Current management of Barrett's oesophagus

Barrett's oesophagus is one of the most common pre-malignant conditions in the world and its incidence is increasing. The management of this disease is currently the subject of research and debate, with medical, endoscopic and operative intervention all having a therapeutic role.

Barrett's oesophagus is one of the most common premalignant conditions in the western world. It can be defined as metaplasia of the oesophageal epithelium; the normal stratified (multilayered) squamous mucosa is replaced by single layered columnar-lined mucosa. If the mucosa contains goblet cells, it is known as intestinal metaplasia and is associated with an increased likelihood of neoplastic progression (Shaheen et al, 2009). The majority of cases of Barrett's oesophagus occur as a result of chronic pulsatile gastroduodenal reflux and oesophageal inflammation, and this condition is strongly linked to gastro-oesophageal reflux disease (Skacel et al, 2000; Fleischer et al, 2010; Zaninotto et al, 2012).

The management of Barrett's oesophagus is currently the subject of debate and research. Barrett's oesophagus may progress from intestinal metaplasia to low-grade dysplasia and then high-grade dysplasia, and finally adenocarcinoma (Garud et al, 2010). In general the management is dependent on the stage of disease (Chennat and Waxman, 2010): Barrett's oesophagus associated with high-grade dysplasia is treated more aggressively with either endotherapy, or less commonly oesophagectomy, while Barrett's oesophagus associated with low-grade dysplasia tends to be treated with proton-pump inhibitor therapy and increased endoscopic surveillance. There are increasing calls for more aggressive intervention at an earlier stage of disease both to prevent progression and decrease the financial burden of surveillance. This argument is balanced by the fact that in the majority of cases of Barrett's oesophagus the disease stays constant, neither progressing to oesophageal adenocarcinoma nor regressing (Jankowski et al, 2010).

Given the uncertainty over disease progression and prognosis, the diagnosis of Barrett's oesophagus is vital as is an understanding of this increasingly prevalent disease by all clinicians.

Aetiology

Barrett's oesophagus develops as a result of chronic oesophageal inflammation that causes increased proliferation and inflammation of mucosal cells, with the possibility of cellular and DNA damage to the oesophagus as well as altering differentiation. The damaged squamous cells of the oesophageal mucosa are replaced by columnar cells as an adaptive phenotype to be resistant to further reflux damage (Shaheen and Richter, 2009).

The majority of cases of Barrett's oesophagus are a consequence of chronic gastroduodenal reflux, although other forms of mucosal inflammation in the lower oesophagus have been linked to the condition (*Table 1*) (Jankowski et al, 2010). Conditions that predispose to gastro-oesophageal reflux disease have an indirect causation in the development of Barrett's oesophagus, including hiatus hernia, lower oesophageal dysfunction, delayed oesophageal acid clearance and duodenogastric reflux (Anwar et al, 2009). Additional risk factors include obesity (in particular central obesity), male gender, smoking and alcohol intake.

Helicobacter pylori may be protective against the development of Barrett's oesophagus by one of two mechanisms: the induction of atrophic gastritis by the organism which results in decreased acid production, and the production of neutralizing ammonia independent of

Table 1. Conditions associated with the development of Barrett's oesophagus

Condition	Percentage of cases
Chronic oesophageal reflux	> 60%
Congenital retardation syndromes	1%
Non-steroidal anti-inflammatory drugs	1%
Chemotherapy	< 1%
Viral oesophagitis	< 1%

From Jankowski et al (2010)

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gastric atrophy (Wood and Yang, 2008). Thus the impact of acid erosion on the oesophageal mucosa may not be the overall predominant feature in the development of Barrett's oesophagus.

Incidence

The incidence of Barrett's oesophagus is 1–2% in the western hemisphere (Cameron et al, 1990; Ronkainen et al, 2005). The mean age of diagnosis is 62 years (range 50–70 years), with a male predominance of 2:1 and is more prevalent in white populations (Watson et al, 2005; Anwar et al, 2009; Garud et al, 2010). The global incidence rates are increasing by 2% a year, which appears to be a true increase rather than better endoscopic recognition of the disease (Fleischer et al, 2010; Jankowski et al, 2010). The prevalence of disease is greater in symptomatic patients undergoing endoscopy at up to 6.8% (Hirota et al, 1999; Rex et al, 2003).

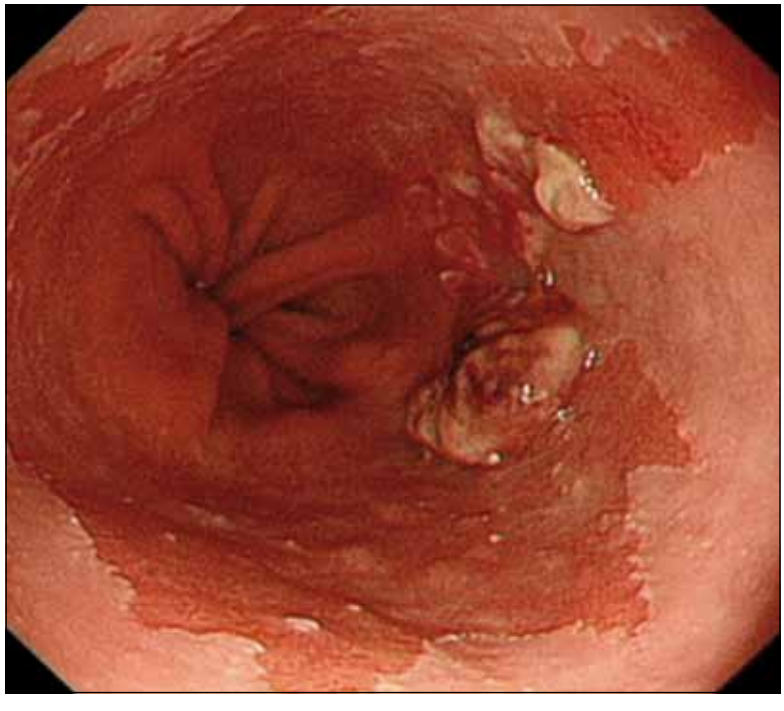
Assessment and diagnosis

A pathological diagnosis of Barrett's oesophagus requires corroboration with endoscopic findings to ensure biopsies have been taken from the oesophagus and not mistakenly from within a hiatus hernia. Histological confirmation of endoscopically visible glandular epithelium results in the highest diagnostic accuracy (Watson et al, 2005).

Endoscopic assessment

Areas of columnar epithelium should be readily identifiable at endoscopy as they appear salmon coloured on a background of normal pale pearly white oesophageal squamous mucosa (Garud et al, 2010). Barrett's oesophagus can occur in patchy islands or in tongues which can make detection difficult (*Figure 1*). It is important to record accurately the total length of diseased mucosa; a segment measuring more than 3 cm is defined as long segment Barrett's oesophagus, with shorter lengths termed short segment Barrett's oesophagus (Anwar et al, 2009). Clinicians are advised to use the Prague C & M criteria when recording the circumferential (C) and maximal extent (M) of segments of Barrett's oesophagus (International Working Group for the Classification of Oesophagitis, 2004).

Figure 1. Nodular multifocal high-grade dysplasia in Barrett's oesophagus.



Pathological assessment

The presence of squamous lined oesophageal gland ducts and columnar epithelium is diagnostic of columnar lined oesophagus (*Table 2*) (Schlemper et al, 2000). Histological findings may reveal that the epithelium resembles cardiac or fundic gastric mucosa and may demonstrate intestinalization characterized by the presence of goblet cells (*Figure 2*). Intestinalized metaplasia is more likely to be found with an extensive biopsy protocol and must be identified in order to diagnose Barrett's oesophagus in the USA (Fleischer et al, 2010). There can be significant inter-observer error during histological assessment, and thus two independent gastrointestinal histopathologists should be involved in diagnosis.

Progression to malignancy

The association between Barrett's oesophagus and the development of oesophageal adenocarcinoma has been recognized as the most significant association with this disease (Cameron and Carpenter, 1997; Anwar et al, 2009). It is thought that patients with Barrett's oesophagus are 40 times more likely to develop adenocarcinoma than the general population (Gamliel, 2000). Overall there is a 5% lifetime risk for male patients with Barrett's oesophagus to progress to adenocarcinoma (3% for women) (Shaheen and Richter, 2009; Jankowski et al, 2010). Important clinical risk factors for progression to adenocarcinoma include male gender, age >45 years, white ethnicity, extended segment (>8 cm) disease, duration of reflux history, early age of onset of gastro-oesophageal reflux disease, duodeno-gastro-oesophageal reflux (although 40% of patients with adenocarcinoma do not have symptoms of gastro-oesophageal reflux disease), mucosal damage (ulceration and stricture) and family history, either with an underlying genetic change or family clustering as a result of similar lifestyles (Watson et al, 2005).

The development of oesophageal adenocarcinoma can be thought of as a step-wise progression. Recurrent episodes of squamous oesophagitis lead to metaplasia, which in turn leads to low-grade and then high-grade dysplasia and ultimately adenocarcinoma. The steps all involve genetic (damage to the DNA in cells) and epigenetic (indirectly influencing the expression of the genome) changes. For example, the development of

metaplasia is associated with alterations in genes controlling stem cells, and progression to dysplasia linked to loss of heterozygosity or methylation of the adenomatous polyposis coli gene. Further progression typically commences following loss of expression or mutations in P16 and P53 (Jankowski et al, 2010).

These morphological changes represent surrogate markers of increasing risk of oesophageal adenocarcinoma. Non-dysplastic changes represent a 200 times risk of progression to malignancy (0.5% per patient year), with low-grade dysplasia associated with a 560 times risk (0.6% per patient year) and high-grade dysplasia a 2200 times risk (up to 27% at 3 years) compared to the general population (O'Conner et al, 1999; Weston et al, 2000; Sharma et al, 2006; Wani et al, 2009b). Originally it was thought that 40–70% of oesophagi resected for high-grade dysplasia harboured an unsuspected adenocarcinoma, but with increasingly advanced endoscopy and endoscopic resection this figure is lower (Skacel et al, 2000; Barr et al, 2005).

Management

Although in the majority of cases Barrett's oesophagus stays constant, as many as 10% of patients develop high-grade dysplasia (Jankowski et al, 2010). There are two key management objectives: the treatment of gastro-oesophageal reflux disease and the avoidance of morbidity and mortality associated with adenocarcinoma. Strategies for the latter include early treatment to eradicate metaplastic and dysplastic epithelium, with the intent to reduce the incidence of adenocarcinoma, or surveillance to detect incident cancer at an early stage with the intent to reduce the likelihood of cancer-related death (Fleischer et al, 2010). Debate exists regarding the treatment of long segment Barrett's disease and whether low-grade dysplasia should be treated more aggressively.

Current guidelines

Current management is based on the severity and the presence or absence of neoplastic disease, either low-grade dysplasia, high-grade dysplasia or T1a adenocarcinoma. A diagnosis of indefinite for dysplasia is often made where there are changes suggestive of dysplasia, but inflammatory changes make the distinction impossible (Watson et al, 2005). Such a diagnosis should prompt early re-evaluation with extensive biopsies following a course of proton-pump inhibitor therapy. If this, together with subsequent endoscopy and biopsies at 6 months, fails to reveal definitive evidence of dysplasia, then the patient can return to routine surveillance.

Low-grade dysplasia should be managed first by extensive re-biopsy after intensive acid suppression for 8–12 weeks. If persisting, surveillance should be 6-monthly as long as disease remains stable. If apparent regression occurs on two consequent examinations, surveillance intervals may be increased to 2–3-yearly. High-grade dysplasia is associated with a focus of invasive carcinoma in 30–40% patients. For this reason, if the changes persist after intensive acid suppression and are confirmed by two expert pathologists, oesophagectomy in a specialized unit is currently recommended in patients considered fit for surgery. In those unfit for surgery, endoscopic ablation or mucosal resection should be considered (Watson et al, 2005).

Short *vs* long segment Barrett's oesophagus

It is currently unknown if short segment Barrett's oesophagus (<3 cm) and long segment Barrett's oesophagus (>3 cm) are clinically and biologically different diseases, or are just topographically different presentations of the same disease (Zaninotto et al, 2012). Although there is little or no evidence of any pathological differences between short segment Barrett's oesophagus and long segment Barrett's oesophagus, long segment Barrett's oesophagus carries a higher risk of progression to adenocarcinoma and thus an argument exists for more aggressive intervention (especially for segments >8 cm).

Intervention for Barrett's oesophagus associated with low-grade dysplasia

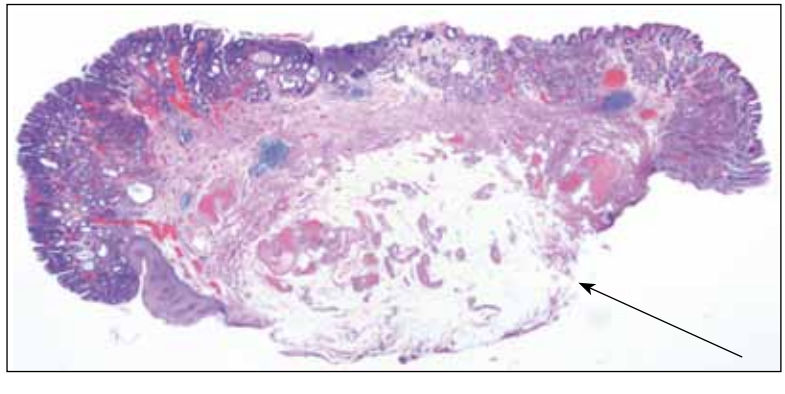
The argument for more aggressive intervention for low-grade dysplasia revolves around two main issues: first that medical therapy is unlikely to induce disease regres-

Table 2. Vienna classification of oesophageal neoplasia

Category	Description	
1	Negative for neoplasia or dysplasia	
2	Indefinite for neoplasia or dysplasia	
3	Non-invasive low-grade neoplasia (low-grade dysplasia)	
4	Non-invasive high-grade neoplasia	4.1 High-grade dysplasia
		4.2 Carcinoma in situ
		4.3 Suspicious of carcinoma
5	Invasive neoplasia	5.1 Intramucosal cancer
		5.2 Submucosal carcinoma or beyond

From Schlemper et al (2000)

Figure 2. Oesophageal tissue at histology following endoscopic mucosal resection of focal high-grade dysplasia (arrow) with clear margins.



sion and will only treat the acidic component of gastroduodenal reflux, and second that treatment of precancerous disease (even at an early stage) is beneficial to minimize cancer risk (Wani et al, 2009a).

Medical

Conservative management of non-dysplastic Barrett's oesophagus or low-grade dysplasia involves lifestyle modification, acid suppression and regular endoscopic surveillance. This strategy aims to control symptoms associated with gastro-oesophageal reflux disease, while detecting any progression of disease. Lifestyle modification involves sleeping more vertically, losing weight and avoiding acidic or irritative foods (e.g. citrus fruits, spices, onions, tomatoes and carbonated drinks) (Garud et al, 2010). These manoeuvres can increase oesophageal acid clearance and decrease the frequency of reflux.

Proton-pump inhibitors provide effective relief of symptomatic gastro-oesophageal reflux disease and heal oesophageal ulceration (Jankowski et al, 2010). They need to be maintained for life, even if the patient is asymptomatic, as they do not cause the metaplasia to disappear, although it is not uncommon to see modest shrinkage of segment length (Ortiz et al, 1996).

Endoscopic surveillance

The overall risk of adenocarcinoma for patients under surveillance is between 0.4% and 1% (Jankowski et al, 2010). The cost effectiveness of surveillance has been estimated to be £40 000 per cancer diagnosed, for less than one quality-adjusted life year gained. However, surveillance of patients with proven intestinal metaplasia on biopsy is more cost effective as they are three times more likely to develop cancer than those without proven metaplasia (Shaheen and Richter, 2009). Current guidelines recommend biennial surveillance for patients with non-dysplastic Barrett's oesophagus, and 6-monthly surveillance for those with confirmed low-grade dysplasia. A diagnosis of high-grade dysplasia is usually an indication to stop surveillance and refer to a tertiary unit for consideration of endoscopic or surgical therapy.

Routine endoscopic surveillance of patients with short-segment, non-dysplastic Barrett's oesophagus is controversial and currently subject to significant debate. The Barrett's Oesophagus Surveillance Study, a large UK multicentre randomized trial, is aiming to assess the value of endoscopic surveillance in patients with Barrett's oesophagus. It is unlikely that this trial will demonstrate a benefit of surveillance for all-comers with Barrett's oesophagus. Future surveillance strategies will likely be reserved for patients with additional risk factors such as long metaplastic segments (>3 cm) or molecular markers of increased risk of progression. Identifying those patients with Barrett's oesophagus who will progress to neoplasia from those who will not remains an important challenge for researchers in this field.

Endotherapies

Endotherapies, either resectional or ablative, are effective methods for eliminating metaplasia or dysplasia within the oesophagus (Barr et al, 2005; Zaninotto et al, 2012). Current UK National Institute for Health and Clinical Excellence recommendations are that patients with Barrett's oesophagus and high-grade dysplasia should be offered endoscopic ablative therapy as an alternative to oesphagectomy, particularly those who decline or are deemed unsuitable for operative intervention (National Institute for Health and Clinical Excellence, 2010). The role of endotherapeutic intervention in low-grade dysplasia is uncertain, with advocates promoting its use to treat the disease and reduce malignant progression (Wani et al, 2009a).

Resectional

Endoscopic mucosal resection

This technique allows the dysplastic epithelium to be removed endoscopically, via a variety of techniques (free hand, lift-and-cut, cap-assisted and band-assisted endoscopic mucosal resection, with or without submucosal injection). The tissue removed can be examined histologically to confirm diagnosis and to ensure resection margins are clear. Endoscopic mucosal resection is safe and effective for the treatment of superficial lesions (Vieth et al, 2004). The type of epithelium that regrows is in part determined by the depth of injury that occurs as a result of treatment. In order to ensure squamous cell regeneration as opposed to recurrence of Barrett's oesophagus, some of the superficial squamous lined ducts of the oesophageal mucus glands must survive (Jankowski et al, 2010).

Complete Barrett's eradication using endoscopic mucosal resection can reduce the risk of synchronous or metachronous lesion development, although this practice has been shown to be associated with a 50% risk of stenosis and an increased risk of bleeding and perforation (May et al, 2002; Chennat and Waxman, 2010). Complete responses to endoscopic mucosal resection have been reported at 76–100%, with most complications amenable to endoscopic treatment (Ell et al, 2000). Endoscopic mucosal resection for the resection of early cancers (T1a) is also highly effective, with 5-year survival rates of 98% reported in patients with early carcinoma and high-grade dysplasia (Jankowski et al, 2010).

Endoscopic submucosal dissection

This technique is similar to endoscopic mucosal resection, but requires a submucosal injection before an incision through the mucosa. Lesions can then be excised en bloc, with dissection into the submucosa with an electrosurgical current, which can improve histological grading (Garud et al, 2010). This allows mucosal resection of lesions larger than 2 cm. However, there is a higher risk of stricture formation compared to endo-

scopic mucosal resection, particularly when more than three quarters of the circumference of the mucosa is resected (Barr et al, 2005).

Ablation

A variety of techniques exist to ablate dysplastic or neoplastic epithelium, which results in a neosquamous layer developing. Two main concerns exist with ablation techniques – the lack of pathological specimens for histological examination and the possibility of progression of buried Barrett's metaplasia or dysplasia under the neosquamous layer (Barr et al, 2005; Garud et al, 2010).

Radiofrequency ablation

Radiofrequency ablation uses a cylindrical balloon to bring electrodes into contact with the oesophageal lining, either in a focal or circumferential fashion, to produce thermal ablation (Barr et al, 2005). A sizing balloon is used, based on pressure measurements at two different locations, to ensure optimal contact with the mucosa (Chennat and Waxman, 2010). The radiofrequency ablation balloon itself is 3 cm long and contains 60 electrode rings placed every 500 μm in a bipolar fashion. Radiofrequency energy (at a dose of 12 J/cm^2) is then delivered for 300 μs; this dose is effective at ablating structures above the muscularis mucosa while preventing damage to deeper tissue (Anwar et al, 2009). Thus, only Barrett's mucosa is destroyed, and this allows healthy tissue to re-grow post-procedure. Two separate applications of radiofrequency energy are used in one therapeutic session, and the destroyed tissue is scraped between applications to ensure adequate and uniform thermal contact.

The efficacy of radiofrequency ablation in treating Barrett's associated dysplasia has been demonstrated in a large multicentre randomized controlled trial in the USA. Radiofrequency ablation was shown to be highly effective in curing Barrett's oesophagus, with reported eradication of low-grade dysplasia in 90.5% of patients and eradication of high-grade dysplasia in 81% (Shaheen et al, 2009). A second study reported 90.2% of patients with Barrett's oesophagus and high-grade dysplasia had a complete response following radiofrequency ablation (Ganz et al, 2008). Median term follow-up data (at 3 years) have demonstrated that these effects are durable. Complications include non-cardiac chest pain (30%), non-transmural lacerations and stricture formation (<10%), bleeding (1%) and perforation (<1%) (Jankowski et al, 2010).

Argon plasma coagulation

This procedure involves the use of a high voltage current to ionize a jet of argon gas to ablate affected tissue. The complete reversal rates range between 61% and 100% (Anwar et al, 2009). The limitations of argon plasma coagulation are that it can be difficult to assess the therapeutic depth and whether the argon plasma coagulation was able to ablate the disease in its entirety. Complications are rare, but include perforation, stricture, effusions and bleeding ulcers (May et al, 2002).

Photodynamic therapy

Photodynamic therapy involves the systemic administration of photosensitizing agents, which are retained selectively in metastatic tissue, followed by endoscopic exposure to an appropriate wavelength of laser light (Jankowski et al, 2010). This results in a cytotoxic reaction that causes cellular destruction (Chennat and Waxman, 2010). Lesions deeper than 2 mm cannot be treated and repeat ablation may be required, thus lifelong surveillance is required. Complete ablation rates of up to 77% have been seen in patients with Barrett's oesophagus and high-grade dysplasia (Overholt et al, 2005). Major side effects include photosensitivity that requires patients to avoid post-procedural skin sunlight exposure, non-cardiac chest pain and stricture formation (in one third of patients), which is higher if more than one therapy is used (up to 50%) (Garud et al, 2010).

Cryotherapy

Cryotherapy involves spraying liquid nitrogen in freeze-thaw cycles to destroy biological tissue. Freezing results in cellular destruction by intracellular disruption and tissue ischaemia, with relative preservation of the extracellular matrix to promote less fibrosis formation (Chennat and Waxman, 2010). Repeat sessions are required every 4–6 weeks to ensure complete remission of the target area. The procedure seems to be well tolerated with only minor complications, including non-cardiac chest pain, dysphagia and a sore throat. Early studies report complete response in 78% of patients with combined low-grade dysplasia and high-grade dysplasia Barrett's oesophagus (Johnston et al, 2005) and 94% in patients with high-grade dysplasia (Greenwald et al, 2010).

Operative intervention

Anti-reflux operations

The main anti-reflux operation is Nissen's fundoplication, whereby a portion of the gastric fundus is wrapped around the distal oesophagus and the cura closed to keep the repaired area within the abdomen. The operation can be performed laparoscopically or via a traditional, open approach. It is effective in controlling symptoms in gastro-oesophageal reflux disease, and may be particularly useful in treating Barrett's oesophagus in patients with hiatal hernia, lower oesophageal sphincter failure and reflux of duodenal contents (Watson et al, 2005). Fundoplication may prevent all constituents of the refluxate, including the contents of the duodenum such as bile, from entering the oesophagus (Jankowski et al, 2010). Patients often do not require proton-pump inhibitors, which may

have an economic benefit for patients on long-term medication. Moreover, surgical intervention may be better at preventing oesophageal stenosis compared to proton-pump inhibitors alone.

However, despite successful operative intervention preventing reflux in 80–90% of patients, the changes to the distal oesophageal microenvironment do not induce the reversion of metaplasia in most patients (Ortiz et al, 1996). Reversion of intestinal metaplasia has been seen in 30–67% of patients with short segment Barrett's oesophagus, but not long segment Barrett's oesophagus (Zaninotto et al, 2012). Complications include dysphagia and vagus nerve injury. In practical terms endoscopic assessment may be difficult postoperatively and the distance from the incisors and squamo-columnar junction may be modified, which can affect measurements when assessing for Barrett's oesophagus (the cardia must be taken as a reference point).

Oesophagectomy

Oesophagectomy was formerly the gold standard for treatment of Barrett's oesophagus with high-grade dysplasia as a result of the suspected risk of harbouring occult invasive carcinoma (Chennat and Waxman, 2010). Endoscopic ultrasound and staging computed tomography is required to investigate oesophageal adenocarcinoma in further detail. Superficial lesions may be suitable for endoscopic resection, but disease associated with lymphatic invasion or which may harbour lymph node metastases can only be treated with oesophagectomy.

The operation either involves a distal oesophagectomy or a subtotal oesophagectomy, both of which require mobilization of the stomach, which is then pulled up into the chest (to create a conduit), and anastomosis. The operation can be performed via a minimally invasive technique, an open technique or a combination of the two. The location of the anastomosis is either within the thoracic cavity or the neck. Oesophagectomy has a significant morbidity and mortality (5%), with complications including anastomotic strictures, infections and anastomotic leaks.

KEY POINTS

- The treatment of Barrett's oesophagus is undergoing a radical overhaul in part because of an increased understanding of the disease and the availability of endoscopic therapies.
- The current successful endotherapies allow Barrett's oesophagus to be treated at an earlier stage, which has a significant impact on disease progression and ultimately cancer development.
- Endotherapy has overtaken surgery as the treatment of choice in the majority of patients with high-grade dysplasia and there is growing evidence to support early endoscopic intervention in patients with low-grade dysplasia.

Conclusions

Combined modality endotherapy (endoscopic mucosal resection followed by ablation) should now be considered the first-line treatment for patients with high-grade dysplasia. Focal lesions should be removed using endoscopic mucosal resection enabling accurate histopathological disease staging and exclusion of invasive malignancy. Subsequent whole segment ablation aims to destroy the entire malignant field. Radiofrequency ablation has become the most widely used ablative modality as there is strong evidence to support its efficacy and it can be easily and rapidly applied to circumferential Barrett's segments. Following successful endoscopic therapy all patients should receive lifelong surveillance endoscopy, even following complete eradication of visible metaplasia to monitor for the presence of buried metaplastic or dysplastic elements. Oesophagectomy still has a role in patients with widespread multifocal nodular high-grade dysplasia provided they are fit and have a long life expectancy. **BJHM**

Conflict of interest: none.

Anwar SA, Kanthan SK, Riaz AA (2009) Current management of Barrett's Oesophagus. *British Journal of Medical Practitioners* **2:** 8–14

Barr H, Stone N, Rembacken B (2005) Endoscopic therapy for Barrett's oesophagus. *Gut* **54:** 875–84

Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA (1990) Prevalence of columnar-lined (Barretts) esophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* **99:** 918–22

Cameron AJ, Carpenter HA (1997) Barrett's esophagus, high grade dysplasia and early adenocarcinoma: a pathological study. *Am J Gastroenterol* **92:** 586–91

Chennat J, Waxman I (2010) Endoscopic treatment of Barrett's esophagus: from metaplasia to intramucosal carcinoma. *World J Gastroenterol* **16:** 3780–5

Ell C, May A, Grossner L, Pech O, Gunter E, Mayer G (2000) Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology* **118:** 670–7

Fleischer DE, Odze R, Overholt BF et al (2010) The case for endoscopic treatment of non-dysplastic and low-grade dysplastic Barrett's esophagus. *Dig Dis Sci* **55:** 1918–31

Gamliel Z (2000) Incidence, epidemiology and etiology of esophageal cancer. *Chest Surg Clin North Am* **10:** 441–50

Ganz RA, Overholt BF, Sharma VK et al; U.S. Multicenter Registry. (2008) Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicentre registry. *Gastrointest Endosc* **68:** 35–40

Garud SS, Keilin S, Cai Q, Willingham FF (2010) Diagnosis and management of Barrett's esophagus for the endoscopist. *Therap Adv Gastroenterol* **3:** 227–38

Greenwald BD, Dumot JA, Horwhat JD, Lightdale CJ, Abrams JA (2010) Safety, tolerability, and efficacy of endoscopic low pressure liquid nitrogen cryotherapy in the esophagus. *Dis Esophagus* **23:** 13–9

Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RK (1999) Specialized intestinal metaplasia, dysplasia and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. *Gastroenterology* **116:** 277–85

International Working Group for the Classification of Oesophagitis (2004) Prague C & M Barrett's Criteria--Overview. http://iwgco.com/e107_plugins/content/content.php?content.5 (accessed 1 April 2012)

Jankowski J, Barr H, Wang K, Delaney B (2010) Diagnosis and management of Barrett's oesophagus. *BMJ* **341:** 597–602

Johnston MH, Eastone JA, Horwhat JD, Cartledge J, Matthews JS,

Foggy JR (2005) Cryoablation of Barrett's Esophagus: a pilot study. *Gastrointest Endosc* **62:** 842–48

May A, Gossner L, Pech O et al (2002) Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. *Eur J Gastroenterol Hepatol* **14:** 1085–91

National Institute for Health and Clinical Excellence (2010) Ablative therapy for the treatment of Barrett's oesophagus. http://guidance.nice.org.uk/CG106 (accessed 27 April 2012)

O'Conner JB, Falk GW, Richter JE (1999) The incidence of adenocarcinoma and dysplasia in Barrrett's esophagus: report on the Cleveland Clinic Barrett's Registry. *Am J Gastroenterol* **94:** 2037–42

Ortiz A, Martinez de Haro LF, Parrilla P et al (1996) Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. *Br J Surg* **83**: 274–8

Overholt BF, Lightdale CJ, Wang KK et al; International Photodynamic Group for High-Grade Dysplasia in Barrett's Esophagus (2005) Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's oesophagus: international, partially blinded, randomized phase III trial. *Gastrointest Endosc* **62:** 488–98

Rex DK, Cummings OW, Shaw M et al (2003) Screening for Barrett's oesophagus in colonoscopy patients with and without heartburn. *Gastroenterology* **125:** 1670–7

Ronkainen J, Aro P, Storkrubb T et al (2005) Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* **129:** 1825–31

Schlemper RJ, Riddell RH, Kato Y et al (2000) The Vienna classification of gastrointestinal neoplasia. *Gut* **47:** 251–5

Shaheen NJ, Richter JE (2009) Barrett's oesophagus. *Lancet* **373:** 850–61

Shaheen NJ, Sharma P, Overholt BF et al (2009) Radiofrequency ablation in Barrett's Esophagus with dysplasia. *N Engl J Med* **360:** 2277–88

Sharma P, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE (2006) Dysplasia and cancer in a large multicentre cohort of patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* **4:** 566–72

Skacel M, Petras RE, Gramlich TL, Sigel JE, Richter JE, Goldblum JR (2000) The diagnosis of low grade dysplasia in Barrett's esophagus and its implications for disease progression. *Am J Gastroenterol* **95:** 3383–7

Vieth M, Ell C, Gossner L, May A, Stolte M (2004) Histological analysis of endoscopic resection specimens from 326 patients with Barrett's esophagus and early neoplasia. *Endoscopy* **36:** 776–81

Wani S, Mathur S, Sharma P (2009a) How to manage a Barrett's Esophagus patient with low-grade dysplasia. *Clin Gastroenterol Hepatol* **7:** 27–32

Wani S, Puli SR, Shaheen NJ et al (2009b) Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. *Am J Gastroenterol* **104:** 502–13

Watson A, Heading RC, Shepherd NA (2005) Guidelines for the diagnosis and management of Barrett's columnar lined oesophagus. A report of the working party of the British Society of Gastroenterology. www.bsg.org.uk/clinical-guidelines/oesophageal/guidelines-for-the-diagnosis-and-management-of-barrett-s-columnar-lined-oesophagus.html (accessed 26 April 2012)

Weston AP, Sharma P, Topalovski M, Richards R, Cherian R, Dixon A (2000) Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol* **95:** 1888–93

Wood RK, Yang Y (2008) Barrett's Esophagus in 2008: an update. *Keio J Med* **57:** 132–8

Zaninotto G, Parente P, Salvador R et al (2012) Long-term follow up of Barrett's epithelium: medical versus antireflux surgical therapy. *J Gastrointest Surg* **16:** 7–15