Summary

Barrett's oesophagus represents the replacement of stratified squamous epithelium by metaplastic columnar epithelium for 3 cm of the distal oesophagus. Gastro-oesophageal reflux, which affects 40% of the adult population, is the principal aetiological factor. This results in predominantly acid but also bile reflux (due to duodenogastro-oesophageal reflux) through the lower oesophageal sphincter, transient relaxation of which accounts for the main mechanism of reflux. Conventional Barrett's oesophagus is reported in 11-13% of patients with symptomatic reflux and short segment Barrett's oesophagus (< 3.0 cm) in 18%. Approximately 50% of these patients have recognised complications on presentation, eg, carcinoma (15%). The disparity between clinical symptoms and endoscopic severity is due to reduced oesophageal mucosal sensitivity as a consequence of prolonged mucosal acid exposure. These rather alarming figures combined with the knowledge that Barrett's oesophagus is a pre-malignant condition (the diagnosis is associated with a 25-130-fold increase of malignancy) may account for the substantial increase in junctional gastro-oesophageal malignancies. Symptomatic Barrett's oesophagus should be managed with full-dose proton pump inhibitors, eg, lansoprazole. Anti-reflux surgery should be reserved for the medically fit patient with recurrent symptomatic relapse in the histological absence of pre-malignant change. There is no evidence suggesting that surgery can be used as a prophylactic measure against malignancy. Encouraging short-term results have been obtained with photodynamic therapy in the management of high-grade dysplasia. However, columnar epithelium has been found underlying the regenerated squamous epithelium, suggesting that life-long surveillance is warranted.

Keywords: Barrett's oesophagus; gastro-oesophageal reflux disease; photodynamic therapy

University Department of Surgery,
The Royal Free Hospital, London
NW3 2QG, UK
R M Navaratnam
M C Winslet

Correspondence to R M Navaratnam, 66 Nursery Road, Pinner HA5 2AR, UK

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Barrett's oesophagus

R M Navaratnam, M C Winslet

Classical Barrett's oesophagus represents the replacement of stratified squamous epithelium by metaplastic columnar epithelium for a distance of at least 3 cm of the distal oesophagus. By contrast, the concept of 'short segment' Barrett's oesophagus is becoming increasingly recognised, primarily due to its presumed aetiological role in oesophageal adenocarcinoma.¹

Barrett's original description was in 1950,² however, it was not until 1953 that Allison and Johnston confirmed the presence of columnar epithelium lining the distal oesophagus and suggested that gastro-oesophageal reflux disease (GORD) may be involved in the pathogenesis.³

Three types of columnar epithelium have been described:

- specialised columnar epithelium characterised by a villiform surface, mucus glands and intestinal type goblet cells
- atrophic, gastric fundic type of epithelium with chief and parietal cells
- junctional type epithelium similar to that found in the gastric cardia.⁴

Epidemiology

Combined data from prospective autopsy studies has estimated that there are approximately one million cases of Barrett's oesophagus in the USA.⁵ A significant proportion of these patients are unaware of their diagnosis, as large numbers of patients self-medicate with antacids, due to the disparity between disease severity and symptoms.⁶ The median age of developing Barrett's oesophagus is approximately 60 years,⁷ although it is recognised in children.⁸ The disorder is twice as common in men (0.97%) as in women (0.49%), and is rare in the negroid population.

Conventional Barrett's oesophagus is reported in 1% of general endoscopy patients and in 11-13% of patients with frequent symptomatic reflux, as demonstrated in prospective endoscopic studies.⁹⁻¹⁰ Short-segment Barrett's oesophagus is reported in 18% of unselected patients.¹¹ The overall high estimated prevalence of Barrett's oesophagus and the well-recognised dysplasia/carcinoma sequence may account for the increased incidence of proximal gastric and gastro-oesophageal junction adenocarcinoma.¹² Convincing data for this is evident in prospective endoscopic surveillance studies which show that, in patients with proven carcinoma, preceding histological biopsies reveal a progressive worsening grade of dysplasia.¹³

Aetiology

GORD has long been recognised as the principal aetiological factor in Barrett's oesophagus. GORD is attributed primarily to acid and to a lesser degree bile reflux, through the lower oesophageal sphincter (LOS).¹⁴ Reflux is thought to occur due to transient relaxation of the LOS or varying degrees of incompetence at this site, leading to retrograde oesophageal flow.¹⁴

Oesophageal manometry has identified LOS parameters responsible for defective function. A resting LOS pressure < 6 mmHg, a total length < 20 mm and an intra-abdominal length < 10 mm have resulted in probability values of 92%, 65-88% and 69-76%, respectively, depending on the number of abnormal variables present.¹⁵

Oesophageal clearance, both volume and acid clearance of the refluxed material, the presence of a hiatus hernia, and the intrinsic resistance of the oesophageal epithelium to the refluxate, are further important contributory factors in the pathogenesis of GORD and thus Barrett's oesophagus.¹⁴ In 1970 Bremner denuded 10 cm of the distal oesophageal squamous mucosa (in the canine model) and demonstrated the regeneration of columnar type epithelium only in the presence of acid reflux.¹⁶ Gastric hypersecretion, however, has not been proven to be an aetiological factor in Barrett's oesophagus. 24-Hour ambulatory pH monitoring studies have revealed no significant difference in gastric acid

Gastro-oesophageal reflux: aetiology

- lower oesophageal sphincter relaxation/dysfunction
- acid reflux
- bile reflux (duodenogastro-oesophageal reflux)

output or pepsin secretion in patients with Barrett's oesophagus, reflux oesophagitis or control patients, when all subjects were matched appropriately.¹⁷

Speculation regarding the synergistic role of 'bile reflux' in the aetiology of Barrett's oesophagus was prompted by its occurrence in patients with pernicious anaemia (and achlorhydria), and in a further group who developed the condition following total gastrectomy without biliary diversion. Bile reflux is thought to occur via a mechanism of duodenogastro-oesophageal reflux.¹⁸ Increased concentrations of bile acids have been detected both by oesophageal aspiration and spectrophotometric analysis of bilirubin in Barrett's oesophagus, in comparison to patients with GORD and normal controls.^{19 20}

A congenital theory for Barrett's oesophagus and the implication of an aetiological role for *Helicobacter pylori* have not been substantiated.^{21 22} However, the aetiological role of free radical generation, with the production of mucosal reactive oxygen species, eg, superoxide anions, hydrogen peroxide and hydroxyl radicals has been described.²³

The mechanism by which columnar re-epithelialisation is thought to occur, is through the differentiation of primordial stem cells intrinsic to the oesophagus rather than by proximal migration of gastric epithelium. This metaplastic process is thought to be precipitated by trophic factors present within the refluxed material.²⁴

Clinical features

The majority of symptomatic patients tend to present with heartburn (81%), dysphagia (51%) and regurgitation (33%), respectively.²⁵ However, a large proportion of patients (23–40%) may be completely asymptomatic,²⁶ and in a further 10–19% the diagnosis was established in the absence of reflux-type symptoms.⁶ Approximately 50% of patients with Barrett's oesophagus have recognised complications on presentation, eg, erosive oesophagitis (20%), carcinoma (15%), peptic stricture (10%), and ulcer (5%).²⁷ The disparity between clinical symptoms and endoscopic severity is thought to be due to prolonged mucosal acid exposure, resulting in decreased oesophageal sensitivity.²⁸

Investigations

Contrast radiology, although used less frequently, has some predictors suggestive of Barrett's oesophagus, namely the presence of a stricture proximal to the gastro-oesophageal junction, ulceration within the body of the oesophagus, and the presence of radiological reflux.²⁹

Endoscopy, with multiple four-quadrant large-sized biopsies and confirmatory histology by two specialist pathologists, is the ideal investigation. Such close scrutiny is needed to identify those high-risk patients who have histologically proven high-grade dysplasia. This is due to the overwhelming evidence which suggests that approximately 50% of patients who undergo an oesophageal resection for high-grade dysplasia are subsequently found to have carcinoma *in situ*.¹³ In addition, it is well recognised that the specialised columnar epithelium found in Barrett's oesophagus may not be endoscopically distinguishable from apparently normal underlying epithelium.³⁰

Brush cytology is also advisable in the presence of macroscopically normal epithelium, especially in high-risk patients. In a retrospective study of paired brushings and biopsies, identical results were obtained in 72% of patients. In eight out of 64 cases, cytology accurately identified the presence of a carcinoma or dysplasia, despite negative histology.³¹

Light-induced fluorescence endoscopy is a new technique, used to differentiate between normal, dysplastic epithelium and early malignant change in the endoscopic presence of macroscopically normal epithelium.³² Abnormal epithelium has a different fluorescence spectrum and intensity when activated by light of a specific wavelength in comparison to normal epithelium. This facilitates screening and enables biopsies to be targeted to abnormal areas.

24-Hour ambulatory pH monitoring and oesophageal manometry are routinely performed pre-operatively when contemplating surgery in the medically fit patient. Neither investigation is obligatory. However, manometry is a measure of oesophageal peristalsis (and hence clearance) as well as assessing LOS parameters. It is an important part of pre-operative evaluation to ensure there is no associated dysmotility.

The Bilitec 2000 is used in the spectrophotometric evaluation of bile reflux in the distal oesophagus. A fibre-optic probe, emitting light of 453 nm, is placed 5 cm above the manometrically determined LOS, in a position similar to that used in 24-hour ambulatory pH monitoring. Bilirubin has a characteristic absorption peak of 453 nm. The instrument works on the principal that an absorption peak

The dysplasia/carcinoma sequence

Progression of metaplastic columnar epithelium to high-grade dysplasia, carcinoma *in situ* and subsequently invasive carcinoma, cf, *de novo* transition

at ~ 450 nm is indicative of bilirubin being present within the refluxate. However, in an acidic environment (pH < 3.5) bilirubin dimerisation occurs, which results in a change in the absorption wavelength to 400 nm, which can affect bilirubin estimation by 30%.³³

Endoluminal ultrasonography can be used to assess epithelial depth in Barrett's oesophagus, especially in the presence of macroscopically normal epithelium. This may be increased in comparison to normal epithelium. Thus far, it has been difficult to differentiate accurately between high-grade dysplasia and carcinoma *in situ*.³⁴

Management

CONSERVATIVE MANAGEMENT

The management of Barrett's oesophagus incorporates symptomatic control (where applicable) and ideally should promote regression of the metaplastic epithelium. The diagnosis alone does not justify surgery, but does warrant surveillance, in view of the potential for malignant transformation.

As GORD is the principal aetiological factor (both acid and bile reflux), symptomatic control through the use of full-dose proton pump inhibitors and prokinetic agents should be initiated. Failure of this regime may be due to the failure of prevention of duodenogastro-oesophageal reflux,²⁷ resulting in primarily bile reflux. Recurrent relapse or patients who prove refractory to conservative management, with no evidence of high-grade dysplasia, should be considered for antireflux surgery.

SURGICAL MANAGEMENT

Various modifications of Nissen's original fundoplication procedure have been described, whose main aims are to correct those parameters which are responsible for defective LOS function, as discussed previously. The surgical principles involved are crural repair of the oesophageal hiatus, with nonabsorbable sutures and full mobilisation of the gastric fundus (with division of the short gastric vessels) to ensure a tension-free wrap. A large oesophageal bougie (50 Fr) further facilitates this. This should enable LOS pressure to be restored (both by a squeeze effect, as produced by the smooth muscle of the gastric fundus, and by the augmentation of the intrinsic action of the LOS, due to the gastric wrap). LOS length is restored, inclusive of intra-abdominal length.³⁵ The production of a supra-competent sphincter may be the cause of the morbidity associated with the procedure.³⁶

The advent of the laparoscopic approach and the high relapse rates associated with conservative management regimes has resulted in the surgical management of GORD gaining in popularity. This has not been mirrored in the management of Barrett's oesophagus as yet.

Anti-reflux surgery may promote partial regression of the metaplastic epithelium, although it is argued that this is due to surgical relocation of the squamocolumnar junction.³⁷ In addition, columnar epithelium has been reported underlying the regenerating squamous epithelium, which suggests that life-long surveillance is warranted.³⁸

Reports of complete regression postoperatively tend to be anecdotal and there is no evidence to support the contention that anti-reflux surgery can be used as a prophylactic measure against adenocarcinoma.³⁰ In fact, there have been many reports of adenocarcinoma following successful anti-reflux surgery.^{39, 40} Bile reflux may be counteracted by a duodenal diversion procedure. This significantly reduces inflammation, but does not promote regression of the metaplastic epithelium.⁴¹

LASER THERAPY

The diagnosis of high-grade dysplasia has resulted in the traditional dilemma of whether one should opt for surgical intervention, namely oesophagectomy, in association with its attendant morbidity and mortality, local endoscopic ablation, or surveillance. Clearly, in view of the high incidence of carcinoma *in situ* diagnosed retrospectively following oesophagectomy (50%) for what was originally presumed to be high-grade dysplasia, some form of intervention is desirable.

Endoscopic laser ablation using the Nd YAG laser in conjunction with full-dose proton pump inhibitors, has failed to produce any regression of the metaplastic epithelium in comparison to controls. However, encouraging results have been produced in a short series with the combination of anti-reflux surgery and subsequent Nd YAG laser ablation.²⁷

Endoscopic argon beam plasma coagulation has demonstrated encouraging early results in the regeneration of squamous epithelium in Barrett's oesophagus and in the cure of early upper gastrointestinal malignancies.⁴² It may prove an

Summary points

- approximately 50% of patients with Barrett's oesophagus have recognised complications on presentation
- light-induced fluorescence endoscopy may be used to differentiate between normal, dysplastic epithelium and early malignant change, in the presence of macroscopically normal epithelium
- the diagnosis of Barrett's oesophagus in the absence of dysplastic epithelium, does not warrant surgery, unless symptomatic relapse occurs following a course of conservative management
- high-grade dysplasia is associated with a diagnosis of carcinoma *in situ* in 50% of cases, following oesophagectomy
- argon beam plasma coagulation and photodynamic therapy are likely to become the therapeutic tools of choice for the management of high-grade dysplasia

alternative option to surgery in the medically unfit, although long-term surveillance remains mandatory in order to monitor the regenerated epithelium.

Local endoscopic mucosal resection, has similarly been reserved for the medically frail. Given its low local recurrence rate (3–7%), a 5-year survival rate of 95–100% and low morbidity,²⁷ it is being used increasingly in the management of Barrett's oesophagus.

The role of endoscopic photodynamic therapy in high-grade dysplasia has generated encouraging short-term results. Following the oral administration of 5-aminolaevulinic acid, the endogenously synthesised photosensitizing agent, protoporphyrin IX, is selectively taken up by dysplastic epithelium. This is detected by fluorescence microscopy, prior to laser-induced necrosis of the dysplastic epithelium.

Barr *et al* reported that squamous epithelial regeneration occurred after the use of proton pump inhibitors in a series of five patients. The presence of non-dysplastic columnar epithelium underlying regenerating squamous epithelium, occurred in two patients, again warranting life-long surveillance. There was no associated morbidity.⁴³

MANAGEMENT OF CARCINOMA

The treatment of choice for a histologically proven early oesophageal adenocarcinoma or where there is a high index of suspicion in high-grade dysplasia, should be a radical subtotal oesophagectomy and lymphadenectomy. Oesophageal adenocarcinomas metastasise to either the para-oesophageal, lower mediastinal, or paracardial nodes, necessitating their removal.⁴⁴ It is debatable whether this can be achieved through a trans-hiatal approach.

The future

The identification, at a molecular level, of tumour markers, cell adhesion molecules or growth factors may have a potential role in the objective differentiation of high-grade dysplasia from carcinoma *in situ*, eg, the reduced or disorganised expression of E cadherin, a calcium-dependent cell adhesion molecule, has been associated with increased metastatic potential in Barrett's oesophagus⁴⁵ and other malignancies. Similarly, overexpression of mutant forms of the tumour suppressor gene p53 have been identified in oesophageal adenocarcinoma. This is particularly pertinent with worsening tumour grade. Identification is not solely restricted to malignancies, but is also evident to a lesser degree in dysplastic epithelium. In Barrett's oesophagus, it has been suggested that the mutation occurs at an early stage, prior to the progression to malignant change.¹²

Surveillance endoscopy is expensive, but can be justified by the fact that the diagnosis of Barrett's oesophagus represents a 30–125-fold increased risk of developing oesophageal adenocarcinoma. The 5-year survival figures for the management of early, lymph-node-negative disease is over 50%, in comparison to 5–10% for advanced disease.

The encouraging results that have been obtained with endoscopic argon beam plasma coagulation and photodynamic therapy in the management of high-grade dysplasia, are currently associated with relatively low morbidity. The adoption of these minimally invasive techniques may result in their use as an alternative to conventional oesophagectomy in the future management of premalignant epithelium in Barrett's oesophagus.

- Hogan WJ. Malignant degeneration of Barrett's esophagus: malignant potential of 'short-segment' Barrett's esophagus. *Dis Esophagus* 1995;8:93–8.
- Barrett NR. Chronic peptic ulcer of the esophagus and esophagitis. *Br J Surg* 1950;38:175–82.
- Allison PR, Johnston AS. The esophagus lined with gastric mucous membrane. *Thorax* 1953;8:87–101.
- Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histological spectrum of Barrett's esophagus. *N Engl J Med* 1976;295:476–80.
- Cameron AJ. Epidemiologic studies and the development of Barrett's esophagus. *Endoscopy* 1993;25:635–6.
- Iascone C, DeMeester TR, Little AG, *et al*. Barrett's esophagus: functional assessment, proposed pathogenesis, and surgical therapy. *Arch Surg* 1983;118:543–9.
- Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. *Gastroenterology* 1992;103:1241–5.

- Hassal E, Weinstein WM, Ament ME. Barrett's esophagus in childhood. *Gastroenterology* 1985;89:1331–7.
- Mann NS, Tsai MF, Nair PK. Barrett's esophagus in patients with symptomatic reflux esophagitis. *Am J Gastroenterol* 1989;84:1494–6.
- Schnell T, Sontag S, Wanner J, Chintam R, Chejfec G, O'Connell J. Endoscopic screening for Barrett's esophagus, esophageal adenocarcinoma, and other mucosal changes in ambulatory subjects with symptomatic gastroesophageal reflux. *Gastroenterology* 1985;88:A157.
- Lambert R. Review article: current practice and future perspectives in the management of gastro oesophageal reflux disease. *Aliment Pharmacol Ther* 1997;11:651–62.
- Schneider PM, Casson AG, Roth JA. Malignant degeneration of Barrett's esophagus: the role of the p53 tumour-suppressor-gene. *Dis Esophagus* 1995;8:99–103.
- Wright TA. High-grade dysplasia in Barrett's esophagus. *Br J Surg* 1997;84:760–6.
- Richter JE. Management of gastro oesophageal reflux disease 1995. Pathophysiological basis of

therapy for gastro oesophageal reflux disease. *Dis Esophagus* 1994;7:223–9.

- Zaninotto G, De Meester TR, Schwizer W, Johansson KE, Cheng SC. The lower esophageal sphincter in health and disease. *Am J Surg* 1988;155:104–11.
- Bremner CG, Lynch VP, Ellis FH. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. *Surgery* 1970;68:209–16.
- Hirschowitz BI. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. *Gastroenterology* 1991;101:1149–335.
- Gillen P, Keeling P, Byrne PJ, West AB, Hennessy TPJ. Experimental columnar metaplasia in the canine esophagus. *Br J Surg* 1988;75:113–5.
- Ifitkhar SY, Ledingham S, Steele RJ, *et al*. Bile reflux in columnar-lined Barrett's esophagus. *Ann R Coll Surg* 1993;75:411–6.
- Champion G, Richter J E, Vaezi M F, Singh S, Alexander R. Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. *Gastroenterology* 1994;107:747–54.

- 21 Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barrett's oesophagus. *Gut* 1997;40:9-13.
- 22 Ricaurte O, Flejou JF, Vissuzaine C, et al. *Helicobacter pylori* infection in patients with Barrett's oesophagus: a prospective immunohistochemical study. *J Clin Pathol* 1996;49:176-7.
- 23 Olyae M, Sontag S, Salman W, et al. Mucosal reactive oxygen species production in oesophagitis and Barrett's oesophagus. *Gut* 1995;37:168-73.
- 24 Pera M, Duranceau A. Malignant degeneration of Barrett's esophagus: epidemiology of Barrett's esophagus and esophageal adenocarcinoma. *Dis Esophagus* 1995;8:86-92.
- 25 Williamson WA, Ellis FH, Gibb SP, et al. Barrett's esophagus: prevalence and incidence of adenocarcinoma. *Arch Intern Med* 1991;151:2212-6.
- 26 Herlihy KJ, Orlando RC, Bryson JC, Bozyski EM, Carney CN, Powell DW. Barrett's esophagus: clinical, endoscopic, histologic, manometric and electrical potential difference characteristics. *Gastroenterology* 1984;86:436-43.
- 27 Salo JA. Malignant degeneration of Barrett's esophagus: the role of laser ablation and anti-reflux surgery. *Dis Esophagus* 1995;8:109-10.
- 28 Johnson DA, Winters C, Spurling TJ, Chobanian SJ, Cattau EL. Esophageal acid sensibility in Barrett's esophagus. *J Clin Gastroenterol* 1987;9:23-7.
- 29 Bremner RM, Bremner CG. Barrett's oesophagus - radiological features in 100 cases. *S Afr Med J* 1990;78:660-4.
- 30 Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. *Lancet* 1994;344:1533-6.
- 31 Geisinger KR, Teot LA, Richter JE. A comparative cytopathologic and histologic study of atypia, dysplasia, and adenocarcinoma in Barrett's esophagus. *Cancer* 1992;69:8-16.
- 32 von-Holstein CS, Nilsson AM, Andersson-Engels S, Willen R, Walther B, Svanberg K. Detection of adenocarcinoma in Barrett's oesophagus by means of laser induced fluorescence. *Gut* 1996;39:711-6.
- 33 Becchi P. Fibreoptic measurement of alkaline gastro esophageal reflux: technical aspects and clinical indications. *Dis Esophagus* 1994;7:131-8.
- 34 Yoshikane H, Tsukamoto Y, Niwa Y, et al. Superficial esophageal carcinoma: evaluation by endoscopic ultrasonography. *Am J Gastroenterol* 1994;89:702-7.
- 35 Little AG. Nissen fundoplication for gastro-esophageal reflux disease: How does Nissen fundoplication prevent reflux? *Diseases of the Esophagus* 1996;9:247-50.
- 36 DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastro-esophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg* 1986;204:9-20.
- 37 Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. *Br J Surg* 1996;83:274-8.
- 38 Skinner DB, Walther BC, Riddell RH, Schmidt H, Iacone C, De Meester TR. Barrett's oesophagus. Comparison of benign and malignant cases. *Ann Surg* 1983;198:554-65.
- 39 Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg* 1993;105:383-8.
- 40 Rosenberg JC, Budev H, Edwards R C, Singal S, Steiger Z, Sundareson AS. Analysis of adenocarcinoma in Barrett's esophagus utilising a staging system. *Cancer* 1985;55:1353-60.
- 41 Spencer J. Surgery in Barrett's oesophagus. *Eur J Cancer Prev* 1992;1:331-5.
- 42 Byrne JP, Armstrong G R, Attwood SEA. Endoscopic argon beam plasma coagulation in the restoration of squamous lining in Barrett's oesophagus. *Endoscopy* 1997;29:302.
- 43 Barr H, Shepherd NA, Dix A, Roberts DJ, Tan WC, Krasner N. Eradication of high-grade dysplasia in columnar-lined (Barrett's) oesophagus by photodynamic therapy with endogenously generated protoporphyrin. *Lancet* 1996;348:584-5.
- 44 Holscher AH, Bollschweiler E, Schneider PM, Siewert JR. Early adenocarcinoma in Barrett's oesophagus. *Br J Surg* 1997;84:1470-3.
- 45 Bongiorno PF, al-Kasspoles M, Lee SW, et al. E-Cadherin expression in primary and metastatic thoracic neoplasms and in Barrett's oesophagus. *Br J Cancer* 1995;71:166-72.