Management of Barrett's oesophagus

Barrett's oesophagus is associated with the development of oesophageal adenocarcinoma. This review highlights the management strategies currently used in the treatment of this condition.

Barrett's oesophagus is a premalignant condition associated with the development of oesophageal adenocarcinoma. The morbidity and mortality of oesophageal adenocarcinoma is significant with an estimated 5-year survival of <3% (Hur et al, 2013). It is imperative therefore that astute endoscopic detection of Barrett's oesophagus and dysplasia occurs and that management is instigated appropriately. This review highlights the medical, endoscopic and surgical management of Barrett's oesophagus based on current evidence.

Medical management

Pharmacological treatment of Barrett's oesophagus is primarily based on the use of proton pump inhibitors. El-Serag and colleagues (2004) analysed data for 236 patients and noted that the cumulative incidence of dysplasia was significantly lower among patients who received proton pump inhibitors after a diagnosis of Barrett's oesophagus than in those who received no therapy or H_2 receptor antagonists (P<0.001). Furthermore, among those on proton pump inhibitors, a longer duration of use was associated with less frequent occurrence of dysplasia. In multivariate analysis, the use of a proton pump inhibitor after a diagnosis of Barrett's oesophagus was independently associated with a reduced risk of dysplasia (P<0.0001) (El-Serag et al, 2004).

Peters et al (1999) analysed 68 patients with acid reflux and proven Barrett's oesophagus in a prospective, randomized, double-blind study with parallel groups, who were treated with profound acid secretion suppression with omeprazole 40 mg twice daily, or with mild acid secretion suppression with ranitidine 150 mg twice daily, for 24 months. Endoscopy was performed at 0, 3, 9, 15 and 24 months with measurement of length and surface area of Barrett's oesophagus; pH-metry was performed at 0 and 3 months. The difference between the regression in the omeprazole and ranitidine group was statistically significant for the area of Barrett's oesophagus (P=0.02), and showed a trend in the same direction for the length of Barrett's oesophagus (P=0.06).

Research allied to the use of non-steroidal anti-inflammatory drugs is sparking debate as to their worth in the management of Barrett's oesophagus. Liao et al (2012) undertook a pooled analysis of six population-based studies within the Barrett's and Esophageal Adenocarcinoma Consortium to evaluate the association between non-steroidal anti-inflammatory drug use and the risk of oesophageal adenocarcinoma and oesophagogastric junctional adenocarcinoma. Individuals who used non-steroidal anti-inflammatory drugs had a statistically significant reduced risk of oesophageal adenocarcinoma (odds ratio = 0.68) and also appeared to have a reduced risk of oesophagogastric junctional adenocarcinoma (odds ratio = 0.83), although this was not statistically significant. Similar reductions in risk were observed among individuals who took aspirin or non-aspirin non-steroidal anti-inflammatory drugs. The highest levels of frequency (daily or more frequently) and duration (≥10 years) of non-steroidal anti-inflammatory drug use were associated with an approximately 40% reduction in risk of oesophageal adenocarcinoma, with odds ratios of 0.56 (P(trend) <0.001) and 0.63 (P(trend) = 0.04) respectively (Liao et al, 2012).

The AspECT trial, a phase III randomized controlled trial of aspirin and esomeprazole chemoprevention in Barrett's oesophagus, aims to ascertain whether esomeprazole with or without aspirin is beneficial in the prevention of Barrett's associated cancer (Jankowski, 2012). This trial is not due to report until 2018.

Endoscopic management

Low grade dysplasia

Numerous studies exist highlighting the potential value of ablative therapies for low grade dysplasia. Ackroyd et al (2003) undertook a long-term follow-up study of 40 patients with low grade dysplasia in Barrett's oesophagus treated with 5-aminolaevulinic acid 30 mg/kg followed by endoscopy. There was a reduction in the area of columnar epithelium in 88% of patients and dysplasia had been

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eradicated at 1 month in all patients. The outcomes had been maintained for a median follow up of 53 months, although one patient developed late carcinoma 3 years after intervention. Widespread use of 5-aminolaevulinic acid is limited in view of the associated morbidity and its cost.

Sharma and colleagues undertook a study of ablation using the HALO system. Primary circumferential ablation was followed every 3 months by further circumferential or focal ablation. A total of 63 patients were treated with a complete response for intestinal metaplasia and complete response for dysplasia of 79% and 89% respectively (Sharma et al, 2009). For patients with low grade dysplasia, complete response intestinal metaplasia was deemed 87% and complete response dysplasia 95%, and for high grade dysplasia, complete response intestinal metaplasia 67% and complete response dysplasia 79%.

Phoa et al (2014) undertook a multicentre randomized controlled trial of 136 patients with dysplastic Barrett's oesophagus, with 68 randomized to receive ablation and 68 control. Ablation reduced the risk of progression to high grade dysplasia or adenocarcinoma by 25.0% (1.5% for ablation *vs* 26.5% for control, $P<0.001$) and the risk of progression to adenocarcinoma by 7.4% (1.5% for ablation *vs* 8.8% for control, $P=0.03$). Treatment-related adverse events occurred in 19.1% of patients receiving ablation ($P<0.001$), the most common adverse event being stricture formation (Phoa et al, 2014). It is important to note that these study group patients had an overall higher rate of progression to high grade dysplasia or cancer than previously documented, implying that such conclusions may not be applicable to the general population of patients with low grade dysplasia and highlighting a need for further risk stratification (Duits et al, 2015).

High grade dysplasia

Endoscopic resection is a worthwhile intervention in this regard. Prasad et al (2009) undertook an analysis of endoscopic and surgical treatment of mucosal T1a oesophageal adenocarcinoma in Barrett's oesophagus and noted that overall survival in patients with mucosal oesophageal adenocarcinoma treated endoscopically appeared to be similar to that of patients treated surgically.

Furthermore a systematic review by Dunbar and Spechler (2012) noted that the risk of unexpected lymph node metastases for patients with mucosal neoplasia in Barrett's oesophagus is in the range of 1–2%. As oesophagectomy has a mortality rate often greater than 2%, the risk of metastasis alone does not indicate a need for additional surgery over endoscopic resection for high grade dysplasia and intramucosal carcinoma.

The procedural aspects of Barrett's oesophagus-associated resection comprise either a cap and snare and band ligation and are worth a brief mention. Pouw et al undertook a randomized controlled trial on endoscopic resection cap *vs* multiband mucosectomy for piecemeal endoscopic resection of early Barrett's oesophagus neoplasia and noted that piecemeal endoscopic resection with multiband mucosectomy was faster and cheaper than with endoscopic resection cap despite the lack of submucosal lifting, but the overall outcomes were similar (Pouw et al, 2011). In a prospective randomized study, May and colleagues (2003) performed 50 endoscopic resections with a 'suck-and-ligate' device without prior submucosa injection and 50 with the cap technique with prior submucosa injection of a dilute saline solution of adrenaline. They found no significant differences between the two groups with regard to the maximum diameters and calculated area of the resected specimens or the maximum diameters and calculated area of the endoscopic resection ulcers after 24 hours. In 41 of 72 patients (57%), further endoscopic therapy after endoscopic resection was necessary because of residual neoplasia at the first follow-up endoscopy after resection (May et al, 2003).

Haidry et al (2013) performed radiofrequency ablation and endoscopic resection for dysplastic Barrett's oesophagus and early cancer, noting that high grade dysplasia was cleared from 86% of patients, all dysplasia was cleared from 81%, and Barrett's oesophagus was cleared from 62% at the 12-month time point, after a mean of 2.5 (range 2–6) radiofrequency ablation procedures. Complete reversal of dysplasia was 15% less likely for every 1 cm increment in Barrett's oesophagus length (odds ratio = 1.156, standard error = 0.048, 95% confidence interval = 1.07–1.26, $P<0.001$). Endoscopic mucosal resection before radiofrequency ablation did not provide any benefit. Invasive cancer developed in 10 patients (3%) by the 12-month time point and disease had progressed in 17 patients (5.1%) after a median follow-up time of 19 months. Symptomatic strictures developed in 9% of patients. Nineteen months after therapy began, 94% of patients remained clear of dysplasia.

Phoa and colleagues (2015) undertook combined endoscopic resection and radiofrequency ablation for Barrett's oesophagus (high grade dysplasia/cancer). After entry-endoscopic resection in 119 patients (90%) and a median of three radiofrequency ablation treatments, complete eradication of neoplasia was achieved in 121/132 (92%) and complete eradication-intestinal metaplasia in 115/132 patients (87%), as per the intention-to-treat analysis. Per-protocol analysis, complete eradication of neoplasia and complete eradication of intestinal metaplasia were achieved in 98% and 93% respectively. After a median of 27 months following the first negative post-treatment endoscopic control, neoplasia and intestinal metaplasia recurred in 4% and 8% of patients respectively. Mild-to-moderate adverse events occurred in 25 patients (19%), all of which were managed conservatively or endoscopically (Phoa et al, 2015).

Imaging options for high grade dysplasia

Kelly and colleagues undertook a systematic review of the staging performance of endoscopic ultrasound noting that this imaging modality proved effective for

discriminating T1 and T2 gastro-oesophageal carcinomas from T3 and T4 (Kelly et al, 2001).

A second study of 100 consecutive patients with suspected early cancer in Barrett's oesophagus were prospectively included in a standardized staging programme with upper gastrointestinal endoscopy, endoscopic ultrasound, computed tomography of the chest and upper abdomen, and abdominal ultrasonography. The results were summarized in accordance with the TNM classification. In patients with suspected early cancer in Barrett's oesophagus, endoscopic ultrasound proved superior to computed tomography for T staging and N staging (Pech et al, 2006).

Larghi et al (2005) performed endoscopic ultrasound in 48 consecutive patients (27 with focal nodular lesions and 21 with microscopic lesions). Overall, endoscopic ultrasound provided accurate staging in 41/48 patients (85%) with one patient overstaged and six patients understaged compared with pathological staging obtained by surgery or endoscopic mucosal resection.

A further study noted in 179 consecutive patients who underwent oesophageal resection for Barrett's adenocarcinoma (n = 134) and squamous cell cancer (n = 45), the sensitivity and specificity of endoscopic ultrasound relative to the T stage were 82% and 91% respectively for T1, 43% and 85% for T2, and 83% and 86% for T3. The overall accuracy for endoscopic ultrasound in identifying the correct T stage was 74%. Positive lymph nodes were diagnosed histologically in 68 patients (38%). The sensitivity, specificity and accuracy of endoscopic ultrasound for the diagnosis of N1 were 71%, 74% and 73% respectively. Evidence highlighted that T2 cancers in particular were frequently overstaged, with a significant effect on the subsequent treatment strategy (Pech et al, 2010b).

May et al (2004) analysed 100 patients with suspected early oesophageal adenocarcinoma and noted the overall diagnostic accuracy of both high resolution endoscopy and high resolution endoscopic ultrasound with a 20 MHz miniprobe in early oesophageal cancer was high (approximately 80%), with no significant differences between the two techniques. A further study noted that high frequency miniprobes are superior to radial endoscopic ultrasound for local Barrett's cancer staging; however, the accuracy of assessment of T was unsatisfactory for both modalities (Pech et al, 2010a). Another study of 25 consecutive patients with a diagnosis of high grade dysplasia or intramucosal adenocarcinoma in Barrett's oesophagus underwent repeat diagnostic endoscopy and conventional endosonography with a radial echo endoscope. Any suspicious lymph nodes that were detected were sampled using endoscopic ultrasound-guided fine-needle aspiration. Conventional endosonography and endoscopic ultrasound with fine-needle aspiration significantly changed the course of management in 20% of patients referred for endoscopic therapy of Barrett's oesophagus with high grade dysplasia or intramucosal carcinoma (Shami et al, 2006).

Flat high grade dysplasia and intramucosal carcinoma ablative methods

Overholt and colleagues (2007) randomized patients with Barrett's oesophagus and high grade dysplasia to photodynamic therapy with Photofrin (n=138) or omeprazole (n=70) during a 2-year trial followed up for 3 or more years. Results noted that Photofrin is a clinically and statistically effective therapy in producing long-term ablation of high grade dysplasia and reducing the potential impact of cancer compared with omeprazole (Overholt et al, 2007)

In a multicentre, sham-controlled trial, Shaheen et al (2009) randomly assigned 127 patients with dysplastic Barrett's oesophagus in a 2:1 ratio to receive either radiofrequency ablation (ablation group) or a sham procedure (control group). Complete eradication of dysplasia occurred in 90.5% of those in the ablation group compared with 22.7% of those in the control group (P<0.001). Among patients with high grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group compared with 19.0% of those in the control group (P<0.001). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia compared with 2.3% of those in the control group (P<0.001). Patients in the ablation group had less disease progression (3.6% *vs* 16.3%, P=0.03) and fewer cancers (1.2% *vs* 9.3%, P=0.045) (Shaheen et al, 2009).

A further study of twenty-six patients with dysplastic Barrett's oesophagus (23 with low grade dysplasia and three with high grade dysplasia) were randomized to argon plasma coagulation (13 patients) or photodynamic therapy (13 patients). Argon plasma coagulation and photodynamic therapy were equally effective in eradicating Barrett's mucosa, with photodynamic therapy being the more expensive treatment. Photodynamic therapy was deemed more effective in eradicating dysplasia but with the extra benefits generated at extra cost (Ragunath et al, 2005).

van Vilsteren at al undertook a multicentre randomized clinical trial of patients with Barrett's oesophagus ≤5 cm containing high grade dysplasia/oesophageal adenocarcinoma randomized to stepwise radical endoscopic resection or endoscopic resection/radiofrequency ablation. Patients in the stepwise radical endoscopic resection group underwent piecemeal endoscopic resection of 50% of Barrett's oesophagus followed by serial endoscopic resection. Patients in the endoscopic resection/radiofrequency ablation group underwent focal endoscopic resection for visible lesions followed by serial radiofrequency ablation. Follow-up endoscopy with biopsies (four-quadrant/2 cm Barrett's oesophagus) was performed at 6 and 12 months and then annually. In patients with Barrett's oesophagus ≤5 cm containing high grade dysplasia/oesophageal adenocarcinoma, stepwise radical endoscopic resection and endoscopic resection/radiofrequency ablation achieved comparably high rates of complete response-intestinal metaplasia

KEY POINTS

- Proton pump inhibitors are the mainstay medical treatment for Barrett's oesophagus.
- Endoscopic resection and/or ablation proves useful in dysplastic cases and early cancer.
- Results are pending as to the value of chemoprevention with aspirin.

and complete response-neoplasia. However, stepwise radical endoscopic resection was associated with a higher number of complications and therapeutic sessions. For these patients, a combined endoscopic approach of focal endoscopic resection followed by radiofrequency ablation may thus be preferred over stepwise radical endoscopic resection (van Vilsteren et al, 2011).

Dunn and colleagues (2013) performed a randomized controlled trial of 5-aminolaevulinic acid *vs* Photofrin photodynamic therapy for high grade dysplasia arising in Barrett's oesophagus. In patients with Barrett's oesophagus length ≤6 cm, preliminary results showed 5-aminolaevulinic acid-photodynamic therapy was associated with significantly higher complete response in the treatment of high grade dysplasia. In longer segments of Barrett's oesophagus, neither photodynamic therapy drug was sufficiently efficacious to warrant routine use.

Surgery

O'Riordan et al (2004) analysed the long-term effect of anti-reflux surgery for Barrett's oesophagus and noted that Nissen fundoplication provided excellent long-lasting symptom relief. Furthermore 35% (20 of 57) of patients showed either partial or complete regression of Barrett's epithelium.

Simonka and colleagues also observed that antireflux surgery can appropriately control reflux disease in a majority of patients who had unsuccessful medical treatment, and may inhibit the progression and induce regression of Barrett's metaplasia in a significant proportion of these patients (Simonka et al, 2012). Zehetner et al undertook long-term follow-up of patients with Barrett's oesophagus post anti-reflux surgery and observed regression in 31%. Progression occurred in 8%, and these patients were significantly more likely to have a failed fundoplication (67% *vs* 16%, $P = 0.0129$). The rate of progression from non-dysplastic Barrett's oesophagus to high grade dysplasia or cancer was 0.8% per patient year, and was seven times higher in patients with a failed fundoplication (Zehetner et al, 2010). However, long-term results of a randomized controlled trial comparing medical and surgical treatment of Barrett's oesophagus showed that there are no differences between the two types of treatment with regards to preventing Barrett's oesophagus progressing to dysplasia and oesophageal adenocarcinoma (Parrilla et al, 2003).

Anvari and colleagues (2011) randomized patients to medical therapy treatment with proton pump inhibitors and laparoscopic Nissen fundoplication. Results noted surgery was associated with more heartburn-free days, showing a mean difference of -1.35 days per week ($P = 0.0077$) and a lower visual analogue scale score ($P = 0.0093$) than medical management. Surgical patients reported improved quality of life on the general health subscore of the Medical Outcomes Survey Short Form 36 (SF-36) at 3 years, with a mean difference of -12.19 ($P = 0.0124$). The groups did not differ significantly in terms of gastro-oesophageal reflux disease symptom score or acid exposure on 24-hour oesophageal pH monitoring at 3 years (Anvari et al, 2011).

Conclusions

The management of Barrett's oesophagus relies on medical intervention as well as the use of endoscopic and surgical methods as it progresses. Further research, such as the AspECT trial, is needed to help clinicians determine the best approach to management. In view of the risk of progression and poor cancer-related outcomes, valuable management is essential in helping to limit patient morbidity and mortality. **BJHM**

Conflict of interest: none.

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