Barrett’s oesophagus is defined as columnar-lined oesophagus of any length containing specialised intestinal metaplasia. Diagnosis depends on close corroboration between the endoscopist and histopathologist. It occurs in 10% of patients presenting endoscopically with reflux symptoms and has an adenocarcinoma incidence of 0.4% to 2%. Surveillance is performed to detect precancerous change (dysplasia) and early stage disease has a good surgical prognosis. Computer models suggest cost efficacy comparable to other health measures. However most patients with Barrett’s do not die of oesophageal cancer and elective oesophagectomy has an appreciable mortality. Endoscopic ablation techniques and improved definition of high risk subgroups will help shape future surveillance programmes.

In 1950 Norman Barrett described the columnar-lined oesophagus, which he considered to be a congenital abnormality. It is now accepted that Barrett’s oesophagus represents the metaplastic adaptation of the distal oesophageal squamous epithelium to a columnar lining containing specialised intestinal metaplasia in response to chronic duodenogastro-oesophageal reflux. Most authorities define “traditional” Barrett’s oesophagus as the presence of three or more centimetres of columnar-lined oesophagus above the gastro-oesophageal junction. This is an arbitrary figure used by earlier investigators to help overcome the technical and practical problems in endoscopic identification of the gastro-oesophageal junction and does not address the issues associated with short segment Barrett’s oesophagus (<3 cm). Specialised intestinal metaplasia is the most significant histological finding and is a form of incomplete intestinal metaplasia containing certain histological and immunohistochemical features of both small intestinal, colonic and gastric epithelium. Its importance is as a marker of an unstable epithelium with a predisposition to neoplastic change. It may appear at a normal appearing gastro-oesophageal junction in 9%–36% of unselected patients undergoing endoscopic examination.

Histology reports can be interpreted in several ways. They can be diagnostic when juxtaposition of native oesophageal structures to glandular mucosa is seen (occurs in only 10% of biopsies), or corroborative if glandular mucosa with intestinal metaplasia is found, or “in keeping with” if gastric type mucosa alone is described. These latter two reports may represent biopsies mistaken

**Box 1: Definition and diagnosis of Barrett’s oesophagus**

- Columnar-lined oesophagus.
- Presence of specialised intestinal metaplasia.
- Any length.
- Close clinical and pathological corroboration.
reported an excess of mortality in patients with Barrett’s but no comparisons with control populations were included.\textsuperscript{26}\textsuperscript{44} The incidence of oesophageal adenocarcinoma from endoscopic surveillance studies varies from 1:46 to 1:441 patient years of follow up, representing a 30 to 125-fold increase compared with the general population.\textsuperscript{32}\textsuperscript{33} The reasons for this wide variation include the small number of cases in most published series and short length of follow up.\textsuperscript{34} Retrospective study design, potential referral bias in reports from tertiary centres,\textsuperscript{35} population bias, and presence of advanced preneoplastic change at entry into surveillance programmes may also contribute. From prospective studies an average risk of about 1% per annum (range 0.4%–2%) is generally accepted,\textsuperscript{36} but more recent studies suggest the cancer risk is lower at around 1:200 patient years.\textsuperscript{37}\textsuperscript{38} There is a strong inverse correlation between study size and malignant risk; the bigger studies giving a lower cancer incidence.

**WHY CARRY OUT SURVEILLANCE?**

The objective of Barrett’s surveillance is to detect oesophageal adenocarcinoma at an early treatable stage. It is proposed that cancer develops progressively through sequential change from metaplasia to dysplasia to invasive adenocarcinoma.\textsuperscript{39}\textsuperscript{40} The restriction of dysplasia into only two grades (high and low) using the recently proposed Vienna classification may enable clearer and more reproducible histological assessment of patients.\textsuperscript{41} In patients presenting de novo the prognosis of oesophageal cancer is poor with overall five year survival rates of about 5%.\textsuperscript{42} Currently only surgery offers the chance of cure, but even in tertiary referral centres oesophagectomy for high grade dysplasia/early cancer carries an appreciable morbidity and mortality between 5% and 10%.\textsuperscript{43}\textsuperscript{44} Operative mortality for palliative resection is at least double this. Cancer survival after oesophagectomy is dependent on the stage of disease with 90% five year survival for stage 1 disease (confined to the mucosa and/or submucosa) compared with 10%–15% if there is lymph node involvement.\textsuperscript{45} Unfortunately some 80% of oesophageal cancers present with advanced and usually unresectable disease.

There is evidence that early stage cancers are more common in surveillance patients compared with those presenting with symptoms. Thus, Wright \textit{et al} demonstrated a higher percentage (52%) of positive lymph node disease in a symptom identified cohort (n=25) compared with 17% of patients diagnosed during surveillance (n=6).\textsuperscript{46} Van Sandick \textit{et al} found that 34 out of 54 patients identified on the basis of symptoms were lymph node positive compared with only one of a surveillance group (n=16).\textsuperscript{47} In another report, Peters \textit{et al} found that 13 oesophagectomies for cancer found during surveillance 12 had early stage disease compared to 10 of 35 cancers presenting de novo.\textsuperscript{48}

A distinct survival advantage is apparent for surveillance detected oesophageal cancer: Streitz \textit{et al} looked at 77 consecutive resections for oesophageal adenocarcinoma and found of those presenting de novo (n=58) 17% had stage 1 disease compared to an endoscopic surveillance cohort (n=19) of whom 58% had stage 1 disease.\textsuperscript{49} Their respective five year survival rates were 20% and 62%.

**ARGUMENTS AGAINST SURVEILLANCE**

The arguments for surveillance should be put into context against a background observation that although there is an increase in cancer incidence, the absolute incidence is still low. Furthermore, most patients at risk are elderly with comorbidity. One group reported that most patients with Barrett’s oesophagus die for reasons other than oesophageal cancer: only two of 135 patients in a cohort study followed up over a mean of 9.3 years died as a direct result of oesophageal carcinoma.\textsuperscript{50} Eight patients had developed cancer after 1440 patient years of follow up representing a pick up of one cancer in 180 years (or endoscopies if annual surveillance had been carried out). Five underwent elective surgery. Of note, seven of the eight patients with cancer underwent endoscopy for symptoms and three had carcinoma in situ. The same group later reported the proportion of a consecutive cohort of patients in whom Barrett’s oesophagus was diagnosed over a five year period likely to benefit from cancer diagnosis and concluded that only 52 (15%) of 335 patients were deserving of surveillance.\textsuperscript{51} Patients they excluded were those with poor prognostic factors such as age and co-morbidity. They also excluded women and males under 60, although the latter group might well have the most to gain from surveillance.

It is likely that most of the population at risk remains unidentified as shown in the classic study from Cameron’s group.\textsuperscript{52} Bytzer \textit{et al} demonstrated, in a Danish study looking at the 20 year incidence of oesophageal adenocarcinoma, that only 1.3% of patients had a diagnosis of Barrett’s more than one year before their oesophageal adenocarcinoma was identified,\textsuperscript{53} and indeed only 19% had identifiable Barrett’s at all (although short segment Barrett’s may have been “swamped” by the tumours). It was concluded that 98% of cancers occurred in patients who could not have entered a screening programme. Hence mortality reduction for oesophageal cancer in the general population is unlikely to be achieved and surveillance of individual “at risk” cases rather than population screening remains the only current intervention.

There are no randomised controlled trials to assess efficacy of surveillance; assuming a cancer incidence of 1%, such a study would require in excess of 5000 patients followed up for 10 years to demonstrate an effect.\textsuperscript{54} It thus seems unlikely that there will ever be such a trial.

**WHAT IS THE SIGNIFICANCE OF DYSPLASIA?**

Early detection of high grade dysplasia could offer a greater survival advantage, although the attendant risks of surgery make the risk/benefit ratio less clear. The natural history of high grade dysplasia has been poorly documented: invasive carcinoma can be found in up to 50% of cases in oesophagectomy specimens after resection for high grade dysplasia.\textsuperscript{55}\textsuperscript{56}
This encourages treating high grade dysplasia as early cancer and indeed this is common practice. Recently, it has been argued that a more intensive surveillance follow up is appropriate in patients found to have high grade dysplasia since short term delay in cancer detection would still mean early stage disease and good surgical outcome while avoiding surgery in those in whom high grade dysplasia remains static or regresses. Although it has been thought that high grade dysplasia invariably progresses to cancer, in fact recent data suggest that the risk of progression from high grade dysplasia to cancer may be as low as 16–28% once concurrent cancers are excluded, and that dysplasia may regress in up to 40% or remain static for many years.

Low grade dysplasia theoretically also presents a cohort of patients at higher risk of cancer development based on the observation of deteriorating dysplasia grade on retrospective histology preceding cancer development. It has been estimated to progress to cancer in 18% of patients over a 1.5–4.3 year follow up but may also regress or remain indolent. Other studies support low grade dysplasia as a variable histological entity remaining indolent in the majority of patients with only 10–25% showing progression to high grade dysplasia during endoscopic surveillance. O’Connor et al reported 73% of patients with low grade dysplasia reverted to no dysplasia on at least one subsequent endoscopy thus hampering its use as a reliable risk marker.

Low grade dysplasia may be histologically confused with active oesophagitis and regenerative changes in biopsies from patients not adequately acid suppressed. This may account for the apparent high rates of low grade dysplasia regression. It is recommended that surveillance biopsies are taken after elimination of erosive oesophagitis to permit better delineation of dysplasia.

CAN HIGH RISK GROUPS WITH BARRETT’S OESOPHAGUS BE IDENTIFIED?

Other risk factors for development of Barrett’s cancer have been described including increased segment length particularly >8 cm. Males have a greater incidence of cancer (even allowing for the greater incidence of Barrett’s in men) with an average ratio of 10:1. Smoking and white race also have increased cancer risk.

The presence of strictures and ulcers may identify a higher risk group. Bile reflux may carry an increased carcinogenic risk but this is not easily quantified. There has been speculation that the rising incidence of cancer mirrors the increasing use of acid suppression with proton pump inhibitors, although cancer incidence was climbing before widespread use of these agents. Unconjugated bile acids are more toxic at neutral pH and thus profound acid suppression may increase mucosal damage and cancer risk.

Proton pump inhibitors may also reduce bile reflux by reduction of refluxate volume, although this is not a universal finding. Obesity has been identified as a risk factor in some American studies but has not been associated with cancer risk in the UK. The UK national registry for Barrett’s oesophagus has identified a high risk population in Tayside suggesting the possibility of environmental and/or genetic risk factors.

Use of molecular markers for increased cancer risk such as cell aneuploidy, p53 expression, E-cadherin reduction, or cyclinD1 expression remain research tools at present and given the multifactorial aetiology of cancer development it is unlikely that any one marker would provide enough sensitivity/specificity to identify higher risk subgroups. Hence at present dysplasia remains the best indicator of cancer risk. Absence of dysplasia on histology combined with normal flow cytometry can identify patients at low risk of cancer development; a 0% cumulative incidence over five years is reported in a cohort of 215 Barrett’s patients.

WHAT IS THE OPTIMUM SURVEILLANCE FREQUENCY IN BARRETT’S?

Surveillance interval has been generally based on observed time intervals from cancer development with and without dysplasia in prospective series. A well accepted figure from these studies sets cancer incidence at around 1%.

More recent larger prospective surveillance studies now indicate cancer incidence to be lower than previous estimates at about 0.4% or one in 200 patient surveillance years. There are no large randomised trials to address the efficacy or cost effectiveness of Barrett’s oesophagus surveillance. Provenzale and co-workers have therefore proposed a computer simulated cohort model (Markov mathematical construct) to determine the most effective strategies to extend life at incremental cost-utility ratios comparable to other medical practices. They found that the cumulative cancer incidence and quality of life after oesophagectomy were the most important factors in deciding surveillance strategy. Given a 0.4% incidence they concluded that a five year surveillance interval was the only cost effective practice giving favourable outcomes compared with cervical cancer screening and heart transplantation. With a 1% cancer incidence 2–3 year surveillance would provide the best quality adjusted life expectancy but would be expensive. A British study calculated costs of £14 868 per cancer detected by yearly surveillance of male Barrett’s oesophagus patients, which equates favourably with other screening programmes such as faecal occult blood screening for colorectal cancer and mammography for breast cancer detection. The costs were far higher if female patients were included in the calculation. Streitz et al have also published work comparing Barrett’s surveillance favourably with breast cancer screening. A recent European report estimated a cost of 33 000 per cancer case detected. These costs are critically influenced by the cancer incidence figure applied.

Cost efficacy of surveillance may be improved by targeting higher risk groups as already described. Improvement in detection of dysplasia using a more rigorous biopsy protocol with “jumbo" forceps is recommended, although missed cases of cancer can occur. Methylene blue staining, balloon cytology, and newer techniques such as laser fluorescence spectroscopy, light scattering spectroscopy, optical coherence tomography, and use of endoscopic ultrasound in the detection of early cancer and stricture assessment need to be further studied.

OTHER EMERGING TREATMENTS

No doubt improvements in surgical and perioperative management will have an effect on the cost effectiveness of surveillance detected cancer screening programmes. The morbidity and mortality of oesophagectomy may be avoided by the advent of newer less invasive treatments for high grade dysplasia and early cancer. These include endoscopic thermocoagulation combined with acid suppression for example; argon plasma coagulation, photodynamic therapy with laser ablation, KTP laser, and endoscopic mucosal resection. Initial studies have been promising with all these therapies and they provide an avenue of treatment for patients previously considered unsuitable for surveillance because of biological frailty leading to unsuitability for surgery. However, long term outcome data are still awaited and oesophagectomy with lymph node removal is still advocated in those fit for surgery as 18% of those with intramucosal lesions may have positive nodes.

Ablation of non-neoplastic Barrett’s oesophagus has been advocated as a way of reducing oesophageal cancer risk. Numerous studies have demonstrated the efficacy of techniques such as argon plasma coagulation, multipolar electrosurgery, and laser therapy. The area of Barrett’s epithelium can be substantially reduced or ablated completely in the majority of patients treated and this effect can last for at
least up to one year, although Barrett's recurrence is common." However “buried” Barrett's glands occur beneath a normal appearing neosquamous epithelium in a significant number of treated patients raising concerns about the potential of “masked” cancers developing in the future. Indeed case reports now exist of adenocarcinoma development after thermal ablation therapy, probably representing the outcome of “burying” dysplastic epithelium. It could be argued that this may protect against further refluxate exposure and perhaps prevent further progression along the metaplasia/dysplasia/ neoplasia pathway. The long term value of these new treatments remains guarded at present and cannot be recommended unless part of an ongoing research programme.

Pathological acid reflux is reduced but can persist in Barrett's oesophagus patients on high dose proton pump inhibitor regimens, and the potential risks of bile reflux may lead to policies of increased medical acid suppression or use of antireflux surgery in those patients in high risk categories. The benefits of dysplasia and cancer risk reduction are unclear after antireflux surgery, although some Barrett's epithelium regression may occur; there are case reports of cancers occurring after surgery suggesting that the molecular preneoplastic changes could well have preceded the surgery.

RECOMMENDATIONS FOR BARRETT'S SURVEILLANCE: A PERSONAL VIEW

• An experienced endoscopist in conjunction with precise anatomically located histology should make the diagnosis of Barrett's oesophagus.

• Adequate sedation +/- antiperistaltic agents should be used to improve biopsy quality with 2 cm interval quadrantic sampling targeting ulcers, strictures, and raised areas.

• Surveillance biopsies should be taken after healing of erosive oesophagitis and with patients continuing acid suppression.

• Surveillance of all patients with macroscopic Barrett's and specialised intestinal metaplasia should be offered regardless of length provided they are biologically fit for invasive treatment should high grade dysplasia/early cancer be diagnosed.

• Frequency of surveillance: 2–3 yearly for non-dysplastic Barrett's.

• Low grade dysplasia: re-evaluate histology at six months then annually until clear for two years.

• High grade dysplasia: re-evaluate histology then intensive biopsy “hunt” for early carcinoma at three monthly intervals for one year, then six monthly surveillance. Discuss pros and cons of oesophagectomy with patient.

• Consider oesophageal pH studies +/- Bilitec monitoring (for bile reflux) on proton pump inhibitor treatment for those with dysplasia or persistent active oesophagitis to determine need for medication increase or consideration of antireflux surgery.

• Endoscopic thermoablation (+/- photodynamic sensitisation) or resection of dysplastic Barrett's mucosa especially in those not wishing or unfit for oesophagectomy.

THE FUTURE

Improvements in identification of high risk individuals for surveillance within an at risk population by more reliable detection of dysplasia and early cancer, and identification of molecular markers for risk and understanding of the molecular basis of Barrett's metaplasia and its role in the cancer pathway currently attract much attention. The increased use and expertise of less invasive treatment strategies for high grade dysplasia and early cancer may reduce morbidity and mortality associated with oesophagectomy improving the risk benefit ratio of surveillance; but we need to know more about the long term outcome in patients treated with for instance photodynamic treatment for high grade dysplasia. Expansion of surveillance using cheaper and less invasive tests such as balloon cytology may help reduce costs. The role of one-off endoscopic screening of those with chronic reflux symptoms to facilitate Barrett's epithelium detection in the population and identify the at risk population and perhaps ameliorate risk by adequate treatment of active oesophagitis has yet to be evaluated.

QUESTIONS (ANSWERS AT END OF PAPER)

1. What is Barrett's oesophagus?
2. Is Barrett's segment length important?
3. Outline the management of a patient with Barrett's oesophagus?
4. What factors may increase cost efficacy of Barrett's oesophagus surveillance programme?
5. What are the main arguments against surveillance of those with Barrett's oesophagus?

References


Authors’ affiliations

K K Basu, J S de Caestecker, Department of Integrated Medicine, Glenfield Hospital, Leicester, UK

References

Barrett's oesophagus


Barrett's oesophagus is the replacement of the normal distal squamous epithelium of the oesophagus by a metaplastic columnar lining containing specialised intestinal metaplasia; acquired as a result of chronic severe reflux of gastric and duodenal contents.

The presence of intestinal metaplasia is associated with an increased risk of oesophageal adenocarcinoma regardless of the length of the Barrett's segment, although several endoscopic surveillance studies have shown those with longer segments, especially above 8 cm, are at greatest risk.

Options will depend on the patient's fitness and willingness for major surgery. Firstly confirmation of high grade dysplasia by another experienced histopathologist should be undertaken with a further intensive biopsy search to look for carcinoma, which may be present in up to 40%. Elective oesophagectomy is recommended for those who are biologically fit. In others and those refusing surgery, ablative therapy may be considered with stricter control of acid and bile reflux. If surgery is deferred until there is histological evidence of cancer development then three monthly intensive biopsy surveillance followed by six monthly endoscopic surveillance is recommended to pick up early stage disease.

The most important factors determining cost efficacy of surveillance include: oesophageal cancer incidence, the morbidity and mortality of oesophagectomy, and frequency of endoscopic examination. Restriction of endoscopic surveillance to those identified in high risk subgroups such as male smokers with longer segment Barrett's has been proposed. Methods to increase pick up of dysplasia and identification of molecular markers of high risk are under evaluation.

The main arguments centre around the issue that no randomised controlled trials exist to demonstrate the benefits of endoscopic surveillance. The long term epidemiology and progression of high grade dysplasia and early oesophageal cancer is still not clear but oesophagectomy carries an appreciable early mortality.