Surveillance and screening of Barrett's oesophagus

The management of patients with Barrett's oesophagus is a controversial topic which needs attention in view of the alarming increase in oesophageal adenocarcinoma. Current surveillance methods are not cost-effective and better methods for risk stratification are needed. The majority of Barrett's patients are undiagnosed and this has prompted a discussion about a screening programme aimed at detecting all Barrett's patients.

The development of oesophageal adenocarcinoma (AC) is a multi-step process. The oesophageal squamous epithelium (NE) first undergoes a metaplastic change into a columnar-type epithelium called Barrett's oesophagus (BE) and this resultant metaplastic tissue may then progress to AC through a series of histopathological changes according to the multi-step model of carcinogenesis (Hanahan and Weinberg, 2000).

According to the updated guidelines for the diagnosis, surveillance and therapy of BE published by the American College of Gastroenterology (ACG) in 2002, BE is defined as:

> **'a change in the oesophageal epithelium, of any length, that can be recognized at endoscopy and is confirmed to have intestinal metaplasia (IM) by biopsy of the tubular oesophagus and excludes intestinal metaplasia of the cardia' (Sampliner, 2002).**

There are currently no European guidelines, although the British Society of Gastroenterology published guidelines last year (British Society of Gastroenterology, 2005). BE can be diagnosed endoscopically by its salmon pink colour, contrasting with the pale pink NE, extending above the gastro-oesophageal junction into the oesophagus. The endoscopic appearance must then be corroborated by histopathological evidence of columnar epithelium. The likelihood of diagnosing intestinal metaplasia (IM) increases with the number of biopsies taken because of the heterogeneous nature of the mucosa (Levine et al, 1993).

Currently early detection of cancers in people with a history of BE is performed through endoscopic surveillance procedures and the merit of setting up a screening programme to identify new BE cases is being discussed by associations of gastroenterologists worldwide. These issues are subject to controversy. Some parties are vehemently for or against the current surveillance practice, while others wish to create a new composite surveillance/screening programme using more sensitive and specific clinical tools.

Surveillance

Clinical protocols

BE surveillance programmes aim to detect patients at risk of progression to cancer so that therapeutic options can be decided according to the perceived risk of cancer development. The guidelines from the ACG suggest that:

> **'the grade of dysplasia determines the endoscopy interval, and an abnormal epithelial surface such as a nodule or ulcer requires special sampling attention. Surveillance endoscopy intervals are lengthening in the absence of dysplasia on two consecutive endoscopies with biopsy, a 3 year interval is appropriate' (Sampliner, 2002).**

Although not officially endorsed, the 'Seattle protocol' for surveillance has been recommended for optimum detection of IM and high grade dysplasia (HGD) (Levine et al, 1993). This protocol proposes that endoscopists should take quadrantic biopsies at 2 cm intervals along the BE segment with jumbo biopsy forceps. However, this biopsy procedure is not routinely performed. An American study where questionnaires regarding surveillance were sent to 1000 randomly selected members of the clinical practice section of the ACG demonstrated that 96% of respondents performed endoscopic surveillance. Furthermore, 23% of physicians performed random biopsies, 77% performed quadrantic biopsies every 2 cm and most (83%) used standard capacity forceps rather than jumbo biopsy forceps (Falk et al, 2000). In a similar study in the UK, 76% of physicians considered surveillance worthwhile and only 41% followed the Seattle protocol with standard biopsy forceps and 44% biopsied a 'random and suspicious areas protocol' (Mandal et al, 2003).

Arguments for and against surveillance

At gastroenterology meetings and in gastroenterology journals, debates on the usefulness of surveillance have taken place. The main reason advocated for endoscopic surveillance is that a greater proportion of surveillance diagnosed AC were early tumours when compared to newly diagnosed AC (Streitz et al, 1993; Peters et al,

Dr Pierre Lao-Sirieix *is MRC Career Development Fellow and*
Dr Rebecca Fitzgerald *is MRC Programme Leader and Honorary Consultant Gasteroenterologist, MRC Cancer Cell Unit Hutchinson-MRC Research Centre, Cambridge CB2 2XZ*

Correspondence to: Dr R Fitzgerald

1994; Wright et al, 1996). Although many practitioners do not subscribe to the Seattle protocol there are data suggesting that rigorous surveillance increases the pick-up rate of early tumours (Fitzgerald et al, 2001). In the study describing the Seattle protocol, patients who were detected with HGD and early tumours did not require surgery (Levine et al, 1993).

Importantly, early tumours have better 5-year survival rates (62–90%) compared to cancers detected de novo (20%) (Streitz et al, 1993; Peters et al, 1994; Wright et al, 1996). These data suggest that surveillance can be useful for individual patients as less invasive treatment methods may be required when cancer is detected early and their survival is greatly increased. Furthermore, the postoperative survival of surveillance diagnosed AC (12 patients with a mean survival of 107 months) was shown to be greater than that of de novo diagnosed AC (68 patients with a mean survival of 12 months) (Corley et al, 2002). However, it should be remembered that surveillance detected cancers may be prone to lead time bias, i.e. patients may be diagnosed earlier rather than actually surviving longer.

On the other hand, the risk of progression from BE through dysplasia to AC is apparently not as high as previously believed. Indeed in several studies amounting to a total of 780 patients followed up for 2.9–7.3 years, the risk of progression to AC was 2% for non-dysplastic BE, 7% for low grade dysplasia (LGD) and 22% for HGD (Sampliner, 2002). Furthermore, the diagnosis of dysplasia is very subjective with high inter- and intra-observer variability (Reid et al, 1988; Macdonald et al, 1997). The currently accepted incidence rate of AC occurring in BE is 0.5% per patient per year (Shaheen et al, 2000), although in the UK it is likely to be nearer to 1% (Jankowski et al, 2002). Furthermore, it is not clear whether BE is a prerequisite for the development of AC. It has been suggested that only 5% of AC cases had a background of BE (Dulai et al, 2002), but it is likely that tumours encompassing a large amount of the distal oesophagus will have over-grown a potential BE segment. Indeed, preoperative chemotherapy unmasked BE in 91% (72/79) of patients with AC in the distal oesophagus (Theisen et al, 2002). Another consideration is that a significant number of BE patients are asymptomatic and therefore would not have been endoscoped and given the opportunity to enrol in a surveillance programme. It is well known that a large number of patients remain undiagnosed in the population (Gerson et al, 2002).

Taken together these data suggest that only a small proportion of BE patients are surveilled and that the risk of progression in those patients, even those with dysplasia, is small. The question arises therefore, whether the cancer risk warrants a procedure which is so time consuming, expensive and uncomfortable for patients. Indeed most BE patients (97.5%) die of causes unrelated to AC (van der Burgh et al, 1996) and it has been suggested that being involved in a surveillance programme might cause distress to patients, although this last point has never been substantiated by a systematic study examining the effect of surveillance on quality of life. Furthermore, the general consensus is that the current surveillance programme is not cost effective but that a modification of the existing protocol would be. Endoscopic surveillance of non-dysplastic BE patients every 5 years would yield a cost effectiveness similar to that of other medical practice while improving life expectancy (Streitz et al, 1998; Pabst et al, 1999).

The other considerations are practical ones concerning the current reliance on endoscopy, multiple biopsies and the histopathological diagnosis of dysplasia. According to which definition is used, BE may affect up to 1% of the population in the westernized world (Cameron, 2002). The population of the UK is currently around 60 million inhabitants; if 1% of those have BE, the national burden will be approximately 600 000 cases. If these 600 000 patients had to be followed up every 3 years, the endoscopy units would have to cope with 560 patients per day including weekends and bank holidays. Similar calculations can be applied to other parts of the western world and it seems unlikely that most health-care systems could cope with the endoscopic workload that would be generated by surveillance if all cases were identified.

The diagnosis of dysplasia relies on random sampling of the BE segment. In a 6 cm segment, up to 24 jumbo biopsies should be taken in order to have an accurate diagnosis of dysplasia (Levine et al, 1993). Assuming that the segment is circumferential in the oesophagus, that a jumbo forceps takes a 2 mm sample and that the oesophagus is 4 cm in diameter, the surface sampled would be less than 0.5% of the BE segment. Furthermore, it has been demonstrated that the BE segment is not necessarily composed of a single clonal expansion (Maley et al, 2004). Therefore, relying so heavily on luck to biopsy the clone of interest should not be condoned as good medical practice. Currently in the UK, neither the jumbo forceps nor the quadrantic biopsy every 2 cm are being used routinely, reducing even further the surface of the oesophagus being sampled (Mandal et al, 2003).

The need for an alternative to dysplasia as a measure of the risk of progression, with a better sampling technique that would allow for automation, is direly needed (see below). However, even a perfect surveillance test with 100% sensitivity and specificity for identifying curable neoplasms will do little to decrease overall oesophageal cancer mortality if it is used in a minority of the population at risk. As a result, it has been suggested that screening endoscopy should be performed in persons with heartburn, who are most at risk for developing BE and AC (Sampliner, 2002).

Endoscopic screening

While surveillance refers to the monitoring of patients already diagnosed with BE in order to detect HGD and AC, screening aims to detect patients with undiagnosed

BE in the population. Screening could either be applied to the whole population or could be targeted to a particular group of people according to their likely risk of having BE.

The guidelines from the ACG suggest that 'patients with chronic gastro-oesophageal reflux disease (GORD) symptoms are those most likely to have BE and should undergo upper endoscopy'. Although the official American guidelines suggest that screening should be performed on all GORD patients, it is not common practice in the USA and is not practiced routinely in the UK.

Since it is estimated that 10–20% of the population suffer from GORD there is concern about the high cost of performing endoscopies on all patients with GORD. In addition, although the risks associated with endoscopies are low they are not nil and there might be legal consequences if a complication arose (Spechler and Barr, 2004). Furthermore, a cohort of over 400 patients who underwent surveillance for BE showed that only 30% had been referred originally for endoscopy because of GORD symptoms (Macdonald et al, 1997). The other 70% were 'chance' findings in patients endoscoped for other reasons and some of these patients had never suffered from GORD. Screening GORD sufferers for BE will, on the one hand, include an insurmountable number of patients with only a minority having BE and, on the other hand, miss a large number of BE patients. Therefore, identification of risk factors independent from GORD, such as genetic susceptibility factors, might help in identifying patients at risk for development of BE.

From the small body of literature assessing the cost effectiveness of endoscopic screening, such a programme would only be cost effective if men at the age of 50 years underwent a single life-time screen followed by surveillance of dysplastic BE patients only (Soni et al, 2000; Inadomi et al, 2003). However, this favourable outcome depends on a diagnostic test with a high sensitivity and specificity as well as a high prevalence of BE and HGD. In contrast, screening followed by surveillance of non-dysplastic BE at less than 5-year intervals was associated with incremental cost effectiveness ratios without a significant increase in the quality-adjusted life year (Soni et al, 2000; Inadomi et al, 2003).

Alternative approaches to surveillance and screening

In view of the high cost and ineffectiveness of the current endoscopic screening and surveillance techniques, alternative methods are being evaluated.

There has been interest in evaluating a scoring system to help determine which patients are most likely to have BE and should undergo endoscopy. Several patient questionnaires have been developed which take into account the patient demographics and symptoms. Unfortunately the sensitivity and specificity obtained in two studies using symptom questionnaires to detect BE were not high enough to be clinically useful (sensitivity ~60% and specificity of ~80% for both studies) (Gerson et al, 2001; Lock et al, 2003).

A number of endoscopic techniques which utilize the physical properties of dysplastic compared to non-dysplastic tissue are being developed in order to target biopsies towards the mucosal area of interest. For example, the fluorescence emitted by protoporphyrin IX induced following oral administration of amino-laevulinic acid can be measured in pre-malignant lesions. The detection rates of dysplasia are low (28%) with a high number of false positives, mainly as a result of inflammation, but this technique is still in its early stages (Stepinac et al, 2003). Similarly, tissues will scatter photons depending on their molecular composition. Raman spectroscopy uses this property for predicting the histopathological diagnosis of BE. The results obtained were very promising with a specificity of ~70% and a sensitivity of ~90% (Kendall et al, 2003).

The current approach to identify alternatives for the detection of patients at risk of progression is the assessment of biomarkers in biopsy samples. To date more than 60 biomarkers with potential have been identified but only a handful were proven to be markers of progression to AC (for review see Reid et al, 2003). The best predictor of cancer progression, identified by the Reid group in Seattle, is the presence of aneuploidy (multiple chromosome numbers) and loss of heterozygosity (LOH) on 17p with a relative risk of progression of 46 (95% confidence intervals 16–137). The sensitivity and specificity of this test to detect patients who will progress to AC are 95% (Galipeau et al, 2004).

Detection of these markers still relies on biopsies, but work is being carried out to adapt them to cytological techniques using endoscopic brushes and balloons. These techniques are able to sample a larger area of the BE segment at a lower cost (Falk, 2002). Indeed, early studies demonstrated a 75% concordance between cytological and histopathological diagnoses of BE and AC (Geisinger et al, 1992; Geisinger, 1995) but a more recent study reported a detection rate of only 8% for BE (diagnosed by the presence of goblet cells), 3% for LGD, 10% for HGD and 9% for AC compared with standard histopathological assessment of a biopsy (Saad et al, 2003). In 1997, Hardwick et al, using a cohort of 65 non-dysplastic BE and 92 AC or HGD, reported a sensitivity and specificity of 89% for the detection of AC or HGD by cytology. Hence, cytology alone is poor at diagnosing BE although the rates of detection of HGD and AC were adequate. Such an approach is a promising surveillance technique, provided biomarkers are identified that will increase the sensitivity and specificity of cytological diagnosis alone.

To adapt the Reid markers to a cytological sampling system, a number of groups have used fluorescent in-situ hybridization (FISH) with locus-specific probes to iden-

tify regions of LOH. Furthermore, aneuploidy could be identified either by FISH for centromeric probes or image cytometry (Fahmy et al, 2004; Borovicka et al, 2005; Brankley et al, 2005; Rossi et al, 2005). Authors argued that patients at risk of progression could be identified although none compared the results obtained to the accepted method developed by the Reid group.

Simpler methods relying on immunohistochemistry have also been assessed. In a small study, expression of p53 was shown to correlate in 9 out of 11 patients in biopsies and cytology samples from the same patients (Tsai et al, 1997). The expression of villin, a brush border protein expressed by intestinal metaplastic tissue, was assessed in oesophageal brushings to detect BE with a view to being developed as a screening tool; 81% of BE samples (17 out of 21) had brushings positive for villin expression, while none of the squamous or gastric samples were positive (MacLennan et al, 1999).

The authors' group has shown that minichromosome maintenance (MCM) proteins, proteins essential to DNA replication, were markers of progression to AC. Immunostaining for Mcm in endoscopic brushings allowed for the detection of Barrett's patients at risk of progression to cancer (Sirieix et al, 2003). Furthermore, Mcm were used to detect oesophageal cancers using an immunofluorometric assay on gastric aspirates. Although a sensitivity and specificity of 85% for the detection of oesophageal cancers was obtained, this technique has not yet been applied to the detection of BE (Williams et al, 2004).

Although the techniques described above still rely on endoscopy, Gary Falk has proposed the use of non-endoscopic brushing techniques similar to those that have been used in Iran and China for decades. The sensitivity and specificity of detection of LGD, HGD, and AC with non-endoscopic balloon cytology was low and similar to that of brush cytology (Falk et al, 1997). This approach was therefore abandoned. In the advent of newly identified biomarkers, refinement of this approach might lead to a cheap alternative to endoscopic screening and might also help in stratifying patients according to their risk of progression.

KEY POINTS

- Early detection of Barrett's adenocarcinoma is necessary for curative treatment.
- Endoscopic treatment is used increasingly for treating early cancers.
- The current surveillance programme is subject to controversy.
- Alternative surveillance methods are being evaluated.
- A screening programme is needed as a large proportion of Barrett's patients remain undiagnosed.
- Ongoing research includes novel methods for targeting endoscopic biopsies and risk stratification using biomarkers.

Conclusions

Current surveillance protocols are subject to controversy and not all practitioners subscribe to the idea of endoscopic surveillance. For either screening or surveillance to be useful for decreasing the mortality and morbidity associated with AC as well as being cost effective, new technologies and approaches are required. **BJHM**

Conflict of interest: none.

Borovicka J, Schonegg R, Kradolfer D et al (2005) Combined digital image cytometry with fluorescence in situ hybridization of brush cytology identifies patients with Barrett's esophagus at increased risk for neoplastic progression. *Gastroenterology* **128**(4(suppl 2)): 642

Brankley SM, Anderson MA, Harwood AR et al (2005) Genetic alterations detected by FISH in endoscopic brushing specimens taken from Barrett's esophagus with biopsy-proven metaplasia, dysplasia or adenocarcinoma. *Proc Am Assoc Cancer Res* **46:** 1906

British Society of Gastroenterology (2005) *Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus*. British Society of Gastroenterology, Loughborough, Leicestershire (http://www.bsg.org.uk/pdf_word_docs/Barretts_Oes.pdf)

Cameron AJ (2002) Epidemiology of Barrett's esophagus and adenocarcinoma. *Dis Esophagus* **15**(2): 106–8

Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA (2002) Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology* **122**(3): 633–40

Dulai GS, Guha S, Kahn KL, Gornbein J, Weinstein WM (2002) Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. *Gastroenterology* **122**(1): 26–33

Fahmy M, Skacel M, Gramlich TL et al (2004) Chromosomal gains and genomic loss of p53 and p16 genes in Barrett's esophagus detected by fluorescence in situ hybridization of cytology specimens. *Mod Pathol* **17**(5): 588–96

Falk GW (2002) Barrett's esophagus. *Gastroenterology* **122**(6): 1569–91

Falk GW, Chittajallu R, Goldblum JR et al (1997) Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* **112**(6): 1787–97

Falk GW, Ours TM, Richter JE (2000) Practice patterns for surveillance of Barrett's esophagus in the united states. *Gastrointest Endosc* **52**(2): 197–203

Fitzgerald RC, Saeed IT, Khoo D, Farthing MJ, Burnham WR (2001) Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. *Dig Dis Sci* **46**(9): 1892–8

Galipeau PC, Li X, Longton G et al (2004) A panel of molecular and cytmoteric markers in Barrett's Esophagus (BE) predicts progression to esophageal adenocarcinoma (AC). *Gastroenterology* **126**(suppl 2): A–822

Geisinger KR. (1995) Endoscopic biopsies and cytologic brushings of the esophagus are diagnostically complementary. *Am J Clin Pathol* **103**(3): 295–9

Geisinger KR, Teot LA, Richter JE (1992) A comparative cytopathologic and histologic study of atypia, dysplasia, and adenocarcinoma in Barrett's esophagus. *Cancer* **69**(1): 8–16

Gerson LB, Edson R, Lavori PW, Triadafilopoulos G (2001) Use of a simple symptom questionnaire to predict Barrett's esophagus in patients with symptoms of gastroesophageal reflux. *Gastroenterology* **96**(7): 2005–12

Gerson LB, Shetler K, Triadafilopoulos G (2002) Prevalence of Barrett's esophagus in asymptomatic individuals. *Gastroenterology* **123**(2): 461–7

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* **100**(1): 57–70

Hardwick RH, Morgan RJ, Warren BF, Lott M, Alderson D (1997) Brush cytology in the diagnosis of neoplasia in Barrett's esophagus. *Dis Esophagus* **10**(4): 233–7

Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N (2003) Screening and surveillance for Barrett esophagus in

high-risk groups: a cost-utility analysis. *Ann Intern Med* **138**(3): 176–86
Jankowski JA, Provenzale D, Moayyedi P (2002) Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. *Gastroenterology* **122**(2): 588–90
Kendall C, Stone N, Shepherd N et al (2003) Raman spectroscopy, a potential tool for the objective identification and classification of neoplasia in Barrett's oesophagus. *J Pathol* **200**(5): 602–9
Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ (1993) An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* **105**(1): 40–50
Locke GR, Zinsmeister AR, Talley NJ (2003) Can symptoms predict endoscopic findings in GERD? *Gastrointest Endosc* **58**(5): 661–70
Macdonald CE, Wicks AC, Playford RJ (1997) Ten years' experience of screening patients with Barrett's oesophagus in a university teaching hospital. *Gut* **41**(3): 303–7
MacLennan AJ, Orringer MB, Beer DG (1999) Identification of intestinal-type Barrett's metaplasia by using the intestine-specific protein villin and esophageal brush cytology. *Mol Carcinog* **24**(2): 137–43
Maley CC, Galipeau PC, Li X, Sanchez CA, Paulson TG, Reid BJ (2004) Selectively advantageous mutations and hitchhikers in neoplasms: p16 lesions are selected in Barrett's esophagus. *Cancer Res* **64**(10): 3414–27
Mandal A, Playford RJ, Wicks AC (2003) Current practice in surveillance strategy for patients with Barrett's oesophagus in the UK. *Aliment Pharmacol Ther* **17**(10): 1319–24
Pabst O, Zweigerdt R, Arnold HH (1999) Targeted disruption of the homeobox transcription factor Nkx2-3 in mice results in postnatal lethality and abnormal development of small intestine and spleen. *Development* **126**(10): 2215–25
Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR (1994) Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg* **108**(5): 813–21; discussion 821–2
Reid BJ, Haggitt RC, Rubin CE et al (1988) Observer variation in the diagnosis of dysplasia in Barrett's esophagus. *Hum Pathol* **19**(2): 166–78
Reid BJ, Blount PL, Rabinovitch PS (2003) Biomarkers in Barrett's esophagus. *Gastrointest Endosc Clin N Am* **13**(2): 369–97
Rossi E, Della Casa D, Villanacci V et al (2005) Dysplasia in Barrett's esophagus- fluorescence in situ hybridization (fish): a new approach. *Gastroenterology* **128**(4(suppl2)): S1709
Saad RS, Mahood LK, Clary KM, Liu Y, Silverman JF, Raab SS (2003) Role of cytology in the diagnosis of Barrett's esophagus and associated neoplasia. *Diagn Cytopathol* **29**(3): 130–5
Sampliner RE (2002) Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* **97**(8): 1888–95
Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS (2000) Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* **119**(2): 333–8
Sirieix PS, O'Donovan M, Brown J, Save V, Coleman N, Fitzgerald RC (2003) Surface expression of minichromosome maintenance proteins provides a novel method for detecting patients at risk for developing adenocarcinoma in Barrett's esophagus. *Clin Cancer Res* **9**(7): 2560–6
Soni A, Sampliner RE, Sonnenberg A (2000) Screening for high-grade dysplasia in gastroesophageal reflux disease: is it cost-effective? *Am J Gastroenterol* **95**(8): 2086–93
Spechler SJ, Barr H (2004) Review article: screening and surveillance of Barrett's oesophagus: what is a cost-effective framework? *Aliment Pharmacol Ther* **19**(Suppl 1): 49–53
Stepinac T, Felley C, Jornod P et al (2003) Endoscopic fluorescence detection of intraepithelial neoplasia in Barrett's esophagus after oral administration of aminolevulinic acid. *Endoscopy* **35**(8): 663–8
Streitz JM Jr, Andrews CW Jr, Ellis FH Jr (1993) Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg* **105**(3): 383–7; discussion 387–8
Streitz JM Jr, Ellis FH Jr, Tilden RL, Erickson RV (1998) Endoscopic surveillance of Barrett's esophagus: a cost-effectiveness comparison with mammographic surveillance for breast cancer. *Am J Gastroenterol* **93**(6): 911–15
Theisen J, Stein HJ, Dittler HJ et al (2002) Preoperative chemotherapy unmasks underlying Barrett's mucosa in patients with adenocarcinoma of the distal esophagus. *Surg Endosc* **16**(4): 671–3
Tsai TT, Bongiorno PF, Orringer MB, Beer DG (1997) Detection of p53 nuclear protein accumulation in brushings and biopsies of Barrett's esophagus. *Cancer Detect Prev* **21**(4): 326–31
van der Burgh A, Dees J, Hop WC, van Blankenstein M (1996) Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut* **39**(1): 5–8
Williams GH, Swinn R, Prevost AT et al (2004) Diagnosis of oesophageal cancer by detection of minichromosome maintenance 5 protein in gastric aspirates. *Br J Cancer* **91**(4): 714–19
Wright TA, Gray MR, Morris AI et al (1996) Cost effectiveness of detecting Barrett's cancer. *Gut* **39**(4): 574–9