Editorials

Heartburn, Barrett's oesophagus and cancer:

implications for primary care

The incidence of oesophageal adenocarcinoma (OAC) has increased eightfold in the past three decades to become the sixth most common cancer in the UK. Before the 1970s, 90% of oesophageal cancers were squamous but now 70% are adenocarcinomas. The reason for this major epidemiological shift is an increase in gastro-oesophageal reflux disease (GORD) and its principal complication, Barrett's oesophagus, the only known precursor lesion for OAC.[1] Barrett's oesophagus, described in 1950 by thoracic surgeon Norman Barrett, is a replacement of normal squamous epithelium by a metaplastic columnar epithelium in the distal oesophagus consequent on chronic GORD. A landmark Swedish study quantified the link between heartburn and OAC, finding an odds ratio (OR) for OAC development of 8 in patients suffering heartburn once weekly, OR = 11 in those with the more damaging nocturnal reflux, and OR = 44 in those with severe, long standing heartburn.[2] Therefore, heartburn, previously regarded as a trivial symptom, has a strong association with OAC development.

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THE SIZE OF THE PROBLEM

Approximately 30% of the UK population experience regular heartburn.[3] In 2010, the number of prescriptions for heartburn and/or dyspepsia totalled 58 million at a cost of £336 million.[4] Some 5% of heartburn sufferers, or 1 million people, have Barrett's oesophagus in whom the lifetime risk of OAC development is 7–12.5%. The risk is higher in white males, smokers, obesity, Rh– blood group, and those with Barrett's segments >7 cm.[5] OAC usually presents late and 5-year survival is only 5–10%. To compound these depressing statistics, the incidence of Barrett's continues to increase and age at diagnosis is falling, 27% of the 12 000 patients registered with the UK National Barrett's Oesophagus Registry (UKBOR) being diagnosed aged <55 years.

Controversial issues in management of heartburn and its sequelae include endoscopy prior to long-term proton pump inhibitors (PPI) therapy, the role of fundoplication, the management of Barrett's oesophagus, and how deaths from OAC may be reduced.

MANAGEMENT OF GORD

Symptoms of heartburn may be controlled by lifestyle measures and over-the-counter medications or by a short course of PPIs followed by maintenance therapy with an H_2RA or low dose PPI. In those whose symptoms are not controlled and in whom long-term, full-dosage PPI therapy is contemplated, opinion is divided as to whether prior endoscopy is necessary. While many practitioners will prescribe long-term, full dosage PPIs with impunity, there is a body of opinion, shared by the authors of this Editorial, that the counsel of perfection before committing patients to a lifetime of powerful antisecretory drugs with not insignificant side effects, is to refer for endoscopy. The rationale for this is primarily to establish a diagnosis. Gallbladder disease and oesophageal motility disorders, particularly achalasia, may present with heartburn. If GORD is present, it is important to grade the oesophagitis and to establish whether Barrett's is present. If Barrett's is suspected at endoscopy, assessment of its circumference and length, according to the Prague classification, is important in addition to histological confirmation. This staging approach, which enables response to treatment to be accurately documented, is favoured in some European countries, notably Belgium, where endoscopy is mandatory prior to prescribing long-term PPI therapy. Diagnosis of Barrett's should result in surveillance, with the aim of early diagnosis of OAC should it arise. Views have been expressed that this approach would generate an unacceptably high endoscopy workload but this has not been the experience of the authors nor was this reported in the Department of Health Heartburn Awareness pilot studies.[6]

While the majority of patients will respond to long-term PPI therapy, with dose escalation if necessary, 10–40% will not and in these patients further assessment is necessary with repeat endoscopy, oesophageal manometry, and impedance or pH monitoring. Non-responders will usually be found to have persistent, severe oesophagitis, a significant hiatus hernia, high levels of oesophageal acid and alkaline (duodenal juice) exposure and lower oesophageal sphincter (LOS) failure. Such patients who have no contraindication to surgery do well with a laparoscopic fundoplication, as the only modality capable of addressing hiatal hernia, LOS failure, and the carcinogenic alkaline reflux. Fundoplication has a ≥90% success rate and is frequently requested by patients who are controlled by long-term PPI therapy but who are intolerant to them or the concept of long-term medication.

MANAGEMENT OF BARRETT'S OESOPHAGUS

The aims of management of Barrett's comprise symptom control and efforts directed towards cancer prevention. In practice, management is governed by two principles; the first that because the metaplastic columnar epithelium is acid-resistant, many Barrett's patients have few or no symptoms and thus an amelioration of symptoms in a reflux patient may herald the onset of Barrett's. Second, Barrett's represents the extreme end of the spectrum of severity of GORD, with the pathophysiological features described in non-responders above. In Barrett's

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patients, there is poor correlation between symptoms and reflux control and studies have shown that even using maximal dose PPI, high levels of oesophageal acid/alkaline exposure may be present in the absence of symptoms.[7] The finding that effective reflux control in Barrett's patients aids associated stricture resolution and prevention and the theoretical objective of reducing the carcinogenic stimulus support the desirability of attempting effective reflux control, even in the absence of symptoms. In these circumstances, the indications for fundoplication are fulfilled in a larger proportion of Barrett's patients than those with uncomplicated GORD. Several studies have suggested a protective effect of fundoplication against cancer development, although other studies have failed to confirm this.

Regardless of the treatment used to control GORD, Barrett's patients should be offered endoscopic surveillance with the aim of preventing OAC or diagnosing it at an early, curable stage. Endoscopy and multiple biopsies are performed usually every 2 years or if alarm symptoms present in the interim. Biopsies should be of any visible lesion often seen with enhancement techniques or otherwise four quadrant biopsies at 2 cm intervals along the length of the segment to look for dysplasia. Dysplasia may be low grade, with a 5% risk of cancer development requiring shortening of the surveillance interval to 6-monthly. High grade (HGD) has a 50% chance of developing cancer within 8 years and some patients with HGD will already have a focus of invasive cancer.[8] Detection of HGD used to mandate oesophageal resection, but recently a series of effective endoscopic ablative therapies have been developed of which the most popular are radiofrequency ablation (RFA) and endoscopic mucosal resection (EMR).[9] Studies are currently ongoing, with encouraging results, of ablation of the entire Barrett's segment with RFA, but this is not yet recommended for routine use.

While several series have shown that cancers detected during surveillance are at an earlier stage than those presenting clinically, others have reported interval cancers developing between surveillance. There is no clear evidence that current surveillance practice saves lives or is cost effective and there are associated negative issues such as psychological morbidity and the small risks associated with repeated endoscopy. For these reasons, the British Society of Gastroenterology Guidelines[10] fall short of advocating surveillance in all cases, but recommends its consideration and discussion with patients pending the results of the UK randomised trial of surveillance (BOSS). International efforts are being directed towards identification of molecular markers which would predict risk of cancer development at a much earlier stage in the metaplasia-dysplasia sequence.

REDUCING DEATHS FROM OESOPHAGEAL CANCER

An alternative approach to OAC prevention is currently being discussed between oesophageal specialists, charities, and the Department of Health, based on the known link between heartburn and OAC. Current NICE guidelines for dyspepsia and upper GI cancer are directed primarily towards gastric cancer, which is diminishing in frequency, and do not reflect the escalating incidence of OAC, occurring in increasingly younger age groups. In *Improving Outcomes: A Strategy for Cancer 2011*, the Department of Health aims to save 950 lives annually by bringing survival rates for oesophagogastric cancer closer to the European average, principally by earlier diagnosis. As part of its Be Clear on Cancer campaign, the Department of Health launched pilot studies in seven UK districts during 2012, increasing patient awareness of the importance of persistent heartburn and recommending early consultation with their GP with a view to early referral for endoscopy. This resulted in a 20% increase in oesophageal cancers diagnosed following 2-week wait referral, the greatest increase among the five cancers targeted. On the strength of this, a regional campaign with press and TV advertising is to be launched in the North East in February 2014. It is of interest that reports of the pilots did not comment on any unmanageable increase in endoscopy demand.

Implications for primary care include advising patients that persistent heartburn is not a trivial complaint, especially if unresponsive to lifestyle changes and OTC medication and encouraging consultation with their GP. GPs will need to reconsider advice in current NICE dyspepsia guidelines for these patients in view of the pilot results and consider referring for endoscopy early, rather than the current practice of treating blindly with acid suppression, with the hope of improving the dreadful survival figures of OAC by early diagnosis and effective management of its only known precursor lesion.

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