Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study

Christopher E Macdonald, Anthony C Wicks, Raymond J Playford

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Leicester General Hospital NHS Trust, Leicester LE5 4PW
Christopher E Macdonald *research registrar*
Anthony C Wicks *consultant gastroenterologist*
Department of Gastroenterology, Hammersmith Hospital, London W12 0NN
Raymond J Playford *professor of gastroenterology*
Correspondence to: R J Playford r.playford@ic.ac.uk

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Abstract

Objectives To review the benefit of an endoscopic surveillance programme for patients with Barrett's oesophagus.
Design Observational study.
Setting University teaching hospital.
Participants 409 patients in whom Barrett's oesophagus was identified during 1984-94; 143 were entered into the annual surveillance programme.
Main outcome measures Development of dysplasia and cancer and mortality.
Results The average period of surveillance was 4.4 years; 55 patients were reassessed in 1994 but only eight remained in the programme in 1999, withdrawal being due to death (not from carcinoma of the oesophagus), illness, or frailty. Five of the patients who entered surveillance developed carcinoma of the oesophagus. Only one cancer was identified as a result of a surveillance endoscopy, the others being detected during endoscopy to investigate altered symptoms. Of the 266 patients who were not suitable for surveillance, one died from oesophageal cancer and 103 from other causes. Surveillance has resulted in 745 endoscopies and about 3000 biopsy specimens.
Conclusion The current surveillance strategy has limited value, and it may be appropriate to restrict surveillance to patients with additional risk factors such as stricture, ulcer, or long segment (>80 mm) Barrett's oesophagus.

Introduction

The presence of metaplasia within the oesophagus (Barrett's oesophagus) is generally accepted to be a premalignant condition, predisposing the patient to subsequent development of oesophageal adenocarcinoma.[1 2] The time it takes for metaplasia to develop into dysplasia and then carcinoma is, however, unknown. The definition of Barrett's mucosa is also debated, with the length (>30 mm, short, ultra short) and histological subtypes (intestinal metaplasia with acid mucin or just columnar glandular epithelium) being the main points of contention.[3]

Many centres have established surveillance programmes for patients with Barrett's oesophagus in an attempt to identify dysplastic changes before carcinoma develops and also to detect cancers before they disseminate into the lymph nodes, when the chances of cure are much poorer. The World Health Organization advises that any screening or surveillance programme must meet several criteria to be considered effective: the natural course of the disease must be understood, there should be an asymptomatic stage in which screening or surveillance can detect a lesion that is amenable to treatment, and treatment should alter outcome to the patient's or community's benefit.[4] In addition, the test must be effective and acceptable to those undergoing it. Little evidence exists, however, that surveillance of Barrett's oesophagus fulfils these criteria or provides any major clinical benefit.

Leicester General Hospital offers annual surveillance to all patients with Barrett's oesophagus who are considered potentially fit for oesophageal surgery should this be required. We have published our initial findings from the patients who were entered into the programme during 1984-94.[5] Over the past five years, we have continued to follow these patients as well as those who were considered unfit to enter the programme. As almost all of the patients have now left the programme, we can report the overall outcome of our surveillance programme and review the clinical progress of patients with Barrett's oesophagus who did not participate.

Participants and methods

The patient cohort was identified as previously described.[5] Briefly, all of the written reports from endoscopies performed during 1984-94 (total 29 374) were reviewed by one person (CEM). Patients were regarded as having Barrett's mucosa only if endoscopy showed an area of abnormality ≥30 mm in length and biopsy samples confirmed the presence of columnar metaplasia. This definition excludes patients who are now considered to have "short segment" Barrett's oesophagus, but reflects the practice of assessment at the beginning of the study.

At each endoscopy the endoscopist recorded the length of macroscopically affected mucosa and the presence of any other abnormality such as ulceration or stricture. Biopsy samples were usually taken from all four quadrants at the midpoint of the affected mucosa, with additional multiple samples taken from any region that showed additional abnormality. The affected area was not mapped. Barrett's mucosa was reported if glandular mucosa was present in a biopsy sample from the oesophagus. Any coexisting intestinal metaplasia (recognised by prominent goblet cells) was also reported. Areas of dysplasia were defined as mild, moderate, or severe depending on the degree of nuclear atypia and pseudostratification.

Surveillance endoscopies were defined as examinations done only for surveillance. Endoscopies to investigate deteriorating symptoms in a patient in the surveillance programme were not included as surveillance endoscopies.

All patients with proved Barrett's oesophagus were considered for entry into our surveillance programme. To be eligible the patient had to be potentially suitable for major surgery should a lesion be detected, which usually meant patients younger than 70 who had no serious coexisting disease. We monitored subsequent follow up and surveillance of patients through hospital records. In addition, we obtained details of subsequent illness and deaths for all patients who had Barrett's oesophagus from the notes of other local hospitals,

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Further details of patients who developed oesophageal cancer are available on the BMJ's website

general practitioners, and mortality records. Patients recruited into our surveillance programme since 1994 are not included in this report.

Results

Characteristics of patients identified

During 1984-94, 409 patients (1.4% of all endoscopies) met the criteria and were identified as having Barrett's oesophagus. The distribution of sexes was roughly equal (52% men), and the mean age at diagnosis was 63 years. These characteristics are typical of patients with Barrett's oesophagus throughout the United Kingdom.[6] The mean length of metaplasia at the initial endoscopy was 76 mm, with stricture present in 35 patients (9%).

In all, 143 (35%) of patients with Barrett's oesophagus were considered suitable for surveillance, the main reasons for exclusion being age >70 (39% of total cohort) and coexisting serious illness (10% of total cohort). A similarly high exclusion rate has been described by others.[7] Our surveillance group had a slight male predominance (60%) and a slightly lower mean age (57 years) than the group as a whole (table 1). The main symptoms or clinical indications precipitating diagnostic endoscopy in the surveyed group were epigastric pain (33, 23%), gastro-oesophageal reflux disease (30, 21%), dysphagia (29, 20%), anaemia (16, 11%), and haematemesis (10, 7%). The distribution was similar to that found in the entire group with Barrett's oesophagus. The mean length of metaplasia at initial endoscopy among patients suitable for surveillance was 81 mm, with 23 (16%) also having a stricture.

Duration of participation in surveillance and mortality

The average period of surveillance for the cohort was 4.4 years. Fifty five patients were still under surveillance when the last participant was recruited at the end of 1994, but only eight were under surveillance in November 1999. The main reasons for leaving the programme were death (27, 20%), development of serious comorbidity (36, 27%), age and general frailty making continued surveillance inappropriate (43, 32%), default from follow up (14, 11%) and moving away from the area (13, 10%). Of the 27 people who died, only two died from carcinoma of the oesophagus. The mean age of the patients who defaulted from follow up was 46 years, and they participated for a mean of 5.2 years. Default from the programme and movement away from our area were the main reasons for withdrawal among younger patients.

By January 2000, 33 of the 143 patients (23%) who had entered the programme had died (three from cancer of the oesophagus). Table 2 gives the causes of death.

Table 1 Demographics of patients identified with Barrett's syndrome who were and were not included in surveillance programme

	Surveillance (n=143)	No surveillance (n=266)
Mean (range) age (years)	57 (17-69)	69 (17-94)
No (%) of men	86 (60)	125 (47)
Mean (range) length of metaplasia (mm)	81 (30-200)	73 (30-200)
No (%) with stricture	23 (16)	12 (5)
Mean (range) period of surveillance (years)	4.4 (1-11)	—

Table 2 Causes of death in patients with Barrett's syndrome who did and did not enter surveillance programme

Cause of death	No (%) with surveillance (n=33)	No (%) with no surveillance (n=104)
Ischaemic heart disease	6 (18)	28 (27)
Other vascular disease	3 (9)	15 (14)
Pneumonia	5 (15)	19 (18)
Cancer of oesophagus	3 (9)	1 (1)
Cancer of stomach	1 (3)	2 (2)
Cancer of other specified site	11 (33)	20 (19)
Cancer of non-specified site*	2 (6)	12 (12)
Other	2 (6)	7 (7)

*Unlikely to be oesophageal cancer from clinical details.

Results and workload of surveillance programme

Cancer—Five patients who were recruited into the programme subsequently developed oesophageal cancer (see *BMJ*'s website for further details). Two had an oesophageal stricture at the time of enrolment and two defaulted from the programme, subsequently presenting with symptoms that would have resulted in an urgent endoscopy on standard clinical grounds.

Dysplasia—Five patients were found to have mild dysplasia, three of whom had a strong history of alcoholism. Three of these patients had normal biopsy specimens on subsequent review, suggesting regression of the dysplasia. One patient was lost to follow up. The fifth patient was a 67 year old woman who had a 70 mm length of Barrett's mucosa with intestinal metaplasia recognised in 1992 during investigation of haematemesis. She was followed up annually for five years with no progression of her Barrett's mucosa or evidence of dysplasia until low grade dysplasia was noted on her last surveillance endoscopy. She is being regularly reviewed with four quadrant biopsy samples taken every 20 mm and continues treatment with acid suppressants.

The total endoscopic workload resulting from the surveillance programme has been about 745 endoscopies, generating about 2980 biopsy specimens.

Clinical outcomes of patients unfit for surveillance

During the 10 year surveillance, 266 patients were found to have Barrett's mucosa but were not entered into the surveillance programme because they were considered unfit for surgery. A total of 104 have died, but only one from carcinoma of the oesophagus (table 2). This 75 year old woman had a 100 mm length of Barrett's mucosa with intestinal metaplasia diagnosed in 1987 during the investigation of epigastric pain. She was considered to be too frail to enter surveillance, started on acid suppressants, and discharged. Eight years later she died of carcinoma of the oesophagus and chronic renal failure.

Discussion

Of the 409 patients who had Barrett's oesophagus diagnosed , 143 were suitable for surveillance and participated for an average of 4.4 years. Although five of these patients developed cancer, the programme identified only one patient, who died postoperatively. The natural course of Barrett's oesophagus is poorly understood. The quoted risk of development of adenocarcinoma varies widely, but it is probably around 1 per 150 patient years.[1] Our results are therefore in keeping with quoted figures.

Gastro-oesophageal reflux disease is strongly linked with Barrett's oesophagus,[8] although the relation between the severity of symptoms and the degree of macroscopic damage seen at endoscopy is poor.[9] Symptoms can therefore not be used to select patients at high risk of developing Barrett's oesophagus. Postmortem studies suggest that about 2% of the adult population have Barrett's mucosa,[10] although most will have few if any symptoms. Surveillance programmes therefore review only a small proportion of the population at increased risk. Cancer of the oesophagus causes about 100 deaths a year in Leicestershire, and the standardised mortality ratio in 1994-8 was 103 (95% confidence interval 95 to 113, Leicestershire Health Authority, unpublished data).

Value of surveillance

Five patients who were entered into our programme developed oesophageal cancer. In the two patients who developed adenocarcinoma within a stricture, the tumour was probably present at the time of initial diagnosis, although examination of extensive biopsy samples did not identify it. Two patients had defaulted from the programme, one subsequently presented with haematemesis and the other with dysphagia. Only one of these patients has had curative treatment. The fifth patient had an early asymptomatic adenocarcinoma identified as a result of a standard surveillance endoscopy but died postoperatively. We therefore consider that no patient in this cohort has been helped by our programme.

We took biopsy samples from four quadrants at the midpoint of the affected area with additional samples from any abnormal regions (such as strictures or ulcers). The world congress of gastroenterology recommended a more intensive protocol in which four quadrant biopsy samples are taken every 20 mm.[11] However, review of the clinical progress of our patients who developed carcinoma does not suggest any would have benefited. The two patients who developed tumour within the strictures had had biopsy samples taken from an extensive area, in accordance with our standard protocol, and the third patient died postoperatively, a scenario unlikely to have been changed by this alternative approach. The two other patients both defaulted from the programme, returning with symptoms two and four years later. As the time course of the development of dysplasia and carcinoma is unknown, we cannot tell whether a more intensive biopsy approach at the last surveillance endoscopy would have influenced the outcome in the patient who died. The patient who has been identified as having mild dysplasia is having more rigorous surveillance, although the benefits are not yet apparent.

Workload

The total endoscopic workload generated by the surveillance programme has been about 745 endoscopies, leading to about 2980 biopsies. Despite this investment in time and money, we consider that no patient has benefited from our programme and have therefore not formally evaluated the costs and benefits. If we had followed the world congress recommendations, a further 8940 biopsies specimens would have been obtained, based on an average additional 12 specimens per patient. In addition to extra costs being incurred, the more intensive protocol would have increased the time required to perform each endoscopy, which may have resulted in longer waiting lists as fewer patients could be examined per session. These factors probably help explain why few centres in Britain are following the world congress recommendations in full.[12]

What is already known on this topic

Barrett's oesophagus affects about 2% of the adult population and increases the risk of developing oesophageal adenocarcinoma

Many centres have adopted regular endoscopic surveillance programmes to detect dysplasia or early (curable) carcinoma

What this study adds

Most patients with Barrett's oesophagus die of diseases unrelated to oesophageal carcinoma

None of the patients in the 10 year cohort benefited from surveillance

Surveillance of the cohort involved 745 endoscopies and almost 3000 biopsy specimens

Taking many more biopsy specimens would have been unlikely to improve clinical outcome

In conclusion, the value of our surveillance programme seems extremely limited, and use of a more intensive biopsy protocol would not have altered clinical outcome. Centres that have recruited large numbers of patients into surveillance programmes should formally audit the value of their own programmes and publish the results so that meta-analyses can be performed. This may also allow comparison of results from centres that use the more intensive protocol with those that do not. Until further information from prospective studies is available, it may be more appropriate to offer surveillance only to patients with intestinal metaplasia and additional risk factors such as ulceration, stricture, or long segment (>80 mm). Alternatively, research into the potential value of molecular markers within the Barrett's mucosa may allow us to identify patients at greatest risk of developing cancer.[13]

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Contributors: CEM analysed the endoscopy database to identify the patients described in this paper. He also followed up the subsequent clinical course of patients and participated in the analysis and writing of the paper. ACW helped develop the surveillance programme at Leicester General Hospital. He contributed to the initial core idea of analysing the value of this programme and participated in the interpretation and writing of the manuscript. RJP initiated the research and supervised the design, execution, and interpretation of the study as well as preparation of the manuscript. CEM and RJP are the guarantors.

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Maternal morbidity and mortality associated with interpregnancy interval: cross sectional study

Agustin Conde-Agudelo, José M Belizán

Abstract

Objective To study the impact of interpregnancy interval on maternal morbidity and mortality.
Design Retrospective cross sectional study with data from the Perinatal Information System database of the Latin American Centre for Perinatology and Human Development, Montevideo, Uruguay.
Setting Latin America and the Caribbean, 1985-97.
Participants 456 889 parous women delivering singleton infants.
Main outcome measures Crude and adjusted odds ratios of the effects of short and long interpregnancy intervals on maternal death, pre-eclampsia, eclampsia, gestational diabetes mellitus, third trimester bleeding, premature rupture of membranes, postpartum haemorrhage, puerperal endometritis, and anaemia.
Results Short (<6 months) and long (>59 months) interpregnancy intervals were observed for 2.8% and 19.5% of women, respectively. After adjustment for major confounding factors, compared with those conceiving at 18 to 23 months after a previous birth, women with interpregnancy intervals of 5 months or less had higher risks for maternal death (odds ratio 2.54; 95% confidence interval 1.22 to 5.38), third trimester bleeding (1.73; 1.42 to 2.24), premature rupture of membranes (1.72; 1.53 to 1.93), puerperal endometritis (1.33; 1.22 to 1.45), and anaemia (1.30; 1.18 to 1.43). Compared with women with interpregnancy intervals of 18 to 23 months, women with interpregnancy intervals longer than 59 months had significantly increased risks of pre-eclampsia (1.83; 1.72 to 1.94) and eclampsia (1.80; 1.38 to 2.32).
Conclusions Interpregnancy intervals less than 6 months and longer than 59 months are associated with an increased risk of adverse maternal outcomes.

Introduction

Both short and long interpregnancy intervals have been found to increase the risk of various adverse perinatal outcomes, such as low birth weight, preterm delivery, infants small for gestational age, stillbirth, and neonatal death.[1–5] The effect of interpregnancy interval on maternal morbidity and mortality has received less attention. In 1944, Eastman examined the effect of the interpregnancy interval, defined as "the interval between births," on some maternal outcomes in a cohort of 5158 parous women.[6] He found no association between interpregnancy interval and maternal anaemia, postpartum haemorrhage, puerperal fever, and maternal mortality. The risk of toxaemia, defined as pre-eclampsia and eclampsia with or without chronic hypertension, increased steadily with increasing interval between pregnancies. This investigation, however, did not control for confounding factors, and the number of women with short intervals was small. Since then, few studies have examined the association between interpregnancy interval and maternal outcomes.[7–9] Two were case-control studies that looked only for association between interpregnancy interval and maternal mortality and provided apparently contradictory results[7 9]: one showed an association whereas the other found no association. The other study evaluated the risk of anaemia according to intervals between pregnancies.[8]

The Latin American and Caribbean Perinatal Information System database, which comprises information on maternal sociodemographic characteristics and outcomes of pregnancy, provides an opportunity to study the effects of interpregnancy interval on maternal morbidity and mortality.

Participants and methods

The Perinatal Information System database in Montevideo, Uruguay, was devised by the Latin American Centre for Perinatology and Human Development (CLAP) in 1983.[10] Currently, this database is used for over half a million births each year. From 1985 to 1997 our database has recorded pregnancies of women who were born in Uruguay, Argentina, Peru, Colombia, Honduras, Paraguay, El Salvador, Chile, Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, and Venezuela.

Only parous women delivering singleton infants and whose previous pregnancy ended in live birth or fetal death after 19 weeks' gestation were included in the study. A complete description of the database has been published elsewhere.[11 12] From the first antenatal visit until discharge of both mother and neonate, the attending physicians or nurses collect data on demographic

Latin American Centre for Perinatology and Human Development (CLAP), Division of Health Promotion and Protection, Pan American Health Organisation, World Health Organisation, Montevideo, Uruguay
Agustin Conde-Agudelo *perinatal researcher*
José M Belizán *director*
Correspondence to: A Conde-Agudelo condeagu@uniweb.net.co

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