Barrett's oesophagus and oesophageal adenocarcinoma

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Abstract

Oesophageal adenocarcinoma has increased rapidly in the western world over the past 20 years. It is preceded by a condition Barrett's oesophagus in which the distal squamous epithelium is replaced by a columnar lined epithelium which is characterised histopathologically by gastric and intestinal cell types. The endoscopic and histopathological definitions continue to evolve over time. The risk of progression from Barrett's to adenocarcinoma is 0.6% per year and since symptomatic adenocarcinoma has a poor prognosis surveillance of Barrett's oesophagus is generally recommended in order to detect high grade dysplasia and intramucosal carcinoma lesions at an early curative stage. Endoscopic diagnostic and therapeutic technologies for early lesions are advancing rapidly. Screening is also being more seriously considered with the realisation that Barrett' oesophagus is a common condition and most cases are undiagnosed. Oesophageal adenocarcinoma is staged using a combination of CT and EUS and staging informs management which currently still mainly involves cytotoxic chemotherapy and oesophagectomy, although surgical techniques are becoming more minimally invasive to reduce morbidity. Molecular targeted therapies are beginning to be applied but this has lagged behind progress in other cancers. Curative and palliative treatment involves close liaison between members of the multidisciplinary team.

Keywords biomarkers; dysphagia; endoscopic mucosal resection; endoscopy; oesophagectomy; radiofrequency ablation; screening; staging; surveillance

Although the oesophagus normally has a squamous epithelial lining, the most common cancer arising in the oesophagus in the western world is oesophageal adenocarcinoma rather than squamous cell cancer. This cancer is thought to develop via an initial metaplastic replacement of the squamous epithelium of the lower oesophagus with a columnar epithelium, known as Barrett's oesophagus (Figure 1). The metaplastic Barrett's epithelium (BE) may then progress to dysplasia and subsequently to adenocarcinoma.[1] Since BE begins at the gastro-oesophageal junction (GOJ) and can extend a variable distance up the oesophagus, associated cancers normally lie in the lower oesophagus and those within 5 cm of the GOJ are termed GOJ cancers.

What's new?

- Biomarkers (such as aneuploidy or p53 loss of heterozygosity) are being developed to identify which patients with Barrett's oesophagus are at particular risk of getting cancer and other prognostic biomarkers being assessed for invasive disease
- Cheaper less invasive techniques to screen for Barrett's oesophagus in the general population are under development
- Endoscopic therapies for early cancer such as EMR and RFA mean that patients no longer necessarily have to be fit for oesophagectomy to have treatment
- Laparoscopy-assisted, minimally invasive oesophagectomy techniques are being increasingly applied with a more rapid recovery time

Barrett's oesophagus

Epidemiology

Gastro-oesophageal acid reflux (GORD) (particularly of prolonged duration) is the main risk factor for the development of BE which is found in approximately 3% of those who undergo gastroscopy for this indication. There is an association between the presence of BE and larger hiatus hernia length. The

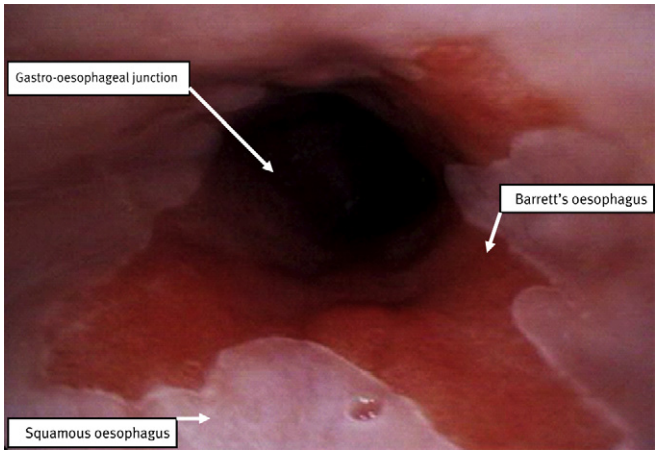

Figure 1 Endoscopic appearance of Barrett's oesophagus. The transition between the pale pink squamous oesophagus with the darker columnar metaplasia that has replaced it in the lower oesophagus can easily be detected endoscopically, but early cancers are often not macroscopically identifiable.

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The Vienna histological classification

Category	Classification
1	Negative for neoplasia/dysplasia
2	Indefinite for neoplasia/dysplasia
3	Non-invasive low-grade neoplasia
4	Non-invasive high-grade neoplasia
5	Invasive neoplasia

Source: Adapted from Schlemper et al., 2000.[7]

Table 1

prevalence of BE increases with age, until the 70s, where it plateaus and the male to female ratio is 3:1.

In the western world the increase in incidence of BE has been dramatic, rising 62% (independently of the number of gastroscopies performed) in the 5 years between 1997 and 2002[2,3] although increased awareness and the inclusion of short (<3 cm) segments in the definition of BE may have contributed to this rise. Other suggested risk factors include adiposity (although this also contributes to GORD, a confounding factor), and diets deficient in fruit and vegetables and high in animal fats. Smoking is thought to be only a moderate risk factor in contrast to its association with squamous cell cancer.

Diagnosis of BE

The endoscopic measurement of BE has been standardized using the Prague classification in which the maximum circumferential extension of the columnar epithelium from the GOJ in centimetres (the C score) and the maximal total extension of the metaplasia from the GOJ (the M score) are documented.[4] Variability in measurement arises from difficulties determining the site of the GOJ (at the top of the gastric folds), variation in degree of air insufflation, and wide spacing of distance markers on the endoscope (usually every 5 cm). The British definition of BE includes not only the macroscopic appearance but also the microscopic evidence of columnar metaplasia with or without an intestinal phenotype (i.e. typified by the presence of goblet cells). In contrast, the current American guidelines require the microscopic identification of goblet cells for the definition of BE, although this is expected to change shortly to a definition that incorporates any length of columnar epithelium predisposing to oesophageal adenocarcinoma. The difficulty lies in defining the precise characteristics of mucosa with a future cancer risk.[5]

Risk of progression from BE to cancer

Those with BE have an approximately 0.6% chance of developing oesophageal adenocarcinoma each year.[6] The only marker of risk of progression currently in clinical use is the presence of dysplasia found in biopsies of BE. Routine endoscopy should include four (quadrantic) biopsies every 2 cm to maximize the chances of detection of dysplasia, which can be present in a mosaic-like pattern. The Vienna protocol attempts to unify the pathologists' classification of the degree of dysplasia and is summarized in Table 1.[7]

Surveillance

Surveillance involves repeated endoscopy in patients known to have BE, to allow early, pre-symptomatic detection of cancer. At this stage therapy is more effective and associated with improved survival.[8]

The British Society of Gastroenterology guidelines (last updated in 2005) do not recommend surveillance for all patients because of a lack of randomized controlled trial data to show improved survival (the American guidelines are similar). The guidelines suggest that risks and benefits for surveillance should be discussed and, if the patient wishes to enter the programme, gastroscopy could be performed every 2 years in the absence of dysplasia.[9] During surveillance, careful inspection for nodules, ulceration or strictures is made as these have a high association with the presence of cancer and must be thoroughly biopsied. In the absence of these findings, four biopsies are taken every 2 cm. If dysplasia is detected in these biopsies, frequency of surveillance is increased and therapy considered (Table 2).

Endoscopic technology designed to improve detection of dysplasia and early cancer is advancing rapidly, but as yet no single technique has been shown consistently to improve detection and decrease the need for the random biopsy protocol. Many endoscopic techniques, including confocal endomicroscopy, narrow band imaging and optical coherence tomography, provide magnified images of small mucosal areas. Their narrow field of view limits their ability to examine the entire BE mucosa in a timely manner. Many high magnification techniques also require expert histological interpretation of images and they

Summary of British Society of Gastroenterology Guidelines (2005) for surveillance of Barrett's oesophagus adapted in light of emerging evidence

No dysplasia	Endoscopy every 2 years
Indefinite dysplasia	Changes suggest dysplasia, but inflammatory changes make distinction impossible. Increase PPI and re-biopsy
Low-grade dysplasia	Expert pathological confirmation is essential. And patients need extensive re-biopsy after increased acid suppression for 8–12 weeks. If this persists, repeat biopsies every 6 months while situation remains unchanged. If confirmed, 13% per year progress to high-grade dysplasia or adenocarcinoma.[10] Others remain static or regress
High-grade dysplasia	Extensive biopsies required as this can be associated with a focus of invasive adenocarcinoma not initially detected due to sampling bias. If changes are confirmed by two expert pathologists, oesophagectomy or endoscopic therapy is recommended. Endoscopic mucosal resection of any associated focal lesion very helpful to accurately stage depth of invasion

Table 2