Debate

Endoscopic surveillance of patients with Barrett's oesophagus

H Barr

I propose that a patient with a clinical diagnosis of Barrett's oesophagus (BO) must have regularly endoscopic surveillance and protocol biopsy. BO is defined by endoscopically visible oesophageal columnar epithelium with intestinal metaplasia. The purpose of screening is detection of dysplastic change and early cancer, to allow early intervention and prevention of the suffering of symptomatic oesophageal adenocarcinoma and premature death.

OPENING ARGUMENT

The quandaries and uncertainties that occur in the minds of both the patient and their doctor when confronted with a diagnosis of BO illustrate the dilemmas of post modern evidence based medicine. Presentation of the facts leads to diverse interpretations. Surveillance can reveal ubiquitous human folly, best exposed by Swift's wretched Struldbrugs decaying into immortality (*Gullivier's Travels*, 1726). I will argue that Barrett's surveillance prolongs life not death, relieving suffering. The current myopic approach to patients with BO exposes the "shoulder shrug" of restrictive reactive medicine.

THE WEIGHT OF EVIDENCE
Is the disease an "important" health problem?

To justify screening, the disease must meet criteria of "importance", gauged by incidence, mortality, morbidity, and public perception. Over 25 years there has been a fivefold increase in oesophageal adenocarcinoma; the rate of increase exceeds that of any other cancer (8% per annum).[1][2] Symptomatic adenocarcinoma is a lethal disease; 50% of patients have extensive locoregional or metastatic disease.[3] Of those selected for resection, 73% have invasive tumours (>pT2), 60% have lymph node metastases, and 18% other metastases.[4] Invasive cancer (>pT1) has a devastating biological predeterminism as 80% of patients have bone marrow micrometastatic disease.[5] A median five year survival rate of 21% and a perioperative mortality of 7% demonstrate the impotence of current approaches with radical surgery and multimodal therapy.[6][7]

Is there a detectable preclinical phase?

There is now a clear causal relationship between symptomatic gastro-oesophageal reflux and oesophageal adenocarcinoma.[8] Chronic reflux results in Barrett's metaplastic change, and the route to carcinoma is a stepwise progression through dysplasia, invasive carcinoma, and metastatic disease, with adenocarcinomas invariably associated with Barrett's mucosa.[9][10][11] Progression is not inevitable and is related to the increasing length of the Barrett's segment, obesity, socioeconomic status, and White males. Between 3% and 5% of patients with reflux symptoms undergoing endoscopy have BO with metaplasia compared with only 0.73% having endoscopy for all indications. Autopsy data demonstrate that the true incidence is 376 per 100 000.[12] A more specific preinvasive phenotype can be recognised, with distinct morphological changes of dysplasia.[13] The prevalence of dysplasia in long segment (>3 cm) is twice that of short segment Barrett's which is four times that of oesophagogastric intestinal metaplasia.[14] The time to dysplasia and carcinoma progression is significantly faster in patients with visible BO, and the only reliable method of dysplasia detection is an endoscopic biopsy protocol.[15]

Is treatment of the disease before it is symptomatic advantageous?

Detection of mucosal cancer is an end to surveillance and treatment with surgery or endoscopic ablation. However, high grade dysplasia can be managed by further surveillance, surgery, or mucosal ablation. Earlier stage disease is found in patients undergoing screening and is the major predictor of survival following surgery. Five year survival is 70% for mucosal cancer and 20% for invasive cancer. A non-randomised study reported significantly improved survival following surgical resection of surveyed patients compared with those with symptoms.[16][17] The alternative strategy is to perform endoscopic ablation. A prospective study of 64 patients reported the complete eradication of high grade dysplasia and early type I, Iia, Iib, and IIc (<20 mm diameter) cancers.[18] Over 45 patients treated by endoscopic ALA photodynamic therapy were free of high grade dysplasia (follow up 1–72 months).[19] Effective reflux control may stabilise the metaplastic mucosa. A randomised double blind study has confirmed endoscopic regression of the metaplastic segment following proton pump inhibitor therapy.[20]

Is surveillance acceptable to the patient and health care provider?

Our society devotes considerable resource to the education of the individual about the importance of early detection of cancer, based on the assumption that the informed patient will seek help, participate in screening, and take some responsibility for cancer prevention. The message is confused if on detection of a premalignant condition we inform the patient to return when symptomatic, at which time treatment, if possible, is unlikely to cure and may be a monstrous medieval combination of mutilating surgery and toxic oncology.

H Barr
Cranfield Postgraduate Medical School in Gloucestershire, Great Western Road, Gloucester GL1 3NN, UK; prof.barr@themail.co.uk

Debate

CLOSING ARGUMENT

Patients with Barrett's oesophagus are the blameless victims of our deliberations. A patient with a colonic polyp with a 1 in 10 chance of malignant degeneration will have polyp clearance and screening. A similar risk in the metaplastic Barrett's patient cannot be ignored. As proponents of surveillance we must convince our colleagues and heathcare providers that early detection and intervention in these patients is the only realistic method to impact on the disaster diagnosis of symptomatic oesophageal adenocarcinoma.

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ANTAGONIST

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R J Playford

R J Playford
Gastroenterology Section, Imperial College School of Medicine, Hammersmith Hospital Campus, Du Cane Rd, London W12 0NN, UK; r.playford@ic.ac.uk

Numerous reviews and guidelines encourage us to undertake surveillance of patients with Barrett's oesophagus (BO). Despite this, many experienced gastroenterologists consider there is insufficient evidence to support this approach. The definition of what constitutes BO remains an issue and is an important element of critically analysing reports. The previous idea that patients could be selected by the length of the Barret's segment (>3 cm) appears incorrect as it does not have a major influence on the subsequent risk of carcinoma.[1] The presence of intestinal metaplasia (IM) is important in the pathogenesis of cancer development but the absolute requirement to identify an area of IM before making a diagnosis of BO appears irrational. This is because virtually all patients with a columnar lined oesophagus also have some IM if enough biopsies are taken.[2]

Depending on the definition, 0.25–2% of the general population have BO.[3][4] The introduction of surveillance for this huge number would there-fore have a major impact on NHS finance and endoscopic resources. Most patients in surveillance programmes are initially identified as a result of an endoscopy for a reason other than reflux.[5] The vast rump of BO therefore remains undetected in the community. Surveillance programmes, even if shown to be successful for the occasional individual patient, will therefore have little impact on the overall treatment of oesophageal cancer for the community as a whole.[5]

Studies following up case notes of patients with BO report the vast majority die of unrelated causes and, even in those who do develop oesophageal cancer, many will die from other pathologies.[6] These studies provide no information however as to whether surveillance benefits patients.

Studies comparing the stage of disease and survival of patients identified from a surveillance programme against those presenting from the community have suggested a beneficial effect.[7]

However, these papers (studying very small numbers) do not analyse on an "intention to treat" basis, do not provide the total cost/benefit of their programmes, and fail to statistically separate dysplasia/cancer identified as a result of a true surveillance endoscopy from those having symptoms which would have resulted in an additional (unplanned) procedure. In addition, survival values for the surveillance group tend to consist of patients diagnosed with high grade dysplasia pooled with those having cancer. As the natural history of progression of such lesions is a matter of debate, with values varying from a cumulative cancer incidence at three years of 56%[8] to a five year cumulative cancer incidence of only 9%,[9] these comparisons have significant flaws.

The numbers of published works that allow a critical review of actual surveillance programmes are few. It is clear however that the median length of time that patients stay in surveillance programmes is short. This is usually less than five years and computer cost benefit modelling stating that the maximal benefit might be achieved if surveillance occurs every five years, for example, shows the limitations of such approaches. Our own review of patients entered into the Leicester General Hospital surveillance programme makes depressing reading. Of the 145 patients surveyed, five developed cancer but in only one was this detected as a result of a surveillance procedure, the remainder being diagnosed from endoscopy outside of surveillance protocol (due to previous default of the patient or the development of new symptoms).[5] Importantly, we also showed that this result would not have been altered by following a more extensive biopsy protocol.[5] Similarly, Nilsson *et al* identified five cancers from 199 patients with a mean surveillance duration of 3.9 years, quoting a value of $38 000 per cancer detected.[10] However, of these five, one was unfit for surgery and two died early postoperatively and so received little benefit from such intervention.

The main paper that does suggest a benefit is from Wright *et al* who surveyed 166 patients with annual endoscopy for an average of 2.8 years. The vast majority died from causes unrelated to BO or became unfit for further surveillance.[11] This study detected six cancers, five of which were apparently asymptomatic. The subsequent outcome of these patients is unclear although five were reported as having apparent node negative disease. Caution has to be shown however in basing a worldwide programme on one small publication. In addition, their apparent rate of cancer development was about three times higher than that generally considered to be true (0.5 per 100 patient years).[12] It is also of interest that 3/6 of their surveyed patients who developed cancer did not have IM detected at initial endoscopy and should therefore not have been entered into the study according to some guidelines.

Some form of surveillance programme *may* be beneficial for patients with BO. However, an evidence based approach requires us to provide firm data in support of this expensive time consuming activity that uses up valuable endoscopy resources. Patients with dysplasia should

Key points

- Most people with Barrett's die from unrelated causes.
- Impact of surveillance programmes on the amount of oesophageal cancer in the community is minimal but ties up expensive resources.
- Studies to date have failed to adequately show any major benefit in altering patient outcome.
- Guidelines recommending surveillance are inadequately evidence based.
- Randomised trials showing differences in survival between regularly surveyed patients and no surveillance (or long surveillance intervals if considered unethical) are needed.

probably be monitored. However, in the vast majority of patients with BO, the relatively high workload for every cancer detected means that we should be attempting to find ways of identifying those subjects who are at higher risk.

For patients without dysplasia, randomised trials with differences in death rates from oesophageal cancer are required, ensuring a distinction between those cancers diagnosed due to a surveillance procedure from those diagnosed from an additional endoscopy. Guidelines induce doctors to perform surveillance for fear of litigation. Based on current evidence, they should also state that not performing routine surveillance is a reasonable course of action.

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