include the suggestion that lesions greater than 2mm in depth cannot be effectively removed (53), although the photosensitising agent used can influence this. For example, some studies have shown sodium porfimer to have an increased treatment depth of 3-4mm in comparison to other agents (54-55). However limited depth of penetration overall can compromise the ability of PDT to effectively treat high-grade dysplasia. Other common complications post PDT include stricture formation with some studies reporting rates as high as 30% overall and 50% in patients undergoing more than one procedure (56). Although high, long term complications related
to this are not reported and most cases are relieved with endoscopic dilatation. Similarly other endoscopic techniques, photodynamic therapy may be inadequate at eliminating dysplastic tissue that is not visible on endoscopy. The issue of buried glands is an area of great interest due to the implication that a treated patient with macroscopically normal tissue may have dysplastic or even malignant tissue beneath. This highlights the importance of regular follow-up endoscopies with a thorough biopsy protocol. An additional complication with photodynamic therapy is the lack of histological samples post therapy, which might be used to assess the completeness of resection as in EMR.

Despite its limitations, photodynamic therapy has been proven an effective treatment for BO in numerous trials and case reports. Future directions include steps to improve photosensitiser agents, dosimetry, and light parameters which should help minimise the associated complication rate.

Radiofrequency Ablation

Radiofrequency ablation is one of the newer endoscopic treatment modalities to show promise in preventing the progression of Barrett’s oesophagus and eliminating the lesion completely. The technique utilises a balloon, 3cm long and consisting of a 60 electrode rings spaced narrowly together every 500micrometres in a bipolar fashion (HALO360 system, Barrx Co, Sunnyvale, CA, USA). A sizing balloon is used to ascertain the circumference of the area to be treated before the ablation balloon is introduced. The system then delivers radiofrequency energy to the tissue circumferentially for 300milliseconds. A dose of 12J/cm² has been shown to be effective in achieving depth penetration accurately above the muscularis mucosae thus limiting the complications involved with damaging deeper tissues (57). The close spacing of electrodes allows uniform penetration of the entire treated circumference and thus this technique can be used circumferentially with reports of stricture formation being minimal (58). This ability to control the depth of ablative penetration means that many other adverse side effects seen with alternative endoscopic techniques are greatly reduced. These include lower rates of chest pain, odynophagia, perforation and pneumothorax in comparison with laser and thermal ablation techniques.

One recent paper reviewed the progress of 142 patients with endoscopically identifiable Barrett’s oesophagus and high-grade dysplasia managed at 16 separate academic and community centres. These patients underwent a total of 229 radiofrequency ablations and were followed up with repeat endoscopy and systematic biopsy for a median length of 12 months. The only adverse event of note was a stricture noticed on endoscopy in an asymptomatic patient. At follow-up, biopsy specimens were negative for high-grade dysplasia in 90% of patients. 80% of patients had no dysplasia on biopsy and 54% of patients were negative for intestinal metaplasia (59). These results are very encouraging, particularly as high-grade dysplasia carries the greatest risk of malignant progression.

Other benefits include minimal post-procedure discomfort with patients able to go home within hours of the procedure. Regarding the issue of buried glands, a study following 102 patients post circumferential ablation showed no evidence of buried glands in 4306 biopsy samples taken over a year follow-up (60). This once again highlights the advantages of RFA in comparison to other endoscopic techniques.

Conclusion

The surveillance and treatment of Barrett’s Oesophagus remains an area of interest and controversy. This is heightened by the inability to discriminate those patients with BO which are most likely to progress to high grade dysplasia and then to adenocarcinoma of the oesophagus. This places greater emphasis on the endoscopic surveillance programme to identify this potentially pre-malignant state at an early stage. Future advances, particularly in endoscopic techniques, will help to increase efficacy of treatment and minimise complication rates. Further developments include progress in identification of genetic biomarkers which may help elucidate those patients at greatest risk. The management of Barrett’s Oesophagus is becoming increasingly more important, particularly with the rise in incidence of oesophageal carcinomas in the Western world. The issues to address therefore include the identification and screening of at-risk groups and the further management from diagnosis of BO. Patients with chronic GORD symptoms are most in need of screening. Currently this should include the gold-standard four quadrant biopsy technique. This may include techniques to enhance visualisation as described above. In the authors opinion, non-biopsy screening does not carry enough evidence to support its use in replacement of biopsy as of yet. Medical treatment with PPI (if necessary in high-dose) as well as surgical treatment of GORD are essential considerations in the prevention and treatment of BO. Their use in combination with endoscopic therapy has proven benefits as outlined. Of the endoscopic therapies, the lack of complications combined with excellent post-procedure rates of disease elimination seen with RFA are most encouraging. Oesophagectomy should be reserved for those patients with disease not amenable to conservative or endoscopic therapy. Continual research is required to help us gain more understanding into the pathogenesis of this condition, enabling us to effectively target and manage BO appropriately.
REFERENCES