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Barrett's oesophagus: an overview

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ABSTRACT Barrett's oesophagus is common and there is evidence that it is becoming more common. This is significant because of the malignant potential of the condition. The professional gastroenterology societies of the UK and USA now recommend 2–3 yearly endoscopic surveillance with systematic biopsies for those diagnosed with Barrett's oesophagus. However, surveillance is controversial because the number of patients identified with early cancer is relatively small for the large amount of work that is required. In the future it is hoped that new imaging techniques should help target biopsies more effectively and new therapeutic endoscopic techniques should enable some patients to avoid mutilating surgery and offer therapy to patients who had previously been considered unfit for surgery. At present, chemoprevention and population screening for Barrett's oesophagus offer the best chance of reducing the current considerable national mortality from oesophageal cancer.

KEYWORDS Barrett's oesophagus, dysplasia, oesophageal cancer, reflux

DECLARATION OF INTERESTS The author is on the trial management group of the AspECT trial.

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OVERVIEW

Barrrett's oesophagus is named after Norman Barrett, who first described the mucosal change in the lower tubular oesophagus in 1950. The mucosa becomes columnar in character rather than the usual stratified epithelium, a so-called metaplastic change. It is recognised by the endoscopist by its velvet-like appearance, which is sometimes described as salmon pink in colour (Figure 1).

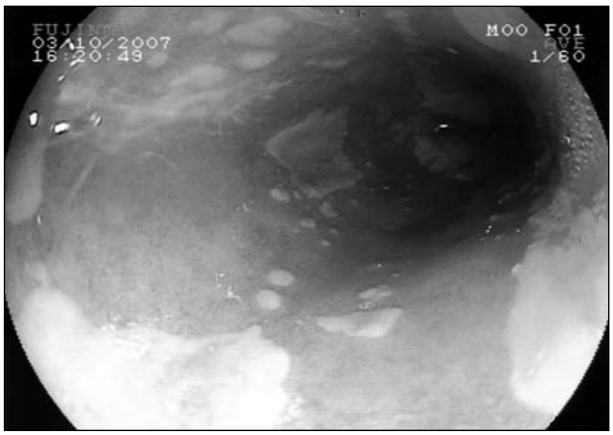

FIGURE 1 Endoscopic appearance of Barrett's oesophagus. In this example the metaplastic columnar mucosa extends circumferentially to a distance of 4 cm from the lower oesophageal sphincter, with tongues reaching a maximum distance of 5 cm. Note the pale islands of squamous mucosa within the columnar mucosa, which make it relatively easy to recognise the condition. (With kind permission of Dr Stephen Hughes, Southmead Hospital, Bristol.)

Traditionally, Barrrett's oesophagus had to be 3 cm in length to ensure that it could be reliably differentiated from hiatus hernia, which is an extension of the upper stomach above the diaphragm and which also has columnar mucosa. It is now considered that endoscopists can reliably diagnose circumferential or partial circumferential (tongues) of Barrett's mucosa 1 cm in length. The main landmarks that the endoscopist uses to determine where the tubular oesophagus ends and the stomach begins are the lower oesophageal sphincter pinch and proximal ends of the gastric folds. Biopsies are taken to confirm its columnar nature.

According to the American College of Gastroenterology (ACG) guidelines, biopsies should show specialised intestinal metaplasia (SIM), i.e. columnar mucosa that resemble the small intestine with villi and goblet cells (Figure 2). This is the most common form of metaplasia and is considered to have the greatest clinical significance (see below). The British Society of Gastroenterology (BSG) guidelines, however, state simply that the histology of the mucosa is columnar. Specialised intestinal metaplasia, although often present, is not required for diagnosis. This is because it is thought that the presence or absence of SIM is related to the number of biopsies taken, i.e. the more biopsies, the greater the chance of finding SIM.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Barrett's oesophagus is common, being found in 2–3% of patients undergoing gastroscopy and in a higher percentage of patients who are being investigated for gastro-oesophageal reflux. There is a marked gender difference, with it being more common in men than women and most common in older men. Post-mortem studies indicate that the majority of cases are not

recognised during life. There is evidence that the condition is more common now than 20–30 years ago.

It is very likely that gastro-oesophageal reflux is a major aetiological factor, as indicated by the epidemiological association (see above). This is supported by the higher than normal levels of acid reflux measured by 24-hour oesophageal pH monitoring in Barrett's patients. The level of acid reflux in these patients is also higher than in patients with erosive reflux oesophagitis. The metaplastic change is probably an adaptive response to the chronic irritation of gastric refluxate. Despite high levels of reflux these patients frequently have low levels of symptoms. This is due to the relative insensitivity of the Barrett's mucosa to acid, which probably explains why only a minority of cases come to investigation and are diagnosed.

CLINICAL SIGNIFICANCE

Barrett's oesophagus is significant for only one thing: its malignant potential. There was a tendency to over-estimate this at one time due to reporting bias, i.e. authors tended to report series with a high incidence, whereas series with low cancer incidence were not reported. With the advent of large-scale population-based studies the true incidence of cancer development is agreed to be 0.5–1.0% per year.

Oesophageal adenocarcinoma is increasing in incidence faster than any other cancer in the Western world. The current incidence in many developed countries is two to three times higher than it was 30 years ago. This is in contrast to squamous cancer of the oesophagus, for which the incidence has remained steady. At one time squamous cancer of the oesophagus was twice as common as adenocarcinoma of the oesophagus, but now the situation is reversed and adenocarcinoma is twice as common. Oesophageal cancer of both types accounts for 7,500 cases per year in the UK and is the fifth most common cause of cancer death in the UK. The majority of patients present with the features of advanced disease (dysphagia, weight loss), and the prognosis is very poor, with a five-year survival of about 7%. The annual mortality is equal to incidence. The number of cases occurring in patients with previously recognised Barrett's oesophagus is only about 2% of the total, although it is believed that the majority of adenocarcinomas arise in unrecognised Barrett's oesophagus.

Progression of metaplasia to neoplasia goes through dysplasia. This is recognised histologically by increasing disorganisation of the normal cellular structure such as aneuploidy, where there are variable numbers of nuclear chromosome sets, and disorganisation of tissues, e.g. pseudostratification and abnormal cellular proliferation but without invasion, which is a feature of neoplasia. Histopathologists recognise low-grade dysplasia, where these changes are mild, and high-grade, where the changes are more severe. There can be considerable disparity between pathologists, particularly for low-grade dysplasia, and it is important that the diagnosis of high-grade dysplasia is supported by an independent expert pathologist when important clinical decisions are being based on this diagnosis. The cellular changes of dysplasia are associated with genetic molecular changes, e.g. the expression of abnormal and ineffective suppressor oncogene *P53*. The time for this progression to occur is variable but is usually of the order of two or more years.

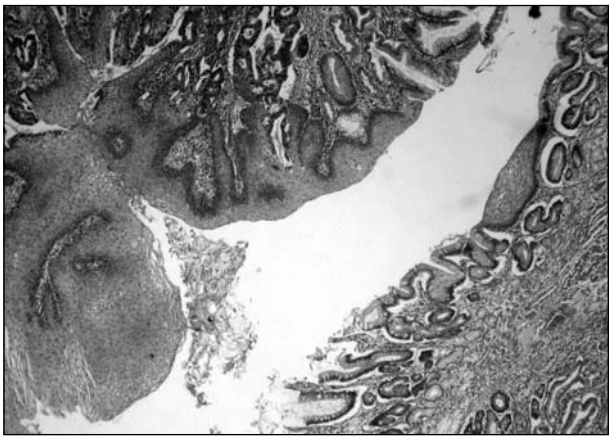

FIGURE 2 Histology showing squamous mucosa (left lower corner), adjacent Barrett's mucosa (right lower corner) with typical glandular appearance and adenocarcinoma (upper slide). (With kind permission of Dr Rebecca Harrison, Leicester Royal Infirmary.)

CLINICAL MANAGEMENT

The recognition of Barrett's oesophagus as having malignant potential with slow progression through low- and high-grade dysplasia before developing cancer has led to a policy of regular endoscopic surveillance and systematic biopsies with the object of picking up early changes and appropriate intervention. The presence of confirmed high-grade dysplasia is a good predictor of the presence of cancer, which is not necessarily apparent macroscopically because it may be intramucosal and non-invasive. The treatment of early cancers picked up by surveillance is more successful than cancer patients presenting with symptoms and not in a surveillance programme. The ACG and BSG therefore advocate that Barrett's oesophagus patients should have endoscopic surveillance at 2–3-year intervals and, because dysplasia and even neoplasia may not be apparent macroscopically, systematic quadrantic biopsies should be carried out at 2-cm intervals. However, there has never been a controlled trial to determine if this strategy is effective, although one is approved and planned to start very soon in the UK in 2009 (BOSS: Barrett's Oesophagus Surveillance Study).

A large number of patients are subjected to invasive endoscopy without any benefit. Only a small number of patients will be found to have cancer, and in some of these other co-morbidities will be the cause of death rather than oesophageal cancer. Modelling studies show that the

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strategy of surveillance and surgical resection is only cost effective with an incidence of cancer development of around 1% per annum and a surveillance interval longer than three years. Hence there is a degree of ambivalence and even confusion in the gastroenterology community with regard to surveillance. Surveys show that not all gastroenterologists carry out surveillance of their Barrett's oesophagus patients, and where they do there may be poor adherence to biopsy protocol. This may all change for the better with the introduction of some future developments (see below).

FUTURE DEVELOPMENTS

One of the difficulties with surveillance is the large amount of time required to carry out gastroscopy and biopsy and for the histopathologist to then assess those biopsies. The cumulative time for follow-up of patients over a period of 20 years or more is considerable. Better targeted surveillance and biopsy are therefore required. It is recognised that patients with longer segments of Barrett's oesophagus are at increased risk of having dysplasia. Dysplasia is also more likely to be associated with abnormalities such as ulcers and raised areas. These areas should be carefully targeted.

Chromo-endoscopy is a technique where the mucosa is sprayed with a solution such as methylene blue to highlight areas of metaplasia and dysplasia, which appear pale compared with the normal squamous mucosa that takes up the dye and appears blue. It has been reported to have variable efficacy compared with systematic biopsies and has not proved to be popular. A possible more user-friendly alternative is narrow band imaging which filters out red light. This highlights the vascular pattern of the mucosa and enhances the contrast between metaplasia and normal mucosa and between dysplasia and metaplasia. Together with high-resolution imaging with or without real-time magnification endoscopy, it should be possible to recognise abnormalities more readily and target biopsies more efficiently.

Another likely area of development is in the use of biomarkers such as P53 mentioned above. Expression of this and other markers can be determined by immunostaining of biopsies. The hope is that one of these markers or a combination will accurately indicate a state of instability in the Barrett's oesophagus and accurately predict future development of cancer. Although some biomarkers, such as P53, are often associated with the development of cancer, none alone or in combination have so far proved to be sufficiently accurate to be used for this purpose. However, intensive research continues.

Until recently the accepted treatment for high-grade dysplasia found at surveillance has been surgical oesophagectomy, which has a very significant morbidity and not inconsiderable mortality. Patients therefore tended to be excluded from surveillance if they were thought to be too old and/or too unfit for surgery should the need arise. This has now all changed with the advent of endoscopic treatments for non-invasive cancers. If the cancer/high-grade dysplasia is restricted to the mucosa, as determined by CT scan ± endoscopic ultrasound, it can be removed by endomucosal resection. In this technique, saline is injected under the lesion to lift it up from the submucosa and it is then cut off with a snare. The margins can be checked to ensure that the lesion has been completely removed and if there is evidence of invasion of the submucosa surgery will be necessary.

Endomucosal resection is ideal for localised and well-defined lesions, e.g. a lump, but when the cancer is more diffuse or multifocal and not apparent macroscopically, it will be more appropriate to treat the Barrett's oesophagus more widely. Also there is evidence that the additional ablation of Barrett's mucosa associated with macroscopic lesions reduces the recurrence rate of cancers. Photodynamic therapy, thermal ablation and radiofrequency ablation using a balloon-based catheter system have all been used. Photodynamic therapy appears to carry a significant risk of stricturing as a side effect, and radio frequency ablation (using the 'Barrx' technique) looks the most promising in terms of feasibility and efficacy. With all these techniques, careful subsequent surveillance is necessary to detect recurrence of cancer/high-grade dysplasia and/or Barrett's oesopahgus. Nevertheless, these procedures offer a very attractive alternative to major surgery.

Further areas of potential development are in chemoprevention and screening. Since the prognosis of oesophageal cancer is so poor, prevention might be a better option than treatment. Currently there is a UK national trial of high-dose acid suppression with the proton pump inhibitor esomeprazole and aspirin in the prevention of cancer in Barrett's oesophagus (AspECT – Aspirin and Esomeprazole Chemoprevention Trial of Cancer in Barrett's Oesophagus). If these agents are shown to be successful it could lead to the need for less frequent surveillance or none.

Even if surveillance of Barrett's oesophagus is successful in preventing cancer in these patients, it will have little impact on the population incidence and mortality of oesophageal cancer because most cancers occur in patients who have not been previously recognised to have Barrett's oesophagus. This raises the question of the need for screening for Barrett's oesophagus. The most reliable method currently available for this is oesophagogastroduodenoscopy. It is not feasible to do this in the entire population. Non-invasive alternatives that are being investigated are wireless capsule endoscopy and a sponge that is swallowed and retrieved by a string. Adherent cells on the sponge can then be examined to see if they could have originated from a segment of Barrett's oesophagus. Accurate identification of large numbers of people with Barrett's oesophagus who are not currently recognised could lead to their being given chemoprevention (+/- surveillance) with a view to significantly reducing oesophageal cancer.

KEY POINTS

- Barrett's oesophagus is an adaptive change in response to chronic gastro-oesophageal reflux whereby the mucosa of the lower oesophageal mucosa becomes columnar rather than squamous.
- The condition is diagnosed by endoscopy appearance and biopsy.
- Barrett's oesophagus has the potential to become an adenocarcinoma at a rate of 0.5–1.0% per year.
- The most accurate means of recognising that neoplastic change is occurring is by identifying dysplasia in biopsy specimens.

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EDUCATION

RCPE/RCSED/RCoA JOINT SYMPOSIUM

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Thursday, 28 May 2009

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- *Obesity: a challenge to the nation's way of life* Shona Robison MSP
- *Nature and nurture: genetic aspects of obesity* Prof. Tim Frayling
- *Setting up and running a regional service*, Prof. Mark Bellamy

Session 2: Developing themes
- *Obesity in pregnancy and labour,* Prof. Jane Norman

Stanley Davidson Lecture
- *Clinical decision making and obesity*, Prof. Pat Croskerry

Session 3: Interactive simulated clinical cases
Facilitated by: Dr Graham Nimmo, Mr Colin Halliday, Dr Richard Lyon, Mr Jerry Morse and Dr Ben Shippey
- *Case 1: Emergency medicine*
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Session 4: Clinical challenges in the obese patient
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- *Medical management of obesity*, Prof. Iain Broom
- *Bariatric surgery*, Mr Duff Bruce

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or by contacting Josh Hey-Cunningham, Education Co-ordinator, Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1JQ

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RATIONING, CHARITY AND PRIVATE SUPPORT

HOW MUCH LONGER CAN THE UK SUSTAIN THE NHS?

Monday, 22 June 2009

Less than a year after the National Health Service in the UK celebrated its 60th anniversary, it finds itself under unparalleled financial pressure. As the world experiences global recession, new questions are being asked regarding the sustainability of the NHS. Against this background, the RCPE has convened a one-day Hot Topic Symposium which will seek to address the following questions:

- Can the NHS continue to deliver the quality of care which doctors believe it is essential to provide and which patients expect?
- How much longer can we realistically expect to sustain the NHS?
- Is it now time to consider adopting a different form of healthcare system in the UK?

Speakers will include Sir Michael Rawlins, Chair, National Institute for Health and Clinical Excellence; Dr Ken Paterson, Chair, Scottish Medicines Consortium; Professor Michael Richards, National Clinical Director for Cancer at the Department of Health; and Ms Audrey Birt, Director of Scotland Breakthrough Breast Cancer.

The symposium is open to all with an interest in these issues, whether from the perspective of the NHS, the voluntary and charitable sectors, patients, policymakers or others.

Standard fee: £75; Nurse/AHP: £45. Patients/Volunteers/Retired FRCP Edin: free but £20 if lunch required. Admission is free to medical students who register in advance. However, limited free places are available.

Details at: **http://www.rcpe.ac.uk/education/events/index.php** or from Christina Gray, tel: 0131 247 3607, fax: 0131 220 4393, email: c.gray@rcpe.ac.uk