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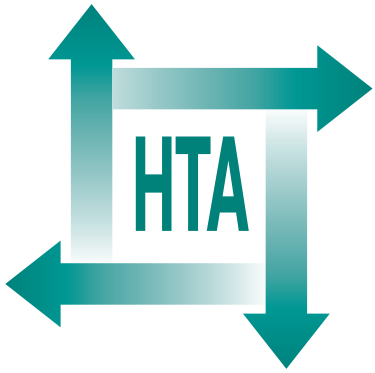

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Abstract

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling

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Objectives: To assess what is known about the effectiveness, safety, affordability, cost-effectiveness and organisational impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus. In addition, to identify important areas of uncertainty in current knowledge for these programmes and to identify areas for further research.

Data sources: Electronic databases up to March 2004. Experts in Barrett's oesophagus from the UK.

Review methods: A systematic review of the effectiveness of endoscopic surveillance of Barrett's oesophagus was carried out following methodological guidelines. Experts in Barrett's oesophagus from the UK were invited to contribute to a workshop held in London in May 2004 on surveillance of Barrett's oesophagus. Small group discussion, using a modified nominal group technique, identified key areas of uncertainty and ranked them for importance. A Markov model was developed to assess the cost-effectiveness of a surveillance programme for patients with Barrett's oesophagus compared with no surveillance and to quantify important areas of uncertainty. The model estimates incremental cost–utility and expected value of perfect information for an endoscopic surveillance programme compared with no surveillance. A cohort of 1000 55-year-old men with a diagnosis of Barrett's oesophagus was modelled for 20 years. The base case used costs in 2004 and took the perspective of the UK NHS. Estimates of expected value of information were included.

Results: No randomised controlled trials (RCTs) or well-designed non-randomised controlled studies were identified, although two comparative studies and numerous case series were found. Reaching clear conclusions from these studies was impossible owing to lack of RCT evidence. In addition, there was incomplete reporting of data particularly about cause of death, and changes in surveillance practice over time were mentioned but not explained in several studies. Three cost–utility analyses of surveillance of Barrett's oesophagus were identified, of which one was a further development of a previous study by the same group. Both sets of authors used Markov modelling and confined their analysis to 50- or 55-year-old white men with gastro-oesophageal reflux disease (GORD) symptoms. The models were run either for 30 years or to age 75 years. As these models are American, there are almost certainly differences in practice from the UK and possible underlying differences in the epidemiology and natural history of the disease. The costs of the procedures involved are also likely to be very different. The expert workshop identified the following key areas of uncertainty that needed to be addressed: the contribution of risk factors for the progression of Barrett's oesophagus to the development of high-grade dysplasia (HGD) and adenocarcinoma of the oesophagus; possible techniques for use in the general population to identify patients with high risk of adenocarcinoma; effectiveness of treatments for Barrett's oesophagus in altering cancer incidence; how best to identify those at risk in order to target treatment; whether surveillance programmes should take place at all; and whether there are clinical subgroups at higher risk of adenocarcinoma. Our Markov model suggests that the base case scenario of endoscopic surveillance of Barrett's oesophagus at 3-yearly intervals, with low-grade dysplasia surveyed yearly and HGD 3-monthly, does more harm than good when compared with no surveillance. Surveillance produces fewer quality-adjusted life-years (QALYs) for higher cost than no surveillance, therefore it is

dominated by no surveillance. The cost per cancer identified approaches £45,000 in the surveillance arm and there is no apparent survival advantage owing to high recurrence rates and increased mortality due to more oesophagectomies in this arm. Non-surveillance continues to cost less and result in better quality of life whatever the surveillance intervals for Barrett's oesophagus and dysplastic states and whatever the costs (including none) attached to endoscopy and biopsy as the surveillance test. The probabilistic analyses assess the overall uncertainty in the model. According to this, it is very unlikely that surveillance will be cost-effective even at relatively high levels of willingness to pay. The simulation showed that, in the majority of model runs, non-surveillance continued to cost less and result in better quality of life than surveillance. At the population level (i.e. people with Barrett's oesophagus in England and Wales), a value of £6.5 million is placed on acquiring perfect information about surveillance for Barrett's oesophagus using expected value of perfect information (EVPI) analyses, if the surveillance is assumed to be relevant over 10 years. As with the one-way sensitivity analyses, the partial EVPI highlighted recurrence of adenocarcinoma of the oesophagus (ACO) after surgery and time taken for ACO to become symptomatic as particularly important parameters in the model.

Conclusions: The systematic review concludes that there is insufficient evidence available to assess the clinical effectiveness of surveillance programmes of Barrett's oesophagus. There are numerous gaps in the evidence, of which the lack of RCT data is the major one. The expert workshop reflected these gaps in the range of topics raised as important in answering the question of the effectiveness of surveillance. Previous models of cost-effectiveness have most recently shown that surveillance programmes either do more harm than good compared with no surveillance or are unlikely to be cost-effective at usual levels of willingness to pay. Our cost–utility model has shown that, across a range of values for the various parameters that have been chosen to reflect uncertainty in the inputs, it is likely that surveillance programmes do more harm than good – costing more and conferring lower quality of life than no surveillance. Probabilistic analysis shows that, in most cases, surveillance does more harm and costs more than no surveillance. It is unlikely, but still possible, that surveillance may prove to be cost-effective. The cost-effectiveness acceptability curve, however, shows that surveillance is unlikely to be cost-effective at either the 'usual' level of willingness to pay (£20,000–30,000 per QALY) or at much higher levels. The expected value of perfect information at the population level is £6.5 million. Future research should target both the overall effectiveness of surveillance and the individual elements that contribute to a surveillance programme, particularly the performance of the test and the effectiveness of treatment for both Barrett's oesophagus and ACO. In addition, of particular importance is the clarification of the natural history of Barrett's oesophagus.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Adenocarcinoma A form of cancer forming gland-like structures, in this case in mucosa of the oesophagus.

Barrett's oesophagus Traditionally, the replacement of the normal squamous lining of the lower oesophagus with metaplastic columnar cells for at least 3 cm of its length. More recently, any length of intestinal metaplasia.

Biopsy Removal of a sample of tissue or cells to assist diagnosis of disease.

Cardia The upper part of the stomach close to the junction with the oesophagus.

Chemotherapy Use of drugs to kill or slow the growth of cancer cells.

Cytology The study of single cells under a microscope.

Distal Remote (opposite to proximal, near), in this case away from the mouth.

Dysphagia Difficulty in swallowing.

Dysplasia Abnormality in the development of cells to a type that may dispose to cancer.

Dumping Abdominal discomfort and diarrhoea after meals. A syndrome that can develop after oesophagectomy.

Expected value of perfect information A type of economic analysis that incorporates uncertainty in available data. This calculates the value of obtaining 'perfect information' about input variables in the economic model. Partial expected value of perfect information assesses the value of individual parameters.

Fundoplication A surgical treatment for reflux symptoms where the lower end of the oesophagus is mobilised and the upper stomach folded (plicated) around it.

Gastro-oesophageal reflux Heartburn/indigestion caused by gastric acid rising out of the stomach.

Incremental cost-effectiveness ratio The incremental cost of producing an extra unit of an outcome. In this case, the cost per quality-adjusted life-year gained.

Kaplan–Meier A method of calculating survival curves. Observations are censored either where a patient drops out before the study ends or has not died at the time of analysis.

Metaplasia A change in cells to resemble those of another tissue or organ.

Oesophagitis Inflammation of the oesophagus.

Proton pump inhibitors Drugs that block acid production in the stomach at a cellular level.

Quality-adjusted life-year An outcome measure combining both quantity and quality of life into a single index. This reflects preferences (utility values) for given health states. It is calculated by the amount of time spent in a health state (years) weighted by the preference for that health state (utility value).

Reflux Regurgitation of stomach and intestinal contents into the oesophagus.

Resection The surgical removal of all or part of an organ, in this case, the oesophagus.

Squamous Flattened cells – the normal type for the oesophageal lining.

Stent A plastic or metal tubular device, in this case used to hold the oesophagus open.

Utility A measure of preference for a given health state where 1.0 is perfect health and 0 is death.

List of abbreviations

ACO	adenocarcinoma of the oesophagus
ASPECT	Asprin Esomeprazole Chemoprevention Trial
BNF	British National Formulary
BSG	British Society of Gastroenterology
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CLO	columnar lined oesophagus
COX-2	cyclooxygenase 2
CT	computed tomography
DEC	Development and Evaluation Committee
ECG	electrocardiogram
EVPI	expected value of perfect information
GERD	gastro-esophageal reflux disease (US spelling)
GI	gastrointestinal
GOJ	gastro-oesophageal junction
GORD	gastro-oesophageal reflux disease
HGD	high-grade dysplasia
HMO	Health Maintenance Organisation
ICER	incremental cost-effectiveness ratio
ID	indefinite dysplasia
IM	intestinal metaplasia
IPAC	International Procedures Advisory Committee
ITT	intention-to-treat
LGD	low-grade dysplasia
LSBO	long-segment Barrett's oesophagus
NGT	Nominal Group Technique
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
NSR	National Schedule of Reference
OR	odds ratio
PDT	photodynamic therapy
PenTAG	Peninsular Technology Assessment Group
PEVPI	partial expected value of perfect information
PPI	proton pump inhibitor
PSA	probabilistic simulation analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SIM	specialised intestinal metaplasia
SSBO	short-segment Barrett's oesophagus
TTO	time trade-off
UKBOR	UK Barrett's Oesophagus Registry

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The NHS Health Technology Assessment (HTA) programme commissioned this project, having established the need for research in this area as a priority. It was, however, unsuccessful in commissioning primary research. The reason for the previous lack of success was thought to be the lack of clarity about the current state of knowledge and areas of uncertainty that might be of most importance to the NHS.

Barrett's oesophagus is a histological diagnosis and occurs when the normal squamous epithelial cells lining the oesophagus are replaced with columnar cells. This metaplasia gives a red appearance to the oesophagus on endoscopic examination. The risk of developing adenocarcinoma of the oesophagus (ACO) is increased with Barrett's oesophagus, although the size of this increased risk is unknown.

Gastro-oesophageal reflux disease (GORD) is associated with Barrett's oesophagus. However, some people with Barrett's oesophagus may be symptom free, and it is probable that only a small minority of those with GORD will have Barrett's oesophagus.

Given a known, unquantified increased risk of ACO with Barrett's oesophagus, endoscopic surveillance of this condition is common and three-quarters of UK gastroenterologists believe it to be worthwhile. However, evidence for this practice is lacking.

Aims of the project

The aims of the project were as follows:

1. to assess what is known about the effectiveness, safety, affordability, cost-effectiveness and organisational impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus
2. to identify important areas of uncertainty in current knowledge for these programmes
3. to identify important areas of research for the HTA Prioritisation Strategy Group to consider addressing by commissioning further research.

Methods

Three strands of enquiry were used to address these aims:

1. A systematic review of the effectiveness of endoscopic surveillance of Barrett's oesophagus was carried out following the methodological guidelines set out by the Centre of Reviews and Dissemination Report No. 4. Electronic databases were searched for published surveillance studies, economic evaluations and current research. Inclusion criteria were broad, reflecting the known lack of randomised trials or other well-designed or controlled studies in this field.
2. We invited experts in Barrett's oesophagus from the UK to contribute to a workshop on surveillance of Barrett's oesophagus, which was held in London in May 2004. At this stage, the systematic review was not complete and the cost–utility model was still in development. We divided the topic of Barrett's oesophagus into four broad sections and asked four individual experts to summarise the current state of knowledge in each section. Small group discussion, using a modified nominal group technique, then identified key areas of uncertainty within each section and ranked them for importance. The subsequent plenary discussion identified some additional questions, but no attempt was made to rank the questions for overall importance.
3. A Markov model was developed in Microsoft Excel by the Peninsula Technology Assessment Group (PenTAG) to assess the cost-effectiveness of a surveillance programme for patients with Barrett's oesophagus compared with no surveillance and to quantify important areas of uncertainty. The model estimates incremental cost–utility and expected value of perfect information for an endoscopic surveillance programme compared with no surveillance. A cohort of 1000 55-year-old men with a diagnosis of Barrett's oesophagus was modelled for 20 years. The base case used costs in 2004 and took the perspective of the UK NHS. Estimates of expected value of information were included.

Results

Systematic review of clinical and cost-effectiveness of surveillance programmes

Clinical effectiveness

No randomised controlled trials (RCTs) or well-designed non-randomised controlled studies were identified, although two comparative studies and numerous case series were found. Only the comparative studies and seven case series with >300 patients were included in the review.

Reaching clear conclusions from these studies was impossible owing to lack of RCT evidence. In addition, there was incomplete reporting of data, particularly clinical details of the subjects under surveillance and their follow-up, details of the diagnostic methods and protocols used, details of treatment for gastro-oesophageal reflux disease (GORD), policies for offering treatment for adenocarcinoma of the oesophagus or high-grade dysplasia (HGD) and mortality from adenocarcinoma of the oesophagus and from other causes. In addition, changes in surveillance practice over time were mentioned but not explained in several studies.

Limiting the included case series to those with >300 patients did not result in better quality studies; choosing other criteria for limiting inclusion such as length of follow-up or the same definition of Barrett's oesophagus might have made synthesis of the results easier, but probably would not have altered the conclusions in the absence of agreed quality criteria by which to assess case series.

Cost-effectiveness

Three cost–utility analyses of surveillance of Barrett's oesophagus were identified, of which one was a further development of a previous study by the same group. Both sets of authors used Markov modelling and confined their analysis to 50- or 55-year-old white men with GORD symptoms. The models were run either for 30 years or to age 75 years.

The first two studies used a Markov model to examine various surveillance and treatment strategies for Barrett's oesophagus. The earlier study found that surveillance of Barrett's oesophagus every 5 years compared with no surveillance was cost-effective, but that the model was very sensitive to the incidence of adenocarcinoma and quality of life (utility value) in the post-oesophagectomy state. The later study from the same authors reached similar conclusions, but the incremental cost-effectiveness ratio for 5-yearly surveillance was no longer within the range usually considered cost-effective.

The third study also used a Markov model to examine various surveillance strategies. The authors concluded that the only cost-effective strategy was once in a lifetime screening of 50-year old white men with GORD, followed by surveillance of those with dysplasia only. Surveillance of non-dysplastic Barrett's oesophagus was not found to be cost-effective.

Both of these models are American, so there are almost certainly differences in practice from the UK and possible underlying differences in the epidemiology and natural history of the disease. In the UK, there is a major difficulty in knowing what proportion of patients with GORD have an endoscopy and at what stage of the disease, whereas in the USA, those who present to health services are more likely to be investigated at an earlier stage. The costs of the procedures involved are also likely to be very different.

Expert workshop

The group which discussed the epidemiology and natural history of Barrett's oesophagus identified six possible questions concerning areas of uncertainty, of which the following was rated as the clear key priority:

- What contributions do risk factors (demographic, environmental, genetic, molecular) for progression of Barrett's oesophagus make, individually and together, to the development of HGD and adenocarcinoma of the oesophagus?

The group that discussed diagnostic tests for Barrett's oesophagus identified seven possible areas of uncertainty. The key priority recognised that the ultimate aim of surveillance of Barrett's oesophagus is to reduce the risk of ACO:

- Is there a technique that we can use in the general population to identify patients with high risk of adenocarcinoma?

The group discussing treatment of Barrett's oesophagus identified seven possible areas of uncertainty and rated two of them as top priorities:

- How effective are any treatments for Barrett's oesophagus in altering cancer incidence?
- How can we best identify those at risk in order to target treatment?

The group discussing the potential impact of surveillance programmes identified nine possible areas of uncertainty and rated two of them as top priorities:

- Should we survey at all?
- Are there clinical subgroups at higher risk of adenocarcinoma?

The final plenary discussion at the workshop brought out questions that were of specific concern for the patient representatives and also identified additional questions that the small group discussions had not raised. No attempt was made to allocate an overall priority to these areas of uncertainty.

Cost–utility model

PenTAG's Markov model suggests that the base case scenario of endoscopic surveillance of Barrett's oesophagus at 3-yearly intervals, with low-grade dysplasia (LGD) surveyed yearly and HGD 3-monthly, does more harm than good when compared with no surveillance. Surveillance produces fewer quality-adjusted life-years (QALYs) for higher cost than no surveillance, therefore it is dominated by no surveillance. The cost per cancer identified approaches £45,000 in the surveillance arm and there is no apparent survival advantage owing to high recurrence rates and increased mortality due to more surgical interventions (i.e. oesophagectomies) in this arm.

The input parameters to which the model is most sensitive, in some cases reversing the results so that surveillance becomes cost-effective, are as follows:

1. the rate of recurrence of adenocarcinoma after oesophagectomy in the surveillance compared with the no surveillance arm
2. the rate at which adenocarcinoma becomes symptomatic once it has developed
3. the utility value (quality of life) attached to the health states for Barrett's oesophagus.

According to one-way sensitivity analyses, which vary just one model input while all the others are fixed, for 3-yearly surveillance to become cost-effective at usual levels of willingness to pay (£30,000 per QALY), the following parameters would need to achieve the following values:

1. if the rate of recurrence of adenocarcinoma after oesophagectomy reduces to 4.5% in the surveillance arm (from the base case of 9.3%) or
2. if the rate of recurrence of adenocarcinoma after oesophagectomy reduces to 7% in the non-surveillance arm (from the base case of 26%) or
3. if progression from undetected to symptomatic adenocarcinoma increases to at least 23% per year (from the base case of 14.3%) or
4. if utility values for Barrett's oesophagus health states fall to ≤ 0.63 (from the base case of 0.81).

These need to be viewed with caution given the uncertainty around many of the model variables. Less drastic alterations in the inputs made in combination could also change the model results. Nonetheless, these scenarios may well be realistic, given the current uncertainty in the literature about the true values for many parameters. The only inherently unrealistic scenario, in current practice, is a utility (quality of life) value for the post-oesophagectomy of nearly unity, which would imply that most people recover from this major procedure to virtually perfect health – an assumption not supported by the literature.

There must be considerable uncertainty about the impact of Barrett's oesophagus on quality of life, given that many people may be asymptomatic. Our model assumed that patients with Barrett's oesophagus referred for endoscopy would have symptoms, and that there would be equal numbers of those with mild, moderate and severe symptoms of GORD as rated by PenTAG's Value of Health Panel (this is a general population panel trained in standard gamble methods). A utility value of 0.81 was given for Barrett's oesophagus. Population norms for the relevant age range are 0.8 using a UK sample and derived from the EQ5D.

Non-surveillance continues to cost less and result in better quality of life whatever the surveillance intervals for Barrett's oesophagus and dysplastic states and whatever the costs (including none) attached to endoscopy and biopsy as the surveillance test.

The probabilistic analyses assess the overall uncertainty in the model. According to this, it is very unlikely that surveillance will be cost-effective even at relatively high levels of willingness to pay. The simulation showed that, in the majority of model runs, non-surveillance continued to cost less and result in better quality of life than surveillance.

At the population level (i.e. people with Barrett's oesophagus in England and Wales), a value of £6.5 million is placed on acquiring perfect information about surveillance for Barrett's oesophagus using expected value of perfect information (EVPI) analyses. This is if the technology (surveillance) is assumed to be relevant over 10 years. As with the one-way sensitivity analyses, the partial EVPI

highlighted recurrence of ACO after surgery and time taken for ACO to become symptomatic as particularly important parameters in the model.

Gaps in the evidence

Most of the published data on Barrett's oesophagus and surveillance come from uncontrolled case series. Reporting of data was generally poor in the studies included in this review.

Few data are available in the literature on the natural history of Barrett's oesophagus, particularly around the progression of Barrett's oesophagus through dysplastic states to ACO and then progression to symptomatic adenocarcinoma. Prevalence of Barrett's oesophagus in the general population and the clinical characteristics of the population presenting for endoscopy are also not well described. Follow-up in most studies is relatively short.

No data were identified on the performance of endoscopy as a test for identifying progression of Barrett's oesophagus to dysplasia or adenocarcinoma.

The current evidence base suggests that there is no intervention yet proven to reduce cancer risk in patients with Barrett's oesophagus, regardless of control of symptoms or regression of Barrett's oesophagus changes to normal.

The major gap in the evidence is the lack of RCT data on the effectiveness of surveillance programmes in reducing morbidity and mortality from adenocarcinoma. The lack of standard diagnostic criteria, diagnostic methods and surveillance intervals all hamper comparison between studies of surveillance programmes.

Possible specific harms of surveillance, either due to physical or psychological/emotional adverse effects, of Barrett's oesophagus are not generally reported in the studies identified here.

Conclusion

The systematic review concludes that there is insufficient evidence available to assess the clinical effectiveness of surveillance programmes of Barrett's oesophagus. There are numerous gaps in the evidence, of which the lack of RCT data is the major one. The expert workshop reflected these gaps in the range of topics raised as important in answering the question of the effectiveness of surveillance. Previous models of cost-effectiveness have most recently shown that surveillance programmes either do more harm than good compared with no surveillance or are unlikely to be cost-effective at usual levels of willingness to pay.

The PenTAG cost–utility model has shown that, across a range of values for the various parameters that have been chosen to reflect uncertainty in the inputs, it is likely that surveillance programmes do more harm than good. They cost more and confer lower quality of life than no surveillance.

Probabilistic analysis shows that, in most cases, surveillance does more harm and costs more than no surveillance. It is unlikely, but still possible, that surveillance may prove to be cost-effective. The cost-effectiveness acceptability curve, however, shows that surveillance is unlikely to be cost-effective at either the 'usual' level of willingness to pay (£20,000–30,000 per QALY) or at much higher levels. The expected value of perfect information at the population level is £6.5 million.

Recommendations for further research

Further research is required before the question of the effectiveness and cost-effectiveness of surveillance of Barrett's oesophagus in reducing morbidity and mortality from ACO can be answered with confidence. In addition, such evidence may form a vital part of any education programme for clinicians to support the decision to continue or cease surveillance. Future research should target both the overall effectiveness of surveillance and the individual elements that contribute to a surveillance programme, particularly the performance of the test and the effectiveness of treatment for both Barrett's oesophagus and ACO. In addition, of particular importance is the clarification of the natural history of Barrett's oesophagus. More detailed research proposals will be discussed separately with the HTA programme to inform their commissioning process.

Chapter 1

Aims

The aims of this project were as follows:

1. to assess what is known about the effectiveness, safety, affordability, cost-effectiveness and organisational impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus
2. to identify important areas of uncertainty in current knowledge for these programmes
3. to identify important areas of research for the HTA Prioritisation Strategy Group to consider addressing by commissioning further research.

Chapter 2
Background

Project background

This project was commissioned by the UK's Health Technology Assessment (HTA) programme following a previously unsuccessful attempt to commission primary research around Barrett's oesophagus. This was felt by the HTA programme to reflect lack of clarity about the current state of knowledge and areas of uncertainty that might be most important for the NHS to investigate. We were asked to identify systematically what was known about surveillance of Barrett's oesophagus and also, using economic modelling methods and structured consultation with experts at a day-long workshop, we were asked to help identify the most important areas of uncertainty to be investigated through primary research projects. A report of the systematic review (Chapter 4), the workshop (Chapter 5) and economic modelling (Chapter 6), including expected value of perfect information (EVPI), form our submission to the HTA programme and may help them to prioritise future areas for primary research.

Description of underlying health problem

The oesophagus is the muscular tube that carries food from the mouth to the stomach. Normally, the oesophagus has a stratified squamous epithelial lining which is pinkish white. Barrett's oesophagus describes the appearance of the oesophagus when normal squamous cells are replaced with columnar cells, giving a red appearance on endoscopic visualisation. This replacement, known as metaplasia, leads to the composition of the oesophageal lining resembling that of the stomach and small intestine. These changes are thought to be the result of chronic exposure of the oesophageal lining to stomach contents and bile as a result of gastro-oesophageal reflux disease (GORD) (acid indigestion or heartburn; US spelling GERD). Although endoscopic appearance is usually characteristic, histological confirmation is required to determine the presence of intestinal metaplasia (IM) and of goblet cells, another characteristic feature of Barrett's oesophagus, which are not seen in the normal oesophageal lining.

The risk of developing adenocarcinoma of the oesophagus (ACO), one type of cancer of the oesophagus, is increased in patients with Barrett's oesophagus. The magnitude of this increased risk, however, remains uncertain.[1] It has been estimated at 30–125 times that of the general population,[2] but it has also been suggested that published estimates of cancer risk among those with Barrett's oesophagus are subject to publication bias. A previous analysis of reported cancer risk in 27 systematically identified case series studies up to 1998 showed a strong negative association between incidence and study size ($p < 0.001$).[3] A funnel plot diagram suggested publication bias with a paucity of small studies showing low risk.[3] In addition, it is unclear whether Barrett's oesophagus is a necessary step in ACO development. In a recent review of the pathogenesis of Barrett's oesophagus, Lagergren and colleagues reported on a Swedish study which found 118/189 Barrett's oesophagus cases in ACO specimens (62%), whereas other studies report 75% association of Barrett's oesophagus in ACO specimens (quoted by Fitzgerald and colleagues[4]).

Outcomes for ACO are poor, with a 1-year survival rate of 21% in men and 25% in women and a 5-year survival rate of 5% in men and 8% in women.[5] Currently, the only accepted treatment is complete oesophagectomy (removal of the oesophagus), an operation which itself has around a 10% mortality rate in clinically presenting cases. The rationale for surveying Barrett's oesophagus patients is that there is a better chance of cure, and therefore survival, from oesophagectomy the earlier ACO is identified and treated. However, entry into a surveillance programme may not be recommended if no survival advantage is envisaged, for example in the very elderly and/or those with co-morbidities in whom oesophagectomy may carry substantial peri- and postoperative risk. Controversy exists as to the value and frequency of surveillance among different population groups.

Symptoms and aetiology

Prolonged symptoms of GORD have been found to be associated with Barrett's oesophagus.[6,7] However, it is not found in all cases and Barrett's oesophagus alone does not appear to cause

symptoms, whereas GORD is a common condition. It has been estimated that 4–9% of adults experience GORD on a daily basis and up to 20% on a weekly basis.[8] Of those suffering from GORD undergoing investigation, 6–14% will have Barrett's oesophagus on endoscopy.[8] There is an unknown pool of undetected Barrett's oesophagus in the community that is undetected precisely because symptoms are absent or mild enough not to lead to endoscopic investigation. Estimates of the impact of Barrett's on quality of life (QoL) are therefore difficult to assess. Prevalence of reflux in the relatives of patients with Barrett's oesophagus is reported to be 2.2–4.8 times that of controls.[9] Hiatus hernia is also associated with Barrett's oesophagus.[10]

GORD occurs when the pinch valve at the distal end of the oesophagus is weak, allowing the backflow of stomach contents. The digestive juices containing acid and bile cause cell damage in the lower oesophageal lining. In addition to symptoms of heartburn, GORD may cause acid regurgitation, food regurgitation, pain on swallowing and coughing. GORD may be aggravated by smoking, alcohol and certain food types such as fats and is associated with obesity.

GORD is associated with other complications such as strictures and erosive oesophagitis.[11] A recent, large Swedish study found a strong relationship between GORD symptoms and ACO [odds ratio (OR) 7.7, 95% confidence interval (CI) 5.3 to 11.4 adjusted for confounding variables].[7] Risk increased with severity and frequency of symptoms but the presence of Barrett's oesophagus had no effect. A recent study comparing cohorts of those with Barrett's oesophagus (n = 1677), oesophagitis (n = 6392) and a reference cohort (n = 13,416) suggested that Barrett's oesophagus was associated with a 10-fold increased risk of oesophageal cancer compared with the general population.[17] However, this study has been criticised for examining all oesophageal cancers rather than ACO separately, being underpowered (only 43 oesophageal cancers were detected in total, 13 in the Barrett's oesophagus group) and possible confounding due to the association of Barrett's oesophagus with long-standing GORD.[13]

Prevalence of dysplasia is strongly associated with age and with length of Barrett's oesophagus,[14] which may be markers of the length of time that Barrett's oesophagus has been present. Little is known about the natural history of dysplasia.[15] Areas of dysplasia within Barrett's oesophagus mucosa may be very small and hard to distinguish at endoscopy. Further, diagnoses of high-grade dysplasia (HGD), low-grade dysplasia (LGD), indefinite for dysplasia (ID) and absent dysplasia may not be consistent either between samples or observers. HGD may regress to LGD, although it is also associated with adenocarcinoma undiagnosed at biopsy. In a summary of 15 publications reporting on resection of patients with HGD, Wright (1997)[16] records the number of resected samples that were found to contain cancer. Although in many studies the number of patients was small, the studies suggest that 0–73% (mean 45%) of all those with HGD also had unidentified ACO at the time of surgery (*Table 1*).

Defining and diagnosing Barrett's oesophagus

The traditional definition of Barrett's oesophagus is the replacement of the normal squamous lining of the lower oesophagus with metaplastic columnar cells for at least 3 cm of its length. At this length, it is more easily defined by endoscopy, but any less than this and it may be harder to distinguish visually between Barrett's oesophagus and the normal gastric mucosa, which also has columnar cells in the epithelium lining the lower oesophagus. This is due to some vagueness of local anatomy at the gastro-oesophageal junction (GOJ), together with a typically weak sphincter in patients with reflux disease and the possibility of hiatus hernia (present in 96% of patients with Barrett's oesophagus[9]). More recent definitions have stated that any segment length of intestinal metaplasia should be defined as Barrett's oesophagus. Those longer than 3 cm are known as long-segment Barrett's oesophagus (LSBO) and those shorter than 3 cm are short-segment Barrett's oesophagus (SSBO). There is some evidence for LSBO showing more acidic exposure and lower sphincter pressure than SSBO, although the two types of disease are qualitatively similar.[17]

Endoscopically suspected Barrett's oesophagus is usually confirmed through biopsy of the area to look for IM and goblet cells. Some protocols recommend four quadrantic biopsy samples taken with jumbo forceps every 1–3 cm of suspected Barrett's oesophagus, although the number of biopsies needed to detect IM has not been determined. Further, there is no evidence to show that this method has a diagnostic benefit over random sampling.[18] More IM is found with increasing numbers of biopsies taken[17] and it has been suggested that most, if not all, patients with Barrett's oesophagus appearance will have IM, although sampling error means this may be

TABLE 1 *Reported rates of adenocarcinoma in oesophagectomy specimens from patients whose endoscopic biopsies showed only HGD*[16]

Authors	Year	No. of patients with pre-operative HGD diagnosis	No. of patients with ACO in resected specimen	Missed cancers (% of those with ACO but HGD diagnosis)
Altoki *et al.*	1991	8	3	38
DeMeester *et al.*	1990	2	1	50
Edwards *et al.*	1996	11	8	73
Hamilton and Smith	1987	3	2	67
Hetimiller	1996	30	13	43
Lee	1985	4	3	75
Levine *et al.*	1993	7	0	0
McArdle *et al.*	1992	3	2	67
Pera *et al.*	1992	18	9	50
Reid *et al.*	1988	4	0	0
Rice *et al.*	1993	16	6	38
Schnell *et al.*	1989	43	21	49
Skinner *et al.*	1983	3	2	67
Streitz *et al.*	1993	9	2	22
Wright *et al.*	1994	15	7	47
Overall[a]	–	176	79	45

[a] Calculated by PenTAG.

missed by biopsy samples.[18] A balance between establishing an accurate diagnosis, patient discomfort and reasonable burden on the pathology laboratory must be established.

Biopsies are also essential to detect and grade the presence of further cell changes to abnormal cells (dysplasia) which may be precursors to adenocarcinoma. Dysplasia may be described as low grade (LGD), high grade (HGD) or indefinite (ID). Patients with Barrett's oesophagus are thought to pass sequentially though stages of LGD and HGD to adenocarcinoma,[15] although it is not proven that all patients with Barrett's oesophagus inevitably progress. Studies of reliability of dysplasia diagnosis have found inter-observer agreement of up to 70% for LGD[2] and HGD reliability slightly better at about 85%.[9] Although this may be increased by extensive biopsy sampling, this is not always practical for either patient or pathologist. If a diagnosis of HGD remains uncertain, repeat biopsy within 1 month is recommended.[15] Acid suppression therapy is necessary prior to repeat endoscopy as oesophagitis can make diagnosis difficult.[15]

Emerging diagnostic techniques

Given the problems of sampling error in accurate diagnosis of dysplasia and IM, a number of other techniques, permitting 'optical biopsies', are being explored. None are yet in use as routine practice.

Staining techniques (chromoendoscopy) have been used to enhance recognition of the abnormal cell changes of Barrett's oesophagus. Targeted methylene blue staining may allow diagnosis with fewer biopsies; however, it is a skilled technique, may prolong the length of endoscopy procedures and reports of the technique's usefulness differ.[17]

Light-induced fluorescence spectroscopy may be used to evaluate the malignant or benign presentation of Barrett's oesophagus, LGD and HGD based on the assumption that different fluorescence patterns will be seen in these conditions compared with normal mucosa.[9]

Endoscopic fluorescence has been used to try to detect dysplasia. This is used after a photosensitising chemical, such as 5-aminolaevulinic acid, has been applied through spray or oral administration; it is transformed within the oesophageal cells to a detectable active compound, concentrated mainly in neoplastic tissue. Reported specificity and sensitivity have not been encouraging.[9]

Light-scattering spectroscopy, a technique using white light from fibre optics during endoscopy, has been used to detect dysplastic nuclei crowding and enlargement. High levels of specificity and sensitivity in identifying LGD and HGD have been reported, but this technique is still experimental.[9]

Epidemiology

Epidemiology of Barrett's oesophagus

About 2% of those referred for endoscopic investigation (for any symptoms) are found to have Barrett's oesophagus.[5] It has been estimated that clinically identified cases of Barrett's oesophagus in the USA (at about 22.6 per 100,000 patients) represent just 6% of the total Barrett's oesophagus in the general population, with undetected rates estimated at 376 per 100,000 based on autopsy studies.[10] Upper gastrointestinal (GI) endoscopy studies in patients without upper GI symptoms but undergoing sigmoidoscopy for colorectal cancer have shown Barrett's oesophagus rates as high as 25%.[10] Although detected cases of Barrett's oesophagus have increased about 28-fold over the last 50 years, endoscopic investigations have also increased about 22-fold.[10]

The UK Barrett's Oesophagus Registry (UKBOR) was formed in 1996 to investigate risk factors for those with Barrett's oesophagus developing adenocarcinoma and risk factors for Barrett's oesophagus itself. It holds demographic data on 5717 people diagnosed with Barrett's oesophagus from 27 UK hospitals, and complete data on 3880. There is a male to female ratio of 1:1.7.[19] The mean age at diagnosis is 62.0 for men and 67.5 for women. Older people are known to be most affected, with two-thirds of cases being diagnosed in those over the age of 65 years. However, given that a large population with Barrett's oesophagus may not be symptomatic and remain undiagnosed, it has been estimated by Falk[20] (quoted in Conio and co-workers[9]) that the mean age of development may be about 40 years. Those with asymptomatic or minimally symptomatic Barrett's oesophagus will not enter into the GORD treatment and investigation process as they will not present to health services. In practice, this behaviour, coupled with no screening of GORD patients, results in more cases of ACO being diagnosed at first endoscopy rather than identified as part of a surveillance programme.[17]

Epidemiology of adenocarcinoma

There has been a marked increase in the incidence of ACO of the lower third of the oesophagus and GOJ in the last 20 years.[8] There are an estimated 7000 new diagnoses and 6000 deaths from oesophageal cancer each year, but these figures include both squamous and adenocarcinoma.[21] ACO is more common in men than in women, with National Statistics showing an annual incidence in England and Wales of 15.8 and 9.0 per 100,000, respectively.[21] Given these figures, a GP with an average list size of 2000 patients may not see even one new patient with oesophageal cancer in a year.[5] A district general hospital serving a population of about 200,000 could expect to deal with 25 people with oesophageal cancer (both squamous and ACO) in a year.[5]

Although Barrett's oesophagus is a known, if currently unquantified, risk factor,[1] most people diagnosed with ACO have not previously been known to have Barrett's oesophagus. A recent US meta-analysis of 12 studies reporting on resected ACOs found that only 4.7% had a prior Barrett's oesophagus diagnosis.[22]

ACO is rare in those under 50 years old, and incidence increases sharply with age, with a median onset of 65–69 years in men and 80–84 years in women (data taken from graph).[21] Smoking and obesity are risk factors for developing adenocarcinoma.[8] White men appear to be most affected.[17] There appears to be a genetic link to GORD (heritability of 30% estimated from twin studies, quoted by Fitzgerald and colleagues[4]), and hence to the development of Barrett's oesophagus and perhaps ACO.

Studies that report a relationship between oesophageal cancer risk and diet do not distinguish between squamous cell cancer and adenocarcinoma. The World Cancer Research Fund, assessing 22 case–control studies, found 18 reported significantly decreased risk of oesophageal cancer with higher fruit and vegetable intake.[22]

Although those with Barrett's oesophagus have been estimated to have an increased risk of ACO of 40 times that of the general population,[24] most individuals with Barrett's oesophagus will not develop ACO and few will die from ACO.

Treatment: GORD and Barrett's oesophagus

The goal of treating diagnosed Barrett's oesophagus is to induce regression or ablation of the metaplastic columnar epithelium. It is assumed that removing the Barrett's oesophagus will reduce the risk of progression to ACO, but there is little evidence to support this.[25] However, given the possible sequential progression of Barrett's oesophagus through dysplastic states to cancer, treatment for GORD and for HGD and adenocarcinoma is also relevant.

Clinical guidelines from the National Institute for Health and Clinical Excellence (NICE) on the use of proton pump inhibitors (PPIs) for patients with

GORD,[26] including those with Barrett's oesophagus, is that they should be treated with a healing dose of PPIs until symptoms have been resolved, after which the dose is stepped down to the lowest that maintains symptom control. If symptoms reappear, the higher dose is recommenced. There is contradictory evidence about the ability of PPIs to cause partial regression of Barrett's oesophagus. The guideline further recommends that all patients over the age of 55 years who newly present with dyspepsia, together with younger patients who also have more serious symptoms (including unexplained weight loss, difficulty in swallowing, anaemia or progressively worsening symptoms), should be referred for endoscopic investigation. The guideline acknowledges that referral for those aged 45–55 years is a grey area. Recently updated guidelines from the American College of Gastroenterology have removed any age limit for referral for endoscopy, observing that those "with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper [GI] endoscopy."[17] Barrett's oesophagus is more prevalent among those with longer duration of GORD symptoms.

Treatment for Barrett's oesophagus has not differed from treatment for GORD until recently, with medical treatment with PPIs, or surgical interventions, such as fundoplication, aiming to control the symptoms of acid reflux.[27] However, symptom control with either method does not necessarily equate to acid reflux control and does not induce significant regression of intestinal metaplasia.[9] This means that studies assessing the effect of reflux control on Barrett's oesophagus may often include patients whose reflux is not properly controlled, hampering meaningful assessment of the effect of treatment on progression to dysplasia or ACO.[27]

Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin may reduce the progression of Barrett's oesophagus to ACO through inhibition of inflammatory pathways such as cyclooxygenase 2 (COX-2), which is over-expressed in Barrett's oesophagus owing to acid exposure. This is currently being investigated in the UK's AspECT trial (ISRCTN 85156844) in 9000 patients with Barrett's oesophagus randomised to receive 20 or 80 mg of esomeprazole, with or without 300 mg of aspirin.[28]

The oesophageal lining of those with Barrett's oesophagus may be ablated using a range of methods; thermal (multipolar electrocoagulation, argon plasma coagulation, Nd:YAG laser, argon laser, potassium titanyl phosphate laser), photochemical [photodynamic therapy (PDT), sodium porfimer, 5-aminolaevulinic acid], mechanical (endoscopic mucosal resection), ultrasound and cryotherapy. So far, none of these methods has proved more effective than the others.[9] A systematic review of treatment by van den Boogert and colleagues[15] identified 28 reports (including 15 abstracts) reporting on a total of 284 patients with Barrett's oesophagus (seven with HGD) who were treated with thermal ablation techniques. Follow-up was for 10–18 months for electrocoagulation and 2–18 months for laser ablation. They concluded that such treatment can reverse Barrett's oesophagus, although multiple sessions may be required. In addition, a total of two perforations were reported. Van den Boogert and colleagues[15] identified reports by nine authors reporting on treatment of 233 patients (63 in published reports). These found that Barrett's oesophagus could be reversed by PDT, although complete remission was only found in a minority of patients. Skin photosensitivity and stricture formation were found with some types of chemical sensitising agents.

While there is a strong association between Barrett's oesophagus and ACO, it is as yet unclear whether it is a necessary prior step, or whether ACO is an inevitable consequence.[4] There is currently no evidence to show that ablating Barrett's oesophagus reduces ACO incidence.[6]

Treatment: dysplasia and adenocarcinoma

As the population with Barrett's oesophagus is typically elderly, evidence suggests that they infrequently die of adenocarcinoma, whereas treatment of ACO, especially in more advanced stages, is associated with increased mortality and morbidity. Current clinical treatment for ACO in the UK is usually removal of a large part of the oesophagus (oesophagectomy). However, only about one-third of patients diagnosed with ACO will be suitable candidates for surgery,[29] as the rest either have an advanced stage of cancer at presentation or are considered too frail owing to age and the presence of co-morbidities. In these cases, palliation to relieve symptoms will be required. This may include chemo- or radiotherapy and the insertion of stents.

Radical oesophagectomy remains the most common treatment aimed at cure for ACO in the UK, whereas in the USA, more patients with HGD may be given surgery. Operative mortality rates of

3–10% have been reported.[15] With short-term morbidity of about 30% (for adverse effects such as pneumonia, mediastinitis and the leaking of digestive fluids) and complications in up to 78%, this is far from a simple treatment option.[15] Overall 5-year survival rates range from 24% to 82% and are affected by the stage of adenocarcinoma and patient characteristics.[15] Given the radical nature of this treatment, frail, older patients and those with co-morbidities are not usually considered suitable. They will be offered palliation, and 1-year survival rates are as low as 10%.[30]

A recent meta-analysis of 11 randomised controlled trials (RCTs) containing a total of 2311 patients suggests that the addition of neo-adjunctive chemotherapy, followed by surgery, confers a modest survival advantage at 2 years compared with surgery alone (absolute difference 4.4%, 95% CI 0.3 to 8.5%).[31] However, treatment-related mortality was increased (combined chemotherapy 1.7%; 95% CI 0.9 to 4.3%). A non-significant increase in survival was also seen with chemoradiotherapy (6.4%, 95% CI –1.2 to 14.0%), which also increased treatment-related mortality by 3.4% (95% CI 0.1 to 7.3%).

It has been suggested that centres with low volumes of this surgery may have worse outcomes. However, this has been challenged by a recent analysis of 1125 patients surgically treated for oesophageal cancer (794 with ACO) treated in one UK region, once patient age and disease factors had been taken into account.[32]

Emerging technologies for treatment of ACO

A number of endoscopic ablative therapies are being developed which may offer the possibility of treatment for patients not currently regarded as suitable for oesophagectomy. Endoscopic ablation can be performed using mechanical, chemical or thermal (electrosurgical or laser) methods.[15] Laser thermal ablation allows the depth of tissue resected to be controlled by the equipment, reducing the chance of user error present in electrosurgery.

Mechanical resection uses a diathermic snare or ultrasound to remove affected areas physically. A review by van den Boogert and colleagues[15] did not find any studies reporting on mechanical ablation of Barrett's oesophagus, although it has been trialled in early ACO.

In PDT, a photosensitising agent is injected into the bloodstream and subsequently absorbed by cells all over the body. The agent remains in cancer cells for longer than it does in normal cells. When these treated cancer cells are exposed to a laser, introduced endoscopically through a fibre-optic cable, the photosensitising agent absorbs the light and produces an active form of oxygen that destroys the treated cancer cells. Light exposure must be timed carefully to occur in the interval when most of the photosensitising agent has left healthy cells but remains in the cancer cells, thereby minimising healthy cell damage.

PDT for HGD in Barrett's oesophagus has been reviewed recently by the NICE Interventional Procedures Advisory Committee (IPAC), and guidelines were finalised in August 2004. The consultation document[33] states that PDT appears to have no major safety concerns and it may be efficacious in downgrading HGD. However, it also states that it is not currently known if the progression of Barrett's oesophagus to ACO is influenced. Clinicians wishing to use PDT among this patient group are therefore advised to inform local clinical governance leads and to ensure that patients are aware of the lack of information about long-term prognosis.

Treatment while in a dysplastic state is controversial, with some advocating oesophagectomy for HGD, despite the risks of this procedure,[17] and management with ablative techniques are being developed.[15] In healthy patients, with cancer identified early and operated on by experienced surgeons, survival may be as high as 80–90% at 5 years.[17]

Surveillance of Barrett's oesophagus

Once Barrett's oesophagus has been diagnosed, patients may enter a surveillance programme, the aim of which is to decrease morbidity and mortality from ACO through earlier detection and treatment. Those considered unfit for surgery may therefore not be entered into surveillance. The American College of Gastroenterology guidelines recommend that 3 years between endoscopies is reasonable where no evidence of dysplasia is seen on consecutive endoscopies.[17] Evidence of LGD leads to a recommendation of endoscopy and biopsies every year. LGD is a transitory phase: loss of dysplasia on consecutive biopsies results in reduced intensity surveillance and progression to HGD increases it to every 3 months. A diagnosis of HGD also invokes a repeat examination to check for missed ACO or confirm HGD.[17]

There is some evidence that patients may not comply well with surveillance programmes. A

German study by Eckardt and colleagues of 60 patients with Barrett's oesophagus found that only 42% complied completely with the surveillance schedule, 42% partially complied and 16% did not return for any further endoscopies.[34]

Evidence for the effectiveness of surveillance of Barrett's oesophagus is weak and varied.[25] It has been shown that among patients diagnosed with ACO, those who were in a surveillance programme are likely to have their cancer detected at an earlier stage than those not under surveillance.[35] Some studies have also shown that survival is greater in patients with adenocarcinoma who are part of a surveillance programme.[36] However, this is open to bias, as those not in a surveillance programme may be older and have more concomitant illness and may also be affected by lead time bias. Further, studies of surveillance programmes have often shown that the number of cancers detected is low, and the death rate from such cancers even smaller, as patients die from other causes. Some patients may not be fit for surgery even if ACO is detected.[37,38]

Identifying those at risk of progression

Surveillance of Barrett's oesophagus patients aims to identify HGD or early ACO so that early intervention (oesophagectomy) can be performed, with its enhanced survival prospects. However, there are a number of problems with HGD as a risk marker, including sampling errors, inter-rater reliability of HGD diagnosis, the fast progression of some patients from HGD to ACO and their frequent presentation concurrently. LGD appears to be a less useful marker of risk of ACO. There are concerns to identify different, more easily definable and predictable markers of risk. Risk of developing dysplasia has been shown to be associated with length of Barrett's oesophagus.[14]

There have been a number of attempts to identify biological measurements that can predict which patients are at greatest risk of developing ACO (biomarkers). More than 60 have been suggested for Barrett's oesophagus alone.[39] A predictive biomarker may identify a clone of cells that has the necessary combination of genetic errors to progress to cancer.[39] Currently, suggested biomarkers that have been studied most intensively are flow cytometric (tetraploidy, aneuploidy) and over-expression of p53.[39] Other potential biomarkers include allelic losses, proliferation indices, accumulation of acidic fibroblast growth factor, expression of blood group antigens and sucrose–isomaltase during the progression of Barrett's oesophagus to ACO.[2] However, all of these are still under investigation, so none of these biomarkers have yet been adopted in clinical practice.

Quality of life

Gastro-oesophageal reflux disease

It is not known what proportion of those with Barrett's oesophagus suffer from symptoms of GORD as there is undiagnosed Barrett's oesophagus in the population as a whole. Of those with Barrett's oesophagus who also experience GORD, an adverse impact on QoL is likely. A recent study in 1011 German and Swedish patients suffering GORD symptoms for at least 1 year found that they experienced considerable impact on QoL. Using a rating scale, the EQ-5D, time trade-off (TTO) and standard gamble methods, the average utility values from each method were 0.69, 0.7, 0.88 and 0.89, respectively.[40] It is not clear what, if any, additional adverse impact compliance with a surveillance programme involves. Expert opinion considers that there may be considerable anxiety attached to anticipation of endoscopy, awareness that they are being monitored for precancerous changes and the discomfort of the actual procedure. However, it is possible that not receiving an offer of surveillance despite being diagnosed with Barrett's oesophagus may also have an adverse affect.

Symptomatic adenocarcinoma

A US study by Wildi and colleagues[41] examined QoL with malignant oesophageal dysphagia in 50 patients with that condition using the TTO method. Those with localised ACO rated it as 0.8, those with regional cancer as 0.54 and those with metastatic cancer rated their health state utility as 0.52. In an effort to simulate societal values, patients were also asked to rate the states of cancer that were not their own, which resulted in values of 0.55 for localised, 0.46 for regional and 0.27 for metastatic cancer. Rates for regional and metastatic cancer received significantly lower ratings by those not in that health state.

Oesophagectomy

Oesophagectomy involves major surgery. Following this procedure, patients are likely to need a change in eating pattern, with smaller, more regular meals recommended. Certain foods, especially soon after surgery, such as bread, milk and fruit may not be eaten, although these may be accommodated later. To avoid regurgitation and acid reflux, patients are advised not to bend down straight after eating or for long periods at any time. Eating shortly before bedtime or lying down is also to be avoided. One main problem post-

oesophagectomy is the 'dumping' of food quickly through the digestive system, which may cause a variety of symptoms such as fainting, rapid heartbeat, sweating and diarrhoea. Although this may resolve, it can also recur, even after several years.

Published utility values for the health state post-oesophagectomy are rare. We located only one study, and this was undertaken in the context of a previously published cost–utility study by Provenzale and colleagues.[42] The authors used the TTO method on an undisclosed number of patients who were alive 1 year after oesophagectomy. This gave a median rate of 0.97, which seems high in the context of published utilities for GORD above, and general population estimates of 0.8 for the age group 55–64 years.[43] As Wildi and colleagues[41] illustrate, it is known that patients with an illness are likely to give better utility ratings for their own condition than the general public. It may be that those patients who are well after surgery do rate their state very highly, given the fatal nature of inoperable ACO.

Current UK practice

A recent survey of UK practice[44] highlights the variation among practitioners about the relevance and specifics of surveillance for Barrett's oesophagus. A survey was posted to 203 members of the British Society of Gastroenterology in 2001. Three-quarters (76%) thought that surveillance of these patients was 'worthwhile' clinical practice. Of these, 83% targeted surveillance to those who were younger, had longer segment Barrett's oesophagus or signs of ulcer or stricture. Nearly two-thirds (62%) did not enter those with SSBO into a surveillance programme.

Over three-quarters (77%) of those undertaking surveillance followed some kind of protocol. Most (58%) performed random biopsies, although most also biopsied suspicious areas, and 41% followed the usual guideline protocol of four quadrantic biopsies every 2 cm.

For Barrett's oesophagus without dysplasia, frequency of surveillance was varied: 46% follow-up every 2 years, 29% less frequently and 13% more frequently. Similarly, nearly half would re-endoscope those with LGD after 6 months (48%, with 29% at 3 months and 23% at 12 months). For those with HGD, follow-up was at 2 weeks (13%), 6 weeks (43%), 3 months (18%) and 6 months (2.5%). The remaining 23% would refer directly for oesophagectomy. Just over half (55%) would get a diagnosis of HGD confirmed by two pathologists.

The majority of respondents (61%) applied an age limit for entry into a surveillance programme: at age 70 years for 20%, 75 years for 30% and 80 years for 10%. One respondent did not survey patients older than 85 years.

Relevant UK guidance

The NHS guidance *Improving Outcomes in Upper Gastro-Intestinal Cancer*[5] recommends that the following patients be referred to the upper GI diagnostic team within 2 weeks if presenting with the following symptoms:

- dysphagia (any age)
- dyspepsia combined with one or more of weight loss, proven anaemia, vomiting
- dyspepsia in patients aged ≥ 55 years, if combined with onset <1 year previously, or continuous symptoms since onset
- dyspepsia combined with at least one of family history of upper GI cancer, Barrett's oesophagus, pernicious anaemia, peptic ulcer surgery over 20 years ago, known dysphagia, atrophic gastritis, intestinal metaplasia
- jaundice
- upper abdominal mass.

The guidelines state that early referral "is likely to reduce patients' anxiety and may improve chance of survival"; however, it notes that no study has related survival time to diagnostic delay.[5] Compliance with these guidelines may bring more Barrett's oesophagus patients to light.

Impact on the NHS

It is estimated that upper GI endoscopy is required annually in 10–15 people per 1000 population.[45] This represents 2500–3750 examinations annually in a district general hospital serving a population of 250,000.[45] The cost to the hospital, using endoscopy and biopsy costs from National Schedule of Reference costs[46] of £170.22, an annual cost for 2500–3750 endoscopies would be £426,000–638,000. For England and Wales, based on a census population of around 52 million,[47] this represents 520,000–780,000 endoscopies annually at a cost of £89–133 million.

Assuming that 1.5% of those presenting for endoscopy for any reason have Barrett's oesophagus,[25] 38–52 patients with Barrett's oesophagus would be identified annually by a district general hospital serving a population of 250,000. If all these patients were to be entered into a surveillance programme, they would require follow-up every 3 years for Barrett's oesophagus

without dysplasia, every year for LGD and every 6 months for HGD. PenTAG's economic model (see Chapter 6) estimates that perfect compliance with such a surveillance programme would entail an average of seven endoscopies per patient over 20 years. This would cost £45,000–62,000 per cohort over 20 years, or an average of £2000–3000 per year in an average district general hospital. Current clinical practice suggests that compliance with surveillance programmes is not as complete as this. Assuming only three endoscopies over 20 years, the cost would be £970–1380 annually. In addition, currently only about half of patients are considered well enough for surgery and therefore suitable for surveillance. If this continues to be the case, the overall costs above would be halved.

In England and Wales, 7800–11,700 cases of Barrett's oesophagus are diagnosed annually. If all these patients were to be entered into a surveillance programme as above, the annual cost to the NHS would be around £500,000–700,000. Assuming three endoscopies over 20 years, the costs would be £200,000–300,000 annually. Again, if only half of those with diagnosed Barrett's oesophagus are considered suitable for surveillance, these costs would also be halved.

Chapter 3

Structure of the report

Project research questions

This technology assessment addresses four questions regarding surveillance programmes for Barrett's oesophagus. It varies from more usual reports in aiming to identify important areas of ignorance and uncertainty, rather than focusing on what is known:

1. What is known about the effectiveness of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus?
2. What is known about the cost-effectiveness of endoscopic surveillance for Barrett's oesophagus?
3. What are the important areas of uncertainty?
4. What is the key primary research question for the HTA Prioritisation Strategy Group to consider?

Chapter 4, a systematic review of the surveillance literature, and Chapter 5, describing the workshop processes and outputs, address Question 1. Cost-effectiveness (Question 2) is explored in Chapter 6. Important areas of uncertainty (Question 3) are discussed throughout the report and synthesised in Chapter 7, which also outlines key areas for future research (Question 4).

Chapter 4

Systematic review of the effectiveness of endoscopic surveillance of Barrett's oesophagus

General methods

The methods of the systematic review generally adhered to guidance laid out in methodological guidelines stated in the Centre for Reviews and Dissemination Report No. 4.

Inclusion and exclusion criteria

Studies were included or excluded from the review if they fulfilled the following criteria:

Inclusion

- **Interventions:** Surveillance programmes monitoring for dysplastic change in patients with Barrett's oesophagus.
- **Comparator:** No surveillance.
- **Population:** Adults presenting with Barrett's oesophagus (including those with LGD or HGD) who are entered into a surveillance programme.
- **Study design:** Systematic reviews, RCTs, comparative studies and case series with at least 300 Barrett's oesophagus patients entered into a surveillance programme. Larger case series were used in an attempt to ensure better quality and to address the possibility of publication bias previously identified in smaller trials.[3]

Exclusion

Study design:

- systematic review superseded by a more recent systematic review
- abstract only available.
- not primary diagnosis of Barrett's oesophagus
- components of surveillance only, rather than a surveillance programme
- not available in English
- not reporting on surveillance.

Assessment of the effectiveness of endoscopic surveillance of patients with Barrett's oesophagus

Search strategy

Electronic databases were searched for published surveillance studies, economic evaluations and ongoing research. Appendix 2 shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant papers. Experts in the field were also asked to provide information. See Appendix 3 for the flow of identified studies and description of excluded studies.

Identification of studies

Identification of relevant studies was made in two stages. Abstracts returned by the search strategy were examined independently by two researchers (RG and NG) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (RG and NG) examined these independently for inclusion or exclusion and disagreements were resolved by discussion.

Data extraction strategy

Data were extracted by one researcher (NG) and checked by another (RG). Actual numbers were extracted where possible. The incidences of dysplasia and adenocarcinoma were calculated using the total years of patient follow-up, where reported.

Quality assessment strategy

Assessments of study quality of case series were performed using the indicators shown below. Results were tabulated and these aspects described.

Internal validity

- size of study
- methods of patient selection and possibility of selection bias
- prospective or retrospective study
- number of patients included, excluded and lost to follow-up (attrition bias).

External validity

- timing, duration and location of study
- age of participants
- co-morbidity
- inclusion criteria
- exclusion criteria
- treatment
- length of follow-up.

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Studies were given a rating of high generalisability if there was a detailed description of the exclusion criteria and patient group, medium if there was some description of exclusion criteria and population group and low if there was no description of exclusion criteria or patient group.

Methods of analysis

Details of the study methodology and results were tabulated and are described in the text.

Results of the systematic review: quantity and quality of research available

Number and type of studies identified

We found two previous systematic reviews. No RCTs of surveillance versus non-surveillance were identified. Nine studies following at least 300 participants with Barrett's oesophagus entered into surveillance programmes were included. Seven were case series, one study compared a historical population informally surveyed with a rigorous surveillance programme and one reported on mortality among 409 patients, 143 of whom were fit to enter a surveillance programme.

Systematic reviews identified

Two systematic reviews of surveillance for Barrett's oesophagus were identified, one by Nandurkar and Talley[48] and the other by Somerville and Milne.[25] The earlier review by Nandurkar and Talley was included and reviewed by Somerville and Milne and therefore has not been further examined here. One systematic review was therefore included.[25] This review concluded that 1–2% (although maybe as high as 10%) of patients presenting for endoscopy have Barrett's oesophagus, but that general population prevalence is uncertain. Risk of ACO in Barrett's oesophagus varies from one in 52 to one in 441 years of patient follow-up. The authors concluded that it was not possible to establish the effectiveness of surveillance in Barrett's oesophagus in reducing morbidity and mortality from ACO. It was noted that less than half of those found to have Barrett's oesophagus appear to be entered into surveillance programmes.

Our evaluation using the QUOROM checklist is shown in Appendix 4.[49] This rapid review was not of high quality. In particular, data sources and search strategies are not reported in detail and there are no details of inclusion and exclusion criteria, validity assessment or data extraction methods. The review is a Development and Evaluation Committee (DEC) report – a format that is an early precursor on which current technology assessment reports are modelled. As such, the QUORUM checklist, designed for Cochrane-style reviews, may not be an ideal evaluation instrument. In addition, it had not been published when this DEC report was written. However, no other relevant evaluation tool is available.

Included studies

Nine studies were included in the current assessment. There were no RCTs. Two were comparative studies and the other seven were uncontrolled case series. The study by Fitzgerald and colleagues[50] compared a rigorous surveillance programme with a historical control group that had received informal surveillance. The study by Macdonald and colleagues[51] examined a cohort of 409 patients with Barrett's oesophagus, of whom 143 were entered into a surveillance programme. We also used an earlier publication reporting on this same cohort published in 1997[52] for additional details of the project. Seven case series of surveillance of patients with Barrett's oesophagus were also included. Details of the included studies are given in *Table 2*, and further details from the extraction sheets can be seen in Appendix 5.

External validity

Comparative studies

The comparative study by Fitzgerald and colleagues[50] examined 358 eligible patients in a UK Hospital Trust, of whom 96 entered an informal surveillance programme between 1992 and 1997, and these were compared with 196 Barrett's oesophagus patients of whom 108 entered into a rigorous surveillance programme between 1997 and 1998. Those under informal surveillance were followed up for a total of 375 patient years and those under rigorous surveillance for a total of 108 patient years. Mean length of follow-up was not stated, but would be <1 year for the rigorous surveillance group. Mean patient age was not given, but there was a 2.8:1 male to female ratio in the informal surveillance group and 3.5:1 in the rigorous surveillance group.

Macdonald and colleagues[51] followed a cohort of 409 patients with Barrett's oesophagus in a UK teaching hospital. We are treating this as a comparative study as they report on outcomes both for the 143 patients who were entered into

an annual surveillance programme and the 266 who were not considered suitable. Patients were recruited from 1984 to 1994 and the surveillance cohort were followed for a mean of 4.4 years (total patient years of follow-up = 629). It is not clear for how many patient years the non-surveillance group were followed up. The surveillance group was younger than the non-surveillance group (57 versus 69 years) and there were more men in the non-surveillance group (60% versus 47%). Furthermore, those unfit for surgery due to frailty or concomitant illness were excluded from the surveillance arm of the study.

Case series
The case series of surveillance took place from 1979 to 2001. One was from a registry in Northern Ireland,[53] one from multiple community clinics[54] and one from multiple GI endoscopy clinics.[55] The remainder were from single sites. Three studies were from the UK[50,53,56] (one of which was the comparative study[50]), two were from the USA,[57,58] two from mainland Europe[55,59] and one from Australia.[54]

The patient populations were slightly different between studies. Between 57.3 and 81% were male. Mean age ranged from 58 to 64 years but was not stated in two studies.[55,58] Details are given in *Table 2*.

Co-morbidity was not described in any study, nor is it stated why the initial endoscopy was undertaken.

Mean follow-up was for between 3.0 and 7.3 years, or from 108 to 11,068 patient years.

Inclusion and exclusion criteria were stated in most of the studies (see *Table 3*), with only Schnell[57] giving no details about inclusion and exclusion. Mostly these are broad, aiming to include only patients with diagnosed Barrett's oesophagus.

Internal validity

Sample size

We only included studies that contained more than 300 participants. The number of patients included ranged from 327 to 2969 (median 742). Schnell[57] reported that 1099 patients with Barrett's oesophagus were identified; however, full follow-up was only reported on a subgroup of 75 patients with HGD.

Selection bias

Comparative studies. Methodological details of the studies are given in *Table 3*. For the study by Fitzgerald and colleagues[50] no inclusion or exclusion criteria are stated for the informally surveyed group. Information about these patients was taken retrospectively from records; those without records or with missing details may not have been included, and this may lead to bias. Those undergoing rigorous surveillance had histologically confirmed Barrett's oesophagus, although other criteria appear to rely only on the time of initial endoscopy. It is possible that the historical group differs from the more recent study group.

Only those with confirmed metaplasia in Barrett's mucosa >30 mm were included in the study by Macdonald and colleagues.[51] The authors acknowledge that this will exclude those now considered to have SSBO. In addition, the two groups followed up differ, with the group entered into the surveillance programme younger and fitter than those not entered into the programme. As data for the group not under surveillance are taken from medical records, it is possible that some details may be missing.

Case series. Inclusion and exclusion criteria were not stated in one case series.[57] For two case series, histologically confirmed Barrett's oesophagus was an inclusion criterion. It was not clear if Barrett's oesophagus had to be confirmed by biopsy in four studies.[53,54,58,59] Differences in definitions of Barrett's oesophagus may lead to different populations being included; in particular, they may have different rates of false diagnosis.

Patients lacking clinical records were excluded from the retrospective study by Bani-Hani and colleagues.[56] This may bias the findings as patients having positive findings may have been more likely to have records. The registry studies by Hurschler and colleagues[59] and Murray and colleagues[53] also assess surveillance retrospectively, which may be more open to bias in patient and data selection than prospective study designs.

Ferraris and colleagues.[55] Hillman and colleagues[54] and Murray and colleagues[53] excluded those who had ACO, or co-morbidity at the initial endoscopy. In addition to these patient groups, Hillman and colleagues[54] and Murray and colleagues[53] also excluded those diagnosed with ACO within 2 and 6 months, respectively, of initial endoscopy. This prevents ACOs present (but not diagnosed) at an index endoscopy (screening) being wrongly counted as identified as part of a surveillance programme.

TABLE 2 *Details of included studies*

Authors Design	Setting	Recruitment dates	No. of oesophagus patients with Barrett's diagnosis	Patient characteristics		Length of follow-up	
				Male (%)	Mean age (range) (years)	Mean (years)	Total (patient years)
Fitzgerald *et al*. (2001)[50] Rigorous surveillance vs informal surveillance historical control group	Havering Hospitals NHS Trust (UK)	1992–7 (Informal surveillance)	358 (96 surveillance)	Surveillance Ratio M:F 2.8:1	Surveillance 62 (28–89)	Not stated	375
		1997–8 Rigorous surveillance)	196 (108 surveillance)	Surveillance Ratio M:F 3.5:1	Surveillance 64 (34–83)	Not stated	108
Macdonald *et al*. (2000)[51] Surveillance vs non-surveillance	University teaching hospital UK	1984–94	409 (143 surveillance)	Surveillance 60 Non-surveillance 47	Surveillance 57 (17–69) Non-surveillance 69 (17–94)	4.4	629
Bani-Hani *et al*. (2000)[56] Case series	Annual surveillance programme at Leeds General Infirmary (UK)	Jan. 1984–Jan. 1995	597 (357 surveillance)	All patients 56.0 Surveillance 58.0	All patients 63 (2–94) Surveillance Male 58 (15–79) Female 65 (28–79)	3.6	1293
Hillman *et al*. (2003)[54] Case series	Community-based gastroenterology clinics (Australia)	Jan. 1981–July 2001	433 (353 surveillance)	Surveillance 71.0	Surveillance 59.2 (18–89)	3.5 (median)	1588
Hurschler *et al*. (2003)[59] Registry study	Institute of Pathology (Switzerland)	1989–99	742[a]	65.0	64.4 (17–90)	4.6 >1 year FU group	966 >1 year FU group
Murray *et al*. (2003)[53] Registry study	Regional Registry (Northern Ireland)	Jan. 1993–Dec. 1999	2969	57.3	Not stated	3.7	11,068
Schnell (2001)[57] Case series	Outpatient endoscopy clinic (USA)	Jan. 1979–July 1996	1099	Stated for HGD subgroup only[b]		7.3 HGD group	548[d] HGD group
Reid *et al*. (2000)[58] Case series	Seattle Barrett's oesophagus project (USA)	July 1983–June 1998	327	81.0	Median 62 (22–83)	3.9[c]	1200

continued

TABLE 2 *Details of included studies (cont'd)*

Authors Design	Setting	Recruitment dates	No. of oesophagus patients with Barrett's diagnosis	Patient characteristics		Length of follow-up	
				Male (%)	Mean age (range) (years)	Mean (years)	Total (patient years)
Ferraris *et al.* (1997)[55] Case series	Multicentre–upper GI endoscopy clinics (Italy)	Nov. 1987–June 1995	344 eligible for surveillance 187 complied with follow-up > 1 year	Eligible patients 73.5 > 1 year follow-up 72.7	Eligible patients (19–75) > 1 year follow-up (14–75) Mean not stated	3.0 (median)	562

[a] Total diagnosed with Barrett's oesophagus at initial or follow-up endoscopy excluding those with ACO.
[b] 12 HGD patients progressed to ACO, 100% male, mean age 60 years; 63 HGD patients remained HGD, 98% male, mean age 64 years.
[c] Reported only for 285 patients without ACO at last contact.
[d] Not reported in text; calculated from extracted data.

Attrition and intention-to-treat analysis
Comparative studies. In the study by Fitzgerald and colleagues,[50] those diagnosed endoscopically between 1992 and 1997 underwent 'informal' surveillance and their records were assessed retrospectively. Those diagnosed between 1997 and 1998 underwent a more formal surveillance regimen and were assessed prospectively. Mortality data were given as all-cause mortality among those diagnosed with ACO; deaths due to ACO were not provided separately. No details of loss to follow-up were stated.

Macdonald and colleagues[51] report that attrition by the end of the study period was extremely high in the surveillance group at 94.4%, although only 18.9% of this was due to default or patients moving out of area. The remainder was due to the development of concomitant illness, increased frailty and death from other causes. Although details of deaths from ACO and from other causes are reported in both groups, it is not possible to identify which patients in the non-surveillance group may have had ACO that did not prove fatal during the study period.

Case series. Both Hillman and colleagues[54] and Reid and colleagues[58] excluded those not returning for at least one subsequent endoscopy from further analysis. These patients should be recorded as lost to follow-up, and intention-to-treat (ITT) analysis performed. Only three studies reported on loss to follow-up. Bani-Hani and colleagues[56] do not give separate details about mortality, although they do report a single loss to follow-up figure for those who left the programme owing to death, age or co-morbidity combined (23.8%). Ferraris and colleagues[55] reported that 46% did not comply with follow-up and Hillman and colleagues[54] that 5.9% did not return for follow-up endoscopy.

Bani-Hani and colleagues[56] do not report on mortality individually but, as stated above, report a combination figure for those lost to follow-up through death, age or co-morbidity. Murray and colleagues[53] and Reid and colleagues[58] also do not report on mortality. Among the other studies, mortality is recorded in a number of different ways. Ferraris and colleagues[55] report death only in those patients who progress to ACO, although both cancer and all-cause mortality are given for this group. Hillman and colleagues[54] report on deaths in those progressing to ACO or to HGD, from cancer and other causes, and also report on perioperative mortality in those undergoing oesophagectomy. Hurschler and colleagues[59] report on mortality among six patients who develop ACO, although these are not separated into cancer and other cause mortality. Schnell[57] reports on mortality in a subset of patients who develop HGD and the number of deaths from ACO and other causes are given. Perioperative mortality is also reported. This is the only included study which used survival analysis on mortality data.

Detection Bias
Methods for diagnosis are summarised in *Table 4*.

Diagnostic methods
Comparative studies. The study by Fitzgerald and colleagues[50] compares a non-standardised, informal surveillance with a defined protocol. The informal surveillance did not require histological confirmation of Barrett's diagnosis and the biopsy protocol was not standardised. The rigorous surveillance programme did require confirmation of IM and specified that quadrantic samples should be taken every 2 cm.

The study by Macdonald and colleagues[51] reports on annual endoscopic surveillance of those fit for surgery. Those with Barrett's mucosa of at least 30 mm were included, and diagnosis was confirmed by the presence of IM at biopsy; quadrantic samples were taken at the midpoint of the affected mucosa and haematoxylin–eosin staining was used. Presence of dysplasia was classed as mild, moderate or severe dysplasia by two consultant histopathologists. Those not in the surveillance programme had a repeat endoscopy only if there if there were further clinical symptoms. Those in the surveillance group could also have additional, non-scheduled endoscopies for clinical symptoms.

Case series. Among the case series, two studies, by Bani-Hani and colleagues[56] and Ferraris and colleagues,[55] only include patients with LSBO (>3 cm). Most biopsy protocols were for quadrantic samples taken every 2 cm of the visually identified Barrett's oesophagus.[54,55,57–59] Details of diagnostic methods were not given in two studies,[53,56] and as the study by Murray and colleagues[53] is registry based, use of variable methods is likely.

Staining techniques varied; none were used by Bani-Hani and colleagues[56] and use was not stated by Murray and colleagues[53] or Reid and colleagues.[58] Haematoxylin–eosin was the most commonly used stain, although not all studies reported on staining. Alcian blue, periodic acid–Schiff, Giemsa, high iron diamin and van

TABLE 3 *Methodological details of included studies*

Study	Inclusion criteria	Exclusion criteria	Prospective/ retrospective	Mortality reported?	Type of mortality data	Loss to follow-up
Fitzgerald *et al.* (2001)[50] Informal surveillance	Initiated in period 1992–7 Unclear. Cohorts defined as ≥ 3 endoscopes over ≥ 2 years	None stated	Retrospective	All-cause mortality in ACO patients in surveyed and non-surveyed patients	*N* deaths among ACO patients	Not stated
Rigorous surveillance	Initiated in period 1997–8	None stated	Prospective	As above	As above	Not stated
Macdonald *et al.* (2000)[51] Surveillance vs non-surveillance	Barrett's mucosa ≥ 30 mm Columnar metaplasia confirmed at biopsy Only those fit for surgery entered into surveillance	Serious co-existing illness Age/frailty	Prospective	All-cause and ACO mortality in both those under surveillance and not	No. of deaths from ACO and other causes	135/143 by 1999 (death 27, co-morbidity 36, age and frailty 43, default follow-up 14, moved away 13)
Bani-Hani *et al.* (2000)[56]	Histologically confirmed diagnosis of Barrett's oesophagus	Lack of clinical records	Retrospective	No	NA	85/357 left the programme owing to death, age or co-morbidity; 96 missed periods of follow-up for non-medical reasons [NB patients are also recorded as 'not entering surveillance' due to death prior to second endoscope (22), failed to attend follow-up (13), moved away (3)]
Ferraris *et al.* (1997)[55]	Histologically proven Barrett's oesophagus No invasive cancer No-life threatening co-morbidity Geographic accessibility	ACO at first follow-up	Prospective	Yes, for ACO patients	*N* deaths from ACO/other causes	157/344 (46%) did not comply with follow-up

continued

TABLE 3 *Methodological details of included studies (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Prospective/ retrospective	Mortality reported?	Type of mortality data	Loss to follow-up
Hillman *et al*. (2003)[54]	Diagnosis of Barrett's oesophagus (SSBE or LSBE) At least one initial and one follow-up endoscopy	Diagnosis of ACO initially or within 2 months, HGD with immediate oesophagectomy, unsuitable for surveillance (age, co-morbidity), single endoscopy only	220 patients up to May 1996 retrospectively analysed, 213 prospectively	Yes, for patients progressing to ACO and HGD	*N* deaths from ACO/other causes Perioperative mortality	21/353 failed to return for follow-up endoscopy No further details
Hurschler *et al*. (2003)[59]	Diagnosis of Barrett's oesophagus during the study period	No diagnosis of Barrett's oesophagus Histological reports of cardiac/fundic mucosa (including ACO) Squamous cell carcinomas	Retrospective	Yes, reported for 6 ACO patients followed for >4 years only	*N* deaths, cause not stated	Not stated
Murray *et al*. (2003)[53]	Adults with identified oesophageal columnar epithelium	Malignancy at initial biopsy or within 6 months Biopsies from GOJ	Retrospective	No	NA	Not stated
Reid *et al*. (2000)[58]	Presence of metaplastic columnar epithelium No history of oesophageal malignancy Baseline endoscopy plus at least one follow-up	Not stated	Prospective	No	NA	Not stated
Schnell (2001)[57]	Not stated	Not stated	Prospective	Yes, for 75 HGD subset only	*N* deaths from ACO/other causes Perioperative mortality Survival curves (Kaplan–Meier)	Not stated

LSBE, long segment Barrett's oesophagus; SSBE, short segment Barrett's oesophagus.

Gieson staining were also used; see *Table 4* for further details.

Two studies, by Bani-Hani and colleagues[56] and Murray and colleagues,[53] did not describe any arrangements for minimising diagnostic error. Hillman and colleagues[54] confirmed dysplasia diagnoses by using two independent pathologists. Endoscopists and pathologists were used by Hurschler and colleagues[59] and Schnell.[57] Training sessions with slides were provided to pathologists prior to the study start by Ferraris and colleagues.[55] Both histological and flow cytology techniques were used by Reid and colleagues[58] and the assessors were blind to the results of the other method.

Surveillance intervals

Comparative studies

Fitzgerald and colleagues[50] looked at the effect of introducing a rigorous annual surveillance programme for those with Barrett's oesophagus, with 3–6-monthly biopsies for those with dysplasia, compared with previous practice which was not standardised. Only those who were fit for surgery entered the surveillance programme.

The study by Macdonald and colleagues[51] describes annual endoscopic surveillance of those fit for surgery.

Case series

A range of surveillance intervals were reported. No standard protocol was used in the studies by Bani-Hani and colleagues,[56] Hurschler and colleagues,[59] and Murray and colleagues,[53] and not reported in that by Reid and colleagues.[58] Annual surveillance was reported by Ferraris and colleagues[55] and Hillman and colleagues,[54] although the latter used more rigorous surveillance (every 3–6 months) for those with severe oesophagitis. Only Schnell[57] reported a programme that undertook different regimens to those with LGD, HGD and Barrett's oesophagus alone (see *Table 4* for details).

Treatment

Comparative studies

Fitzgerald and colleagues[50] report that of those undergoing informal surveillance, 40% were prescribed PPIs and 11% H_2-blockers, whereas this was the case for 60 and 3%, respectively, in the rigorous surveillance arm.

The study by Macdonald and colleagues[51] does not report on treatment among those under surveillance.

Case series

No details about treatment for GORD symptoms or Barrett's oesophagus were given by Bani-Hani and colleagues,[56] Hurschler and colleagues[59] or Murray and colleagues.[53] Use of PPIs or H_2 blockers was reported by Hillman and colleagues,[54] Ferraris and colleagues[55] and Schnell.[57] In addition, Ferraris and colleagues[55] and Hillman and colleagues[54] report the number of patients who had anti-reflux surgery. Reid and colleagues[58] and Schnell[57] also report that patients with HGD were offered oesophagectomy in addition to being informed of alternatives.

Changes in practice over the study period were reported by Hillman and colleagues,[54] Hurschler and colleagues,[59] Reid and colleagues[58] and Schnell.[57]

Results of included studies

Findings at initial endoscopy

Comparative studies

Details of the included population at first endoscopy are given in *Table 5*. The studies by Fitzgerald and colleagues[50] and by Macdonald and colleagues[51] do not describe how many of the study population had dysplasia or ACO at initial endoscopy.

Case series

Different populations were reported in the case series. Both Ferraris and colleagues[55] and Hurschler and colleagues[59] report on subgroups with up to or more than 1 year of follow-up.

Bani-Hani and colleagues[56] do not report on dysplasia or ACO at initial endoscopy. Only two studies, Hurschler and colleagues[59] and Reid and colleagues,[58] include an ID category, and this was reported in 1.8–24.2% of the included population (mean and median 13%). Hillman and colleagues[54] give details on those not eligible for surveillance in addition to those who were.

LGD was reported in 2.7–15.9% of the population (mean 8.8%, median 6.7%). Schnell[57] did not report on the number of people with initial LGD.

HGD was reported in 0% to 23.2% of the population at initial endoscopy (mean 4.8%, median 0.9%).

Three studies, by Ferraris and colleagues,[55] Murray and colleagues[53] and Reid and colleagues,[58] excluded those found to have ACO at initial endoscopy. Of the others, 0–4.7% of the

TABLE 4 *Diagnostic methods and treatment*

Study	Diagnosis of Barrett's oesophagus	Biopsy protocol	Staining technique	Surveillance protocol	Grading/ classification	Treatment for GORD/Barrett's oesophagus	Changes in practice?
Fitzgerald *et al.* (2001)[50] Informal surveillance	Endoscopic – not histological	Not standardised Mean of 4 taken (range 0–6)	None	Not standardised 1–2 years	Not stated	PPIs 40% H_2 blockers 11%	NA
Rigorous surveillance	Histological confirmation of presence of IM	Quadrantic every 2 cm Mean of 12 taken (range 4–20)	None	Barrett's oesophagus (and fit for surgery) annually Dysplasia 3–6 months	Not stated	PPIs 60% H_2 blockers 3%	This rigorous protocol compared with previous informal strategy
Macdonald *et al.* (2000)[51] Surveillance vs non-surveillance	Barrett's mucosa ≥ 30 mm Histological confirmation of IM	Quadrantic biopsy at midpoint of affected mucosa Additional samples from areas of abnormality	Haematoxylin–eosin	Annual surveillance	Mild, moderate or severe dysplasia determined by two consultant histopathologists	Not stated	No
Bani-Hani *et al.* (2000)[56]	Presence of columnar epithelium for ≥ 3 cm above GOJ or IM anywhere within tubular oesophagus	None	None	Not standardised. Recommended that patients fit for surgery be surveyed yearly	Not stated	Not stated	Not stated
Ferraris *et al.* (1997)[55]	Endoscopic evidence of red gastric-like mucosa ≥ 3 cm between GOJ and Z-line Histological confirmation of IM, gastric fundic or gastric junctional epithelium	At least quadrantic every 2 cm. Sample from proximal fundic mucosa of stomach taken as control sample	Haematoxylin–eosin and high iron diamine/ Alcian blue	Annual follow-up	Slide sessions held prior to study to minimise inter-observer variability. All biopsies evaluated at one pathology unit	H_2 blockers, omeprazole 10 patients (2.9%) had anti-reflux surgery	Not stated

continued

TABLE 4 *Diagnostic methods and treatment (cont'd)*

Study	Diagnosis of Barrett's oesophagus	Biopsy protocol	Staining technique	Surveillance protocol	Grading/ classification	Treatment for GORD/Barrett's oesophagus	Changes in practice?
Hillman *et al*. (2003)[54]	Biopsy confirming SIM on at least one occasion and macroscopic Barrett's oesophagus SSBE <3 cm segment LSBE >3 cm segment	Quadrantic every 2 cm, plus areas of nodularity and stricture	Haematoxylin–eosin, Alcian blue and Giemsa	Annual surveillance Severe oesophagitis: 3–6-monthly review	Dysplasia evaluated by 2 independent pathologists	GORD: PPIs 27 patients (7.6%) had anti-reflux surgery	PPI treatment introduced progressively from 1989
Hurschler *et al*. (2003)[59]	Not stated	Quadrantic every 2 cm (followed by 80% of biopsies)	Haematoxylin–eosin or periodic acid–Schiff (before 1994), alcian-periodic acid–Schiff or van Gieson (after 1994)	Not standardised – ≤ 3 years judged 'adequate'	Dysplasia definitions reviewed by pathologist	Not stated	Staining techniques changed in 1994 and surveillance intervals decreased during study period
Murray *et al*. (2003)[53]	Presence of columnar metaplasia in oesophagus	Not stated – "routine clinical practice"	Not stated	Not stated – "routine clinical practice"	Not stated	Not stated	Not stated
Reid *et al*. (2000)[58]	Presence of metaplastic columnar epithelium in oesophageal biopsy	Quadrantic every 2 cm using jumbo forceps (1985–8) Multiple biopsies of visible abnormalities	Not stated	Not stated. Median intervals (months): Barrett's oesophagus 24.4 LGD 15.7 HGD 4.6	Histological analysis by single assessor blind to flow cytology results and vice versa. Aneuploidy diagnosed if two discrete peaks observed on histogram and aneuploid peak represented at least 2.5% of cells in specimen. 4*N* fractions >6% classified as abnormal	HGD offered alternatives to surveillance, including surgery	Changed after 1992 to biopsies every 1 cm for those with previous HGD diagnosis

continued

TABLE 4 *Diagnostic methods and treatment (cont'd)*

Study	Diagnosis of Barrett's oesophagus	Biopsy protocol	Staining technique	Surveillance protocol	Grading/ classification	Treatment for GORD/Barrett's oesophagus	Changes in practice?
Schnell (2001)[57]	Presence of IM epithelium in oesophagus or GOJ	Standard 2.8-mm forceps Minimum 2 per segment ≤1 cm, minimum 4 per segment if ≥2 cm.	Haematoxylin–eosin	Barrett's oesophagus: 3 years LGD: 1 year, then 2–3 years if not HGD HGD: 3 months; 6 months for 1year if no HGD on two successive examinations then 1 year until HGD noted again If HGD on four 3-monthly examinations patient led – 3 months, 6–12 months or cessation	Joint endoscopist, and pathologist examination	Severe oesophagitis: 3 months H_2 blockers/PPIs HGD: choice of follow-up or surgery	Follow-up criteria modified and treatment of oesophagitis changed from H_2 blockers to PPIs during study

[a] Z-line: junction between oesophageal and gastric mucosa.

TABLE 5 *Prevalence of dysplasia and adenocarcinoma at initial endoscopy in included studies – n (%)*

	No. with diagnosis of Barrett's oesophagus at *initial* endoscopy	No dysplasia	ID	LGD	HGD	ACO
Fitzgerald *et al*. (2001)[50]	554	–	–	–	–	–
Macdonald *et al*. (2000)[51]	409 (143 entered into surveillance)	–	–	–	–	–
Bani-Hani *et al*. (2000)[56]	357	–	–	–	–	–
Ferraris *et al*. (1997)[55]	344 (eligible for surveillance)	–	–	–	–	–
	187 (>1 year follow-up)	–	–	5 (2.7)	0 (0)	Excluded
Hillman *et al*. (2003)[54]						
Non-surveillance	80	–	–	–	1 (1.3)[a]	17 (21.3)[a]
Entered surveillance	353	294 (93.3)	–	56 (15.9)	3 (0.8)	0 (0)
Hurschler *et al*. (2003)[59]						
Group A (F-U <1year)	579 (56 ACO, no BE excluded)	509 (87.9)[a]	9 (1.6)	22 (3.8)	5 (0.9)	34 (5.9)
Group B (F-U >1year)	*140*[a] (67 GERD, no BE excluded)	121 (86.4)[a]	4 (2.9)[a]	13 (9.3)[a]	2 (1.4)[a]	0 (0)
All	*719*[a]	630 (87.6)[a]	13 (1.8)	48 (6.7)[a]	7 (1.0)[a]	34 (4.7)[a]
Murray *et al*. (2003)[53]	2969	2779 (93.6)[a]	–	171 (5.8)	19 (0.6)	Excluded
Reid *et al*. (2000)[58]	327	129 (39.4)	79 (24.2)	43 (13.1)	76 (23.2)	Excluded
Schnell (2001)[57]	1099	–	–	–	34 (3.1)	42 (3.8)

–, Not stated.
[a] Not reported in text – calculated by PenTAG from extracted data.

patients in the surveillance programme had ACO at initial endoscopy (mean 4.3%, median 3.8%).

The study by Reid and colleagues[58] appears unusual and may represent a different patient group. There are much higher proportions of patients with dysplasia (24.2% ID, 13.1% LGD and 23.2% HGD) than are shown in the other included studies.

Detected cases of ACO

Table 6 shows the number of ACO cases detected in the total surveillance population of the included studies.

Comparative studies

In the comparative study, Fitzgerald and colleagues[50] report no identified ACO cases in the informally surveyed group and 2/108 in the rigorously surveyed group, giving an incidence per 100 years of patient follow-up of 0.00 and 1.85, respectively.

Case series

The study by Reid and colleagues[58] did not report on the number of ACO cases in the surveillance programme. Schnell[57] reports on mean follow-up for a subset of 75 patients with HGD where 12 ACO cases were seen, giving an incidence of 2.19 per 100 patient years (mean follow-up 7.5 years). It is not possible to calculate the incidence per 100 years of the surveillance group overall as no timescale is provided, but 22 of the 1099 patients developed ACO. Of the other case series, follow-up was between 3.0 and 4.6 years and incidence per 100 years of patient follow-up was between 0.26 and 1.04 (mean 0.67, median 0.57).

Progression and regression between Barrett's oesophagus, dysplasia and ACO

Tables 7–9 show details of progression and regression between dysplastic states and to ACO over the course of the study periods. *Table 7* shows the number of patients who had Barrett's oesophagus without dysplasia at the initial endoscope who had subsequently progressed to dysplasia or ACO at their most recent endoscope. These patients had between 546 and 10282 patient years of follow-up (mean 3180, median 947).

Comparative studies

Table 8 shows most recent progression data for those with an initial diagnosis of ID or LGD (combined in this table by the present authors) and *Table 9* shows the progression of those who had an initial diagnosis of HGD. These details are not provided by Fitzgerald and colleagues.[50]

The study by Macdonald and colleagues[51] reports on three patients who had 'mild' dysplasia, although this classification is not defined. It is also unclear whether these patients had dysplasia at initial or follow-up endoscopies. Five patients are reported to have had a diagnosis of 'mild' dysplasia, three appeared to regress to Barrett's oesophagus, one was lost to follow-up and one continued to have mild dysplasia.

TABLE 6 *Incidence of adenocarcinoma in surveillance patients in included studies*

	Surveillance no.	No. of incident ACO	Mean follow-up (years)	Total patient years	Incidence per 100 patient years	Incidence per patient year
Fitzgerald *et al.* (2001)[50]	96 informal 108 rigorous	0 2	– –	357 108	0.00 1.85	0/357 1/54
Macdonald *et al.* (2000)[51]	266 non-surveillance 143 surveillance	Not stated 5	– 4.4	– 629	0.79	Not known 5/629
Bani-Hani *et al.* (2000)[56]	357	12	3.6	1293	0.93	1/108
Ferraris *et al.* (1997)[55]	187 ≥ 1 year follow-up	3	Median 3.0	562	0.53	1/187
Hillman *et al.* (2003)[54]	353	9	Median 3.5	1588	0.57	1/176
Hurschler *et al.* (2003)[59]	207 ≥ 1 year follow-up	10	4.6	966	1.04	1/97
Murray *et al.* (2003)[53]	2969	29	3.7	11068	0.26	1/382
Reid *et al.* (2000)[58]	327	42	–	–	–	–
Schnell (2001)[57]	1099	22	–	–	–	–
	Subset 75 HGD	12	7.3	548	2.19	1/46

–, Data not provided by report.

Case series

Only two case series, by Hillman and colleagues[54] and Hurschler and colleagues,[59] give complete details of the dysplasia status of all followed-up participants. Bani-Hani and colleagues[56] and Schnell[57] do not give information about the initial diagnosis of patients who progress.

Hillman and colleagues[54] and Hurschler and colleagues[59] report that of those with Barrett's oesophagus and no dysplasia at initial endoscope, 89.5 and 76.1% retained this diagnosis after 3.5 and 4.6 years of follow-up, respectively. Both report that 8.5% had progressed to a diagnosis of indefinite LGD, giving an incidence per 100 years of patient follow-up of 1.85 to 2.43 (mean 2.14). About 1–1.6% progressed to HGD (incidence per 100 years of patient follow-up 0.29–0.35, mean 0.32) (*Table 7*).

Hurschler and colleagues[59] are the only group to report regression rates for those with Barrett's oesophagus and no dysplasia at initial endoscopy. They report that 11.2% of patients had regressed Barrett's oesophagus, subsequently having no evidence of Barrett's oesophagus or dysplasia. Incidence per 100 patient years was 2.43. However, it is unclear whether this is due to disease regression or a correction of initial misdiagnosis (*Table 7*).

Five studies, by Ferraris and colleagues,[55] Hillman and colleagues,[54] Hurschler and colleagues,[59] Murray and colleagues[53] and Reid and colleagues,[58] report on the incidence of ACO in the Barrett's oesophagus group who had no dysplasia at initial endoscopy. However, Reid and colleagues[58] do not provide length of follow-up details. Incidence of ACO was between 0.7 and 3.9% (mean 1.9%, median 1.1%), giving an incidence per 100 years of patient follow-up of 0.18–0.58 (mean 0.36, median 0.33) (*Table 7*).

Table 8 shows progression and regression for those who had a diagnosis of LGD or ID for dysplasia at initial endoscopy. These categories were combined by the present authors for this table, as not all papers reported on ID. The patients in this group were followed up for 15–633 patient years (mean 230, median 47).

Again, only the studies by Hillman and colleagues[54] and Hurschler and colleagues[59] report on all the progression stages of patients initially diagnosed with ID/LGD. Three additional studies, by Ferraris and colleagues,[55] Murray and colleagues,[53] and Reid and colleagues[58] report only on the number of patients from this group progressing to ACO, although Reid and colleagues[58] do not provide information about the length of follow-up (*Table 8*).

Of those initially given a diagnosis of ID/LGD, two studies report that 41.2–50.0% (mean and median 45.6%) were found to have Barrett's oesophagus with no dysplasia at subsequent examinations, and

TABLE 7 *Progression and regression in patients with no dysplasia at initial biopsy*

		Progression/regression at most recent follow-up, *n* (%)					
	No dysplasia: *N*	**Regressed Barrett's oesophagus**	**No dysplasia**	**ID/LGD**	**HGD**	**ACO**	**Mean follow-up (years)**
Fitzgerald *et al*. (2001)[50]	–	–	–	–	–	–	–
Macdonald *et al*. (2000)[51]	–	–	–	–	–	–	4.4
Bani-Hani *et al*. (2000)[56]	–	–	–	–	–	–	3.6
Ferraris *et al*. (1997)[55]	182	–	–	–	–	2 (1.1)	3.0
Hillman *et al*. (2003)[54]	294	–	263 (89.5)	25 (8.5)	3 (1.0)	3 (1.0)	3.5
Hurschler *et al*. (2003)[59]	188	21 (11.2)	143 (76.1)	16 (8.5)	3 (1.6)	5 (2.7)	4.6
Murray *et al*. (2003)[53]	2779[a]	–	–	–	–	19 (0.7)[a]	3.7
Reid *et al*. (2000)[58]	129	–	–	–	–	5 (3.9)	–
Schnell (2001)[57]	–	–	–	–	–	–	7.3

–, Data not provided by the study report.
[a] *N* assumed based on total reported *N* minus those reported to have dysplasia at initial endoscope.

TABLE 8 *Progression and regression in patients classified as ID or LGD at initial biopsy*

		Progression/regression at most recent follow-up, *n* (%)					
	ID/LGD: *N*	**Regressed Barrett's oesophagus**	**No dysplasia**	**ID/LGD**	**HGD**	**ACO**	**Mean follow-up (years)**
Fitzgerald *et al*. (2001)[50]	–	–	–	–	–	–	–
Macdonald *et al*. (2000)[51]	–	–	–	–	–	–	4.4
Bani-Hani *et al*. (2000)[56]	–	–	–	–	–	–	3.6
Ferraris *et al*. (1997)[55]	5	–	–	–	-	1 (20)	3.0
Hillman *et al*. (2003)[54]	56	–	28 (50.0)	22 (39.3)	1 (1.8)	5 (8.9)	3.5
Hurschler *et al*. (2003)[59]	17	2 (11.8)	7 (41.2)	5 (29.4)	0 (0)	3 (17.6)	4.6
Murray *et al*. (2003)[53]	171	–	–	–	-	7 (4.1)	3.7
Reid *et al*. (2000)[58]	122	–	–	–	-	4 (3.3)	–
Schnell (2001)[57]	–	–	–	–	-	10	7.3

–, Data not provided by the study report.

one study also found that two patients (11.8%) no longer had evidence of Barrett's oesophagus. This gives a regression rate of 9.95–14.29 per 100 years of patient follow-up. Again, it is unclear how much of this apparent regression is due to initial diagnostic error (*Table 8*).

Hillman and colleagues[54] and Hurschler and colleagues[59] show that 29.4–39.3% of those with an ID/LGD diagnosis retained this status at the most recent follow-up, giving an incidence per 100 patient years of 8.95–11.22 (mean 10.09). They report that 0.0–1.8% progressed to HGD (0.0–0.51 per 100 years of patient follow-up, mean 0.26) (*Table 8*).

Progression to ACO from initial ID/LGD diagnosis was reported in 3.3–20% of those under surveillance. This gives an incidence per 100 years of patient follow-up of 1.11–6.67 (mean 3.54 median 3.19) (*Table 8*).

Table 9 shows progression and regression for those who had a diagnosis of HGD at initial endoscopy. The patients in this group were followed up for 9.2–248.2 patient years (mean 84.6, median 40.4).

Again, only the two studies by Hillman and colleagues[54] and Hurschler and colleagues[59] report on whether these patients had regressed, although only one patient had done so, receiving a diagnosis of Barrett's oesophagus with no dysplasia. This was 1/3 of all the patients Hillman and colleagues[54] initially reported as having HGD and gives a regression rate of 9.52 per 100 patient years. However, it is again uncertain whether this

TABLE 9 *Progression and regression in patients with HGD at initial biopsy*

	HGD: *N*	Progression/regression at most recent follow-up, *n* (%)					
		Regressed Barrett's oesophagus	No dysplasia	ID/LGD	HGD	ACO	Mean follow-up (years)
Fitzgerald *et al.* (2001)[50]	–	–	–	–	–	–	–
Macdonald *et al.* (2000)[51]	–	–	–	–	–	–	4.4
Bani-Hani *et al.* (2000)[56]	–	–	–	–	–	–	3.6
Ferraris *et al.* (1997)[55]	0	–	–	–	–	–	3.0
Hillman *et al.* (2003)[54]	3	–	1 (33.3)	0	0	2 (66.7)	3.5
Hurschler *et al.* (2003)[59]	2	0	0	0	0	2 (100)	4.6
Murray *et al.* (2003)[53]	19	–	–	–	–	3 (15.8)	3.7
Reid *et al.* (2000)[58]	76	–	–	–	–	3 (3.9)	–
Schnell (2001)[57]	34	–	–	–	–	4 (11.7)[a]	–
						2 (5.9)[b]	7.3

–, Data not provided by the study report.
[a] ACO developed within 12 months of initial biopsy.
[b] ACO developed >12 months after initial biopsy.

apparent regression was in fact the result of initial or subsequent misdiagnosis (*Table 9*).

Five studies, by Hillman and colleagues,[54] Hurschler and colleagues,[59] Murray and colleagues,[53] Reid and colleagues[58] and Schnell,[57] report on progression from HGD to ACO. Reid and colleagues do not supply information about length of follow-up. Schnell[57] reports separately on those who developed ACO within 1 year of initial biopsy and those who developed ACO after 1 year of follow-up (*Table 9*). Between 3.9 and 100% of patients progressed from HGD to ACO in the included studies with an incidence per 100 years of patient follow-up of 2.42–21.74 (mean 11.87, median 11.66) (*Table 9*).

Note that, as expected, most studies show that the incidence of ACO is higher among those initially diagnosed with HGD than LGD, and higher in those initially diagnosed with LGD than those with no dysplasia at initial endoscope (this is the case for Ferraris and colleagues,[55] Hillman and colleagues,[54] Hurschler and colleagues,[59] Murray and colleagues[53] and Schnell[57]). However, the study by Reid and colleagues[58] does not show this trend with similar ACO incidence in patients initially diagnosed without dysplasia as those with HGD (*Table 9*).

Survival

Comparative studies

Survival data were poorly reported (*Table 10*). Fitzgerald and colleagues[50] report on the total mortality of those with ACO in the surveillance and non-surveillance groups; however, it is not reported if these deaths were from ACO or other causes.

The study by Macdonald and colleagues (2000)[51] is the only one to report on deaths among patients with Barrett's oesophagus who did not develop ACO. A total of 21.0% of those in the surveillance programme and 38.7% of those not under surveillance died from other causes over the course of the study. Five patients developed ACO in the surveillance arm; however, only one of these was diagnosed directly as a result of the surveillance programme. Three of these patients died and the other two were well after surgery at the end of the study period. One patient died from ACO in the non-surveillance group but it is not known how many patients developed ACO.

Case series

Four case series report on mortality. Ferraris and colleagues[55] and Hillman and colleagues[54] report on deaths among those with ACO. No deaths were caused by the cancer during the follow-up period and both studies report on one death in this group from causes other than ACO. Hurschler and colleagues[59] report total mortality among the six patients with ACO but do not give the cause of death. Schnell[57] undertook a survival analysis of the 75 patients who had HGD. At 8 years of follow-up, 91% of those not progressing to ACO and 90% of those who had were alive. Again, cause of death is not reported.

TABLE 10 *Mortality:* n *(%)*

		Patients with ACO		
	Patients without ACO	**From ACO**	**Other causes**	**Total mortality**
Fitzgerald *et al*. (2001)[50]				
Surveillance	–	–	–	0/5[a] (0)
Informal surveillance	–	–	–	2/9[a] (22.2)
Macdonald *et al*. (2000)[51]				
Surveillance	30/143 (21.0)	3/5 (60)	0/5	33/143 (23.1)
No surveillance	103/266 (38.7)	1/not stated	Not stated	104/266 (39.1)
Bani-Hani *et al*. (2000)[56]	–	–	–	–
Ferraris *et al*. (1997)[55]	–	0/3 (0)	1/3 (33.3)	–
Hillman *et al*. (2003)[54]	–	0/9 (0)	1/9 (11.1)	–
Hurschler *et al*. (2003)[59]	–	–	–	4/6 (66.7)[b]
Murray *et al*. (2003)[53]	–	–	–	–
Reid *et al*. (2000)[58]	–	–	–	–
Schnell (2001)[57]	–	–	–	–[c]

–, Data not provided by study.
[a] Patients with ACO who died – cause of death not stated.
[b] Total of 85 patients left the surveillance programme owing to death, age or co-morbidity.
[c] Survival analysis – 91% of 75 HGD patients without ACO and 90% of those with ACO survived at 8 years.

Systematic review findings

No RCTs or good controlled trial evidence was found. The included case series, a study design susceptible to a range of biases, also showed poor reporting, particularly around mortality from ACO and from other causes. In addition, details of the population are often incomplete and it is not possible to track the natural history of Barrett's oesophagus from these studies. There is insufficient evidence to establish the effectiveness of surveillance of Barrett's oesophagus.

Discussion of findings

Observational studies of surveillance for Barrett's oesophagus are particularly susceptible to bias. A review by Shaheen[60] summarised the possible key problems of interpretation resulting from the following biases:

1. *Healthy volunteer bias*. Participants in surveillance programmes tend to be healthier than those who are not. Their life expectancy is longer anyway, erroneously inflating the perceived survival advantage of surveillance.
2. *Lead time bias*. Cancers may be detected earlier through surveillance. However, rather than improving survival time, this may simply bring forward the time of diagnosis. The length of survival may appear to be enhanced, whereas in reality the patient dies at the same time, but knows they have cancer for a longer time. Again, this may be wrongly interpreted as a survival advantage for those under surveillance.
3. *Length time bias*. Slow-growing cancers are more likely to be picked up through surveillance than fast-developing cancers, which may mature between examinations. The slow-growing cancers become fatal more slowly. This enhanced survival again may be mis-interpreted as attributable to surveillance.

Case series are a weak form of evidence. Unlike RCTs, there have been no elements of case series quality that have been shown quantitatively to impact on results, so there no agreement about which design elements are most important. A recent assessment exploring the possible impact of various methodological aspects of case series studies did not find a consistent relationship between findings and various methodological aspects of case series noted in existing quality assessment tools (including blinding of outcome measures, prospective data collection and size).[61]

However, some aspects of the studies that may indicate bias or poor quality were noted. Inclusion and exclusion criteria varied and in some cases were not stated beyond a diagnosis of Barrett's

TABLE 11 *Publications reporting the risk of oesophageal adenocarcinoma in Barrett's oesophagus from data provided by Shaheen and Ransohoff[11] and Somerville and Milne[25]*

Study	Journal/source	Year	Average age (years)	Female (%)	No. of patients	Patient years of follow-up	No. cases ACO	Incidence per 100 years of patient follow-up
Achkar and Carey	*Am J Gastroenterol*	1988	56	26	62	166	1	0.60
Bartelsman *et al.*	*Eur J Cancer Prev*	1992	NR	NR	50	260	5	1.92
Cameron *et al.*	*N Engl J Med*	1985	60	31	104	882	2	0.23
Cooper and Barbezat	*Q J Med*	1987	63	38	52	45	0	0.00
Csendes *et al.*	*Surgery*	1998	52	35	151	1147	4	0.35
Drewitz *et al.*	*Am J Gastroenterol*	1997	62	2	170	834	4	0.48
Ferraris *et al.*	*Eur J Gastroenterol Hepatol*	1997	NR	NR	187	562	3	0.53
Hameeteman *et al.*	*Gastroenterology*	1989	59	40	50	260	5	1.92
Iftikhar *et al.*	*Gut*	1992	63	39	102	462	4	0.87
Katz *et al.*	*Am J Gastroenterol*	1998	63	17	102	563	3	0.53
McDonald *et al.*	*J Thorac Cardiovasc Surg*	1996	68	31	112	728	3	0.41
Miros *et al.*	*Gut*	1991	63	25	81	290	3	1.03
Moghissi *et al.*	*Eur J Cardiothorac Surg*	1993	62	31	26	299	4	1.34
Ortiz *et al.*	*Br J Surg*	1996	37	32	59	287	2	0.70
Ovaska *et al.*	*Dig Dis Sci*	1989	59	31	32	166	3	1.81
Reid *et al.*	*Gastroenterology*	1992	62	18	62	176	5	2.84
Robertson *et al.*	*Br J Surg*	1988	62	45	56	168	3	1.79
Sampliner *et al.*	*Gastroenterology*	1991	NR	NR	106	Mean 4	1:212	NR
Savary *et al.*	Springer-Verlag	1984	NR	NR	402	1528	5	0.33
Sharma *et al.*	*Am J Gastroenterol*	1997	NR	NR	59 SSBO	98	1:98	NR
Skinner	Springer-Verlag	1989	NR	NR	45	145	3	2.07
Spechler *et al.*	*Gastroenterology*	1984	NR	NR	105	350	2	0.57
Spechler *et al.*	*JAMA*	2001	58	2	108	1037	4	0.39
Streitz *et al.*	*Am J Gastroenterol*	1998	NR	NR	149	510	7	1.37
Van der Burgh *et al.*	*Gut*	1996	62	42	155	1440	8	0.56
Van der Veen *et al.*	*Gut*	1989	NR	NR	166	Mean 4.4	1:170	NR
Watson *et al.*	*Eur J Gastroenterol Hepatol*	1991	63	51	45	158	1	0.63
Weston *et al.*	*Am J Gastroenterol*	1997	63	24	55	94	2	2.13
Williamson *et al.*	*Arch Intern Med*	1991	56	35	176	497	5	1.01
Wright *et al.*	*Gut*	1996	NR	NR	166	Mean 2.7	1:77	NR

NR, not reported.

oesophagus, which was itself variously defined. Only in some cases were absence of concomitant illness or fitness for surgery, likely to be relevant criteria in clinical practice, stated as inclusion criteria. Where it was reported, high levels of attrition from surveillance programmes were reported. Within the included studies, a range of diagnostic methods were used. Further, the actual number of people developing ACO is small, and follow-up was limited with most studies reporting on surveillance only over 3–4 years. Given that the recommended surveillance interval for non-dysplastic Barrett's oesophagus in the UK is 3 years, such time frames cannot capture the impact of a general surveillance programme.

We excluded surveillance studies of <300 people with Barrett's oesophagus. The results of some of these have been summarised in previous publications. *Table 11* gives the combined information from the previous DEC report,[27] and from a review of GORD, Barrett's oesophagus and ACO by Shaheen and Ransohoff in 2002.[11] Median ACO incidence per 100 patient years of follow-up is 0.80, (mean 1.02, range 0.00–2.84). This compares with a median incidence of 0.57 per 100 patient years (mean 0.67, range 0.26–1.04) in the studies included in our systematic review (*Table 6*). This supports previous work suggesting that smaller studies may overestimate cancer risk in Barrett's oesophagus patients.

It is very difficult to draw conclusions about the effectiveness of endoscopic surveillance of Barrett's oesophagus given the lack of RCT or even well-designed comparative evidence. Without such data, it is not possible to say whether surveillance of those with Barrett's oesophagus leads to reduced mortality, and effectiveness remains uncertain.

Crucially, even in the included studies, poor and variable reporting is a problem. In particular, mortality data were poorly reported – mortality among those without ACO is reported in only one study, and only three studies separate mortality among those with ACO into death from ACO and death from other causes. Only one of these three studies reports any patient with ACO dying from the condition. However, only one diagnosed cancer in this study was detected by surveillance rather than referral for suspicious symptoms. It is not clear in the other studies whether detected cancers truly come from the scheduled surveillance endoscopies. The effect of surveillance of Barrett's oesophagus on cancer deaths and overall mortality is therefore uncertain.

Progression from non-dysplastic Barrett's oesophagus through dysplasia to ACO is also poorly reported in most studies. The natural history of Barrett's oesophagus therefore remains uncertain.

A summary of the systematic review of the effectiveness of endoscopic surveillance is given in *Box 1* on p. 34.

Study methodology
- No RCT or good controlled trial evidence is available.
- Case series are susceptible to a range of biases.
- Possible elements of quality are variable, such as:
  - both prospective and retrospective designs
  - varying definitions of Barrett's oesophagus
  - varying diagnostic protocols
  - short follow-up periods
  - high attrition rates
  - no details of concomitant illness
  - actual number of ACO cases detected is small
  - unclear whether ACO diagnosis comes from scheduled surveillance endoscopies or endoscopies to investigate symptoms.

Reporting
- Reporting in the included case series was poor.
- Mortality, from ACO and other causes, is poorly reported – in most studies it is not possible to tell if a patient has died from ACO.
- It is not possible to track natural history of Barrett's oesophagus from the reporting of these studies.
- Population details are often limited.

Conclusion
- Evidence for the effectiveness of surveillance in Barrett's oesophagus is lacking.

Key areas of ignorance and uncertainty
Given the overall conclusion, there is both global uncertainty and specific uncertainty about many of the individual elements of a surveillance programme. Particularly:

- Is surveillance effective?
- How many patients in surveillance programmes die from Barrett's oesophagus-related or other causes?
- What is the natural history of the disease?

BOX 1 *Summary of the systematic review of effectiveness of surveillance*

Chapter 5

Expert workshop on surveillance of Barrett's oesophagus

Workshop aims

The workshop took place at Senate House, London, on 24 May 2004. The stated aims of the day were:

- To increase PenTAG's understanding of clinical issues in the surveillance of Barrett's oesophagus.
- To identify areas for future research, based on experts' analysis of current gaps in the evidence.
- To identify possible priorities among clinicians and patients for further research.

Workshop participants

In order to identify a group of national experts to participate in the workshop, the HTA programme contacted all applicants who had previously submitted applications to the HTA programme and sought permission for their names to be released to the PenTAG team. Forty-five contact names were provided, and these invitees were encouraged to suggest further relevant experts. In total, 58 clinicians were invited from a range of clinical specialisms. Patient representatives were also identified by contacting the Barrett's Oesophagus Foundation and Oesophageal Patients' Association. Patients wishing to take part in the workshop were given contact details for PenTAG to discuss the aims of the day and how they wished to take part. Four members of PenTAG attended the day. A senior lecturer from the HTA programme was present as an observer. Specialisms of the participants are included in Appendix 6. Given the tight time frame for the assessment and the workshop, not all invited participants were able to attend and 36 were present on the day. All those invited were circulated with the draft report and asked for comments and additions.

Workshop structure

The workshop timetable is shown in Appendix 7. The workshop was chaired by Dr Robert Heading of Edinburgh Royal Infirmary. Surveillance of Barrett's oesophagus was divided into four major topic areas by PenTAG in advance of the meeting:

1. definitions, natural history, epidemiology and prognosis
2. diagnostic methods and sampling
3. treatment of Barrett's oesophagus and adenocarcinoma
4. potential impact of surveillance programmes.

Expert speakers were invited to give 15-minute presentations on each of the above topics, identifying the state of current knowledge and key areas of uncertainty. In addition, the opinions of patient representatives had been sought by PenTAG prior to the workshop, and speakers were asked to incorporate their ideas about important areas of uncertainty into their presentations. Slides from the presentations are available from the authors on request with the kind permission of the speakers. One speaker was unable to give permission for the slides to be reproduced owing to conflicts of copyright.

It was felt important to include perspectives from people with Barrett's oesophagus. Following contact with the Barrett's Oesophagus Foundation, four patients attended and contributed their views through a presentation and in the small group and plenary session discussions.

Following the introductory presentations, the meeting split into four groups, each focusing on one of the key areas. Participants were asked to choose their own interest group and the group composition is shown in Appendix 8. Each group was facilitated by a member of PenTAG. We used a modified version of the Nominal Group Technique (NGT) to structure discussion in the small groups, identify questions and rank them in order of priority.

Small group work – nominal group technique

The NGT is a method of consensus building.[62] It was developed in 1971 by Delberg and Van de Ven

TABLE 12 *Research questions and their ratings for definitions, natural history, epidemiology and prognosis of Barrett's oesophagus*

Question	Score	Scores of 6–8	Scores of 0–2
What contribution do risk factors for progression of Barrett's oesophagus make, individually and together, to the development of HGD and ACO? (demographic factors, environmental – exogenous and endogenous, genetic, molecular markers, endocrine)	62	8	0
Epidemiology of reflux disease and Barrett's oesophagus?	49	3	0
What is the annual risk of progression from Barrett's oesophagus to HGD, ACO and death (note diagnostic uncertainty around HGD)	48	6	0
What proportion of ACO occurs in people without a history of reflux/dyspepsia, I.e. what are the risk factors for ACO?	47	6	0
What is the risk of reflux progressing to Barrett's oesophagus?	47	4	0
How do you achieve a professional consensus and effective communication with patients about epidemiology of Barrett's oesophagus and ACO?	37	2	0

in the context of committee decision-making.[62] It has since been used within the health field, both to identify areas of agreement and where there is lack of agreement. The aim of the NGT is to structure interaction within a group. It aims to elicit private decisions, with formal group feedback, and has an explicit method of aggregation. We used a modified version, with the presentations standing in the place of an initial review of the evidence and only one, rather than two, rounds of rating by participants.

Within each group, therefore, the following structure was used:

1. Individuals were first asked to write down privately the two or three questions, within their group's remit, that they regarded as the most important for research. The questions were written down on a Post-It.
2. Each person was asked to read out their questions and these were discussed in turn by the group.
3. These questions were taken by the facilitator and, through discussion with the group, they were grouped into themed areas on a flip chart.
4. The group further discussed the areas and refined similar questions into a more explicit research question. No limit was placed on the number of final questions identified.
5. Finally, each participant privately rated the importance of each of the refined questions on a nine-point scale from 0 (not important) to 8 (very important).
6. The scores were added up to identify the group's overall priorities. In addition, we looked at the spread of the scores, noting those which all felt were important (all scores 6–9) and those which some felt to be less important (all scores of 0–2).

A member of each group was nominated to feed back the group's discussion, areas of uncertainty identified by the group and their rating to the full meeting in an afternoon plenary session.

Results from small group work

Definitions, natural history, epidemiology and prognosis

Eight participants identified six key areas for research in relation to the definitions, natural history, epidemiology and prognosis of Barrett's oesophagus (*Table 12*). One question, concerning the contribution of individual risk factors, scored much more highly than the others, with all members of the group giving it a score in the 6–8 range, indicating a high level of consensus.

Diagnostic methods and sampling

Seven participants identified seven key areas for future research (see *Table 13*). The highest scoring question, about identifying those at most risk of developing ACO in a general population, also had a high level of consensus with all participants rating it highly (a score of ≥ 6). The question on cost-effectiveness showed the least consensus, with scores ranging from 2 (the lowest score given to any question by participants in this group) up to 8.

Treatment of Barrett's oesophagus and ACO

Six participants identified seven areas for further research concerning the treatment of Barrett's oesophagus and ACO (*Table 14*). Two questions

TABLE 13 *Research questions and their ratings for diagnostic methods for and sampling of Barrett's oesophagus*

Question	Overall score	Scores of 6–8	Scores of 0–2
Is there a technique we can use in the general population to identify patients with high ACO risk?	51	7	0
Can we identify predictive biomarkers from tissue or cells for survival?	47	4	0
Is there a way of sampling the entire Barrett's oesophagus segment to identify high-risk patients?	44	5	0
What is the cost-effectiveness of new compared with old tests?	39	3	2
Within an area of Barrett's oesophagus is there a way of better identifying high-risk mucosa?	36	3	0
Can we improve the reproducibility of current diagnoses (Barrett's oesophagus, LGD, HGD, mucosal invasive ACO)	35	4	1
Can we identify markers that predict response to therapy?	35	3	1

TABLE 14 *Research questions and their ratings for treatment of Barrett's oesophagus and ACO*

Question	Overall score	Scores of 6–8	Scores of 0–2
How effective are any treatments for Barrett's oesophagus in altering cancer incidence?	43	5	0
How can we best identify those at risk in order to target treatment?	42	5	0
How do we select novel methods for treatment trials?	37	4	0
How do we measure success?	32	4	0
What are the long-term side-effects of PPIs?	20	1	3
Is there any treatment for both colon cancer and Barrett's oesophagus?	20	3	3
How effective are treatments aimed at the lower oesophageal sphincter in treating Barrett's oesophagus?	19	1	2

scored similarly highly: one about identifying whether any treatments for Barrett's oesophagus altered progression to ACO and another about identifying high-risk groups. Neither achieved complete consensus – in each case five out of six participants gave scores in the highest third.

Potential impact of surveillance programmes

Eight participants together identified nine areas for research about the impact of surveillance for Barrett's oesophagus (*Table 15*). One score for the question 'Are there clinical subgroups at higher risk of ACO?' was missing. All other participants had rated this with a score of 7 or 8. Even missing one score, this question has the second highest score, and would have been the most highly rated question had the missing score been >3. The question about the benefit of any type of surveillance received a majority of scores in the 6–8 range, although one person thought this question unimportant.

Workshop plenary feedback

Each small group gave a brief summary of their discussion and the results of the NGT exercise, as set out above. The whole group was then able to comment on the output, agree or disagree with the ranking and add in other questions if they wished. No further round of prioritisation of the questions was carried out.

Patients were involved in all the small groups, contributed questions for ranking within the groups and their views were summarised in the whole group session. Their main concerns were:

- Need for good clear information about what is known about Barrett's oesophagus, even if it contains a lot of uncertainties.
- Advice to both relatives and patients specifically around the need for surveillance and at what frequency.
- Understanding possible genetic links.

TABLE 15 *Research questions and their ratings for the potential impact of surveillance programmes of Barrett's oesophagus*

Question	Overall score	Scores of 6–8	Scores of 0–2
Should we survey at all?	55	7	1
Are there clinical subgroups at higher risk of ACO?	52	7[a]	0
Is surveillance effective in reducing death from ACO?	52	6	1
Surveillance vs chemoprevention?	49	5	2
Do biomarkers identify subgroups at higher risk?	46	6	1
Surveillance vs no surveillance RCT?	46	6	2
Cost-effectiveness of surveillance if on acid/aspirin chemoprevention	44	4	2
What are the mechanisms of progression to ACO?	40	3	2
Is surveillance cost-effective?	36	5	1

[a] Note that one participant did not provide a score for this question.

- Determining the contribution of lifestyle to developing Barrett's oesophagus and ACO.

Epidemiology

There was a clear top question and no explicit disagreement from the whole group about the results of the ranking, but a number of other questions were raised in the plenary session:

- Do men and women have different risks for developing Barrett's oesophagus or progression to ACO? Should they therefore be managed differently, i.e. some kept under surveillance and others not?
- Should screening for Barrett's oesophagus be undertaken, rather than surveillance of people already diagnosed? If so, how?
- If 95% of ACOs present without a known preceding history of Barrett's oesophagus, what is the true relevance of a diagnosis of Barrett's oesophagus?
- Is there a different risk from long- and short-segment Barrett's oesophagus?

During discussion, it was suggested that the Barrett's Oesophagus Registry may be able, if expanded, to answer the main epidemiological questions identified in the small group.

Diagnostic markers

It was less clear which question was the most important from this small group, but the highest ranked question refers to the need to identify a suitable screening test for ACO rather than surveillance of Barrett's oesophagus. The group regarded the value of identifying HGD as limited, given the often short lead time from this condition to ACO, and were keen to pursue research into other markers of high risk that allowed earlier warning of high risk. However, no technologies for diagnosis were considered to be close to practical application at this stage, although the field is moving rapidly.

The full meeting did not disagree with the questions or the rankings of the small group. There was, however, some scepticism over whether any current markers would prove useful; it is unclear whether they identify Barrett's oesophagus or high risk for ACO. Some felt that similar markers in other cancers had not proved helpful. So far, no markers had helped to understand the natural history of Barrett's oesophagus and there was still believed to be major uncertainty over the variable progression of Barrett's oesophagus to ACO.

Treatment of Barrett's oesophagus and ACO

This small group had less consensus over the most highly rated questions, with two scoring similarly, but again there was no explicit disagreement from the whole group. It was agreed that trial outcomes must report on death from all causes in addition to death from ACO, owing to the characteristics of the population needing treatment and the nature of the intervention for ACO. Development of ACO and HGD was relevant, but HGD was considered a less clear and so less important outcome. A comment was made that operative mortality varies; in the UK, mortality rates of 5–10% are reported for clinically presenting ACO, whereas US rates were thought to be lower because HGD is more often treated surgically there. Studies from the USA may not be relevant to the UK situation as few patients in the UK are offered surgery for

HGD. Oesophagectomy does reduce QoL, although this may also be influenced by patient expectations and preoperative morbidity.
In discussion, it was suggested that the proposed AspECT trial, which will examine the effect of aspirin on progression to ACO in those with Barrett's oesophagus, was an important study that may address some of the uncertainty on mortality from ACO in this population.

Surveillance programmes

This group produced the least clear-cut results in the small group work. However, questions 'should we survey at all?' and 'Is surveillance effective in reducing death from ACO?' can probably be combined as 'whether we should survey'. This can only be answered if the effectiveness of surveillance in reducing death from ACO is known. That leaves the other crucial question from this group as whether there are clinical subgroups at greater risk from ACO than others. There was considerable disagreement about whether this question should be tested in a trial of no surveillance against surveillance at one or more specified intervals; some preferred the option of testing one surveillance interval against another. They felt that patients in the 'no surveillance' arm would present with symptoms and request further investigation, so that few would continue on the planned intervention arm. Some in the group felt that anyone who was considered eligible for a surveillance programme should be entered into a trial. Others were reluctant because current techniques were not satisfactory. There was some sympathy for the view that many clinicians only operated surveillance programmes because they felt that they should do something, rather than being convinced of any benefit to patients. It was suggested that while surveillance continued, it was important to keep a bank of samples so that these could be used in the future to assess the value of newly discovered biomarkers.

Summary of workshop results

Recurrent themes from the general discussion were as follows:

1. Doubts about the benefits of surveillance, but reluctance to stop current practice (however variable) without good evidence.
2. Lack of information about the natural history of Barrett's oesophagus, specifically about whether all cases of ACO are preceded by the development of Barrett's oesophagus and dysplasia.
3. Need for more information about risk of ACO, so that patients could be stratified into high- and low-risk groups:
   (a) Are there any diagnostic markers that can provide this stratification (plenty around, but no good evidence of their effectiveness)?
   (b) Can treatment be targeted at those at highest risk?
   (c) Can low-risk patients be reassured that their Barrett's oesophagus is unlikely to progress and they need to return only if their symptoms change?
4. Some scepticism over the feasibility of any trial that included a 'no surveillance' arm.
5. The AspECT trial should give the first clear information on effectiveness of treatment, using the only available treatment (aspirin), with some evidence that it reduces cancer risk; this information is not available for any other treatment modality.
6. The possibility of using the AspECT trial to gain additional information about natural history and risk groups.
7. Patients' need for clear, balanced information about risks and benefits of surveillance, including explicitness about current areas of uncertainty.

Discussion of workshop process and conclusions

An evaluation form was sent to all participants on the day after the workshop. Responses were received from 14 people (39%) and the results are given in Appendix 9. On the whole, responses were positive in the eight areas covered: whether the aims of the workshop were clear, and if they were met; the usefulness of the presentations; ease of making views heard in the small group work; satisfaction with the list of key questions produced; usefulness of the final plenary session and rating the venue. Asked if they were happy with the list of questions produced through the group work, most (12/14) were 'very' or 'quite' happy.

Although the NGT encourages each participant to contribute equally, there are difficulties in integrating patients' and clinicians' views equitably. In retrospect, given the number of patients who were ultimately able to attend, it might have been more productive to have a group for the patients alone, perhaps with greater support, so as to enable them to convert their ideas into researchable questions.

A summary of the key areas of uncertainty identified is given in *Box 2* on p. 40.

The workshop highlighted both the global uncertainty about the effectiveness of surveillance and specific uncertainty about many of the individual elements, particularly:

- Who is at greatest risk of developing ACO?
- What is the natural history of Barrett's oesophagus?
- What factors other than Barrett's oesophagus are involved in risk of progression to ACO?
- What treatments for Barrett's oesophagus are effective?
- What is the impact of surveillance of Barrett's oesophagus?

BOX 2 *Summary of key areas of uncertainty identified at the workshop*

Chapter 6

Economic evaluation of endoscopic surveillance of patients with Barrett's oesophagus

Aim of the economic evaluation

We aimed to assess whether or not surveillance of Barrett's oesophagus is likely to be considered cost-effective based on available knowledge obtained from a systematic review of the cost-effectiveness literature and economic modelling. However, it was considered equally important to identify the most important areas of uncertainty to inform prioritisation of further research.

Research questions

- What is the cost-effectiveness of endoscopic surveillance of people with diagnosed Barrett's oesophagus?
- What are the important data for which uncertainty may have large effects on cost-effectiveness?

These questions were addressed using three methods. First, a systematic review of published economic evaluations was carried out. Second, a decision analytic model of surveillance was constructed. Third, using the model of surveillance, the EVPI was estimated at both individual and population levels for each parameter.

Systematic review of cost utility

Methods

Search strategy and critical appraisal methods

Electronic databases were searched using the strategy shown in Appendix 2. The quality of included studies was appraised using a structured framework for cost-effectiveness models,[63] details of which are given in Appendix 10 and summarised in the section 'Summary of findings of previously published cost–utility studies below.

Inclusion and exclusion criteria

Studies were included if they were:

- about surveillance of Barrett's oesophagus
- cost-utility studies.

Results

A total of 13 studies of cost-effectiveness relating to Barrett's oesophagus were found. Ten studies were excluded from further assessment as they did not meet the inclusion criteria. These are listed in Appendix 3.

We found three cost–utility analyses of surveillance for Barrett's oesophagus:

- Inadomi and colleagues (2003),[30] 'Screening and surveillance for Barrett's esophagus in high-risk groups: a cost–utility analysis.'
- Provenzale and colleagues (1994),[64] 'A guide for surveillance of patients with Barrett's Esophagus'.
- Provenzale and colleagues (1999),[42] 'Barrett's oesophagus: a new look at Surveillance Based on Emerging estimates of Cancer Risk'.

Inadomi and colleagues take a third-party payer perspective from the USA. The 1999 paper by Provenzale and colleagues builds on their 1994 paper, and considers cost-effectiveness for a USA Health Maintenance Organisation (HMO).

All papers were assessed using a framework for assessing cost-effectiveness models[63] (Appendix 10). A summary of the results is given below.

Summary of findings of previously published cost–utility studies

Inadomi and colleagues (2003)[30]

A Markov model is used to investigate the cost-effectiveness of screening those with GORD symptoms for Barrett's oesophagus and ACO, surveillance of all patients with Barrett's oesophagus with or without dysplasia and also the cost-effectiveness of no screening or surveillance. Surveillance intervals were every 2–5 years for non-dysplastic Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD. The population modelled was 50-year-old white men with GORD symptoms. The model was run for 30 years.

Survival advantage is accrued by the surveillance arms owing to several parameters. Cancers in the non-surveillance arm are less likely to be operable

owing to more advanced tumour stage (50% versus 95%)[35,36] than those in the surveillance arm and associated with this more advanced tumour stage is a higher risk of operative mortality (5% versus 2.7%) and lower rate of 'cure' (20% versus 80%). In addition, health state utility values for cancer are low (0.5) and for post-oesophagectomy are high (0.97). More of those in the non-surveillance arm will remain untreated in the 'cancer' health state and more of those in the surveillance arm will stay in the 'post-oesophagectomy' state. Other differential utility values could also contribute, but details are not given.

Screening plus surveillance in those with dysplasia cost US$10,440 per quality-adjusted light-year (QALY) compared with no screening or surveillance. Surveillance every 5 years in patients with non-dysplastic Barrett's oesophagus cost US$596,000 per QALY compared with screening and surveillance of those with dysplasia only.

One-way sensitivity analysis showed prevalence of Barrett's oesophagus and annual incidence of ACO to be the most important variables. The annual incidence of ACO must be >1 per 54 patient years of follow-up (1.9%) in order for the surveillance of Barrett's oesophagus every 5 years to achieve an incremental cost-effectiveness ratio (ICER) of <US$50,000. Probabilistic sensitivity analysis using a Monte Carlo simulation produced an ICER of <US$50,000 per additional QALY in 99% of simulations for screening for Barrett's oesophagus and surveillance limited to those with dysplasia strategy. For surveillance of those with no dysplasia, this threshold was found in 0–2% of simulations.

The authors conclude that screening 50-year-old men with GORD to detect ACO, followed by surveillance of those with dysplasia only, is probably cost-effective, but that surveillance of Barrett's oesophagus, even at 5-yearly intervals, is very expensive even though more QALYs may be gained.

Regarding study quality, key issues are:

- Only a simplified model is shown and no further details are given.
- The model cycle is 1 year; however, several states are occupied for shorter periods and surveillance for dysplasia is at shorter intervals than this. It is not clear how this is achieved.
- It is not clear how published data with short-term follow-up have been extrapolated to the 30-year time horizon of the model.
- Utility values are stated for only two health states.
- Distributions used for the Monte Carlo simulation are not given.
- The pattern of surveillance in dysplasia does not correspond to current UK advice.
- Based on US costs in dollars for 2001.

Provenzale and colleagues (1994)[64]

A Markov model was designed to examine the 12 surveillance and treatment strategies listed below:

1. no surveillance, endoscopy for new or worsened dysphagia, oesophagectomy for ACO
2. no surveillance, endoscopy for new or worsened dysphagia, oesophagectomy for HGD
3. endoscopy every year for Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD then endoscopy and oesophagectomy for ACO
4. endoscopy every 2 years for Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD then endoscopy and oesophagectomy for ACO
5. endoscopy every 3 years for Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD then endoscopy and oesophagectomy for ACO
6. endoscopy every 4 years for Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD then endoscopy and oesophagectomy for ACO
7. endoscopy every 5 years for Barrett's oesophagus, every 6 months for LGD and every 3 months for HGD then endoscopy and oesophagectomy for ACO.

8–12. as for 3–7, but with oesophagectomy for HGD.

In each strategy, a cohort of 10,000 55-year-old men diagnosed with Barrett's oesophagus is modelled until death. This allows a calculation of quality-adjusted life expectancy for each arm.

A survival advantage in the surveillance arms accrues owing to several associated factors: ACO being detected before it becomes symptomatic (estimated to take 4–5 years) and the related increased chance of treatment due to less advanced tumour stage (75% versus 49%) and better survival due to less chance of recurrence (5 year survival 64% versus 17%). It is not clear if differential health state utility values are also involved as only the value for oesophagectomy (0.8) is reported.

The authors conclude that aggressive surveillance of Barrett's oesophagus reduces the incidence of ACO and increases life expectancy and quality-adjusted life expectancy. However, the life expectancy gain is relatively modest owing to the low overall risk of developing ACO (maximum difference strategy 1 compared with strategy 8 = 0.96 years). Surgery for HGD gives greater QALY gains than oesophagectomy for ACO alone. Surveillance strategies every 5 years, compared with no surveillance of Barrett's oesophagus, gives an ICER of US$27400 per QALY. More frequent surveillance intervals cause the ICER to rise quickly beyond usual levels of willingness to pay: US$276,400 per QALY at 4-year intervals.

Incidence of ACO was found to be a critical variable in one-way sensitivity analysis, as was the utility value (QoL) for patients who undergo oesophagectomy.

Quality assessment of this study raised the following concerns:

- No influence diagram is shown, so the model structure is not clear.
- Not clear how data from studies with short-term follow-up are extrapolated over the time frame (the model is run until the whole cohort dies).
- Cycle length for the model is not stated.
- It is not clear how single data values stated are calculated from the multiple references given.
- It appears that not all values used in the model are stated.
- Although it is stated that diagnostic error is incorporated in the model, it is not clear how this is done.
- Based on US costs in dollars in 1994

Provenzale and colleagues (1999)[42]

In this study, Provenzale and colleagues build on their 1994 paper,[64] but incorporate new lower estimates for ACO incidence (0.4% annually compared with 1% annually) and higher utility value for the oesophagectomy health state (0.97 compared with 0.8). This was calculated using the TTO method with an unspecified number of patients alive at least 1 year after oesophagectomy.

The ICER for surveillance every 5 years and surgical treatment for HGD compared with no surveillance was US$98,000 per QALY.

Quality assessment identified the same areas for concern as the 1994 paper and, in addition:

- Surgery for HGD is modelled rather than ACO, limiting its relevance to the UK setting.

Given the limitations stated above, the US focus of all the published papers and the need to explore areas of uncertainty, we developed a new economic model from the perspective of the UK NHS.

PenTAG model of surveillance for Barrett's oesophagus

Given the nature of this research project, our model was not developed primarily in order to estimate cost-effectiveness, but rather to ascertain the key areas of uncertainty in making this assessment. In order to assess cost-effectiveness accurately the following parameters, currently uncertain, would need to be known:

- Progression rate of Barrett's oesophagus to and through dysplastic states and to ACO.
- The time taken for ACO to become symptomatic and so be investigated through endoscopy.
- The relative proportions of cancers detected through surveillance and through clinical presentation that are curable.
- The impact on QoL of entering an endoscopic surveillance programme.
- The impact on QoL of oesophagectomy.

Extensive investigation of uncertainty was therefore a feature of our approach.

Structure of the model

A Markov (state transition) model was developed in Microsoft Excel. The structure was informed by current understanding of the progression of Barrett's oesophagus through increasing dysplasia to ACO and by the current practice of surveillance in the UK. The purpose of the model was to assess the cost-effectiveness of a surveillance regimen for patients with Barrett's oesophagus compared with no surveillance and to identify and quantify important areas of uncertainty. Specifically, the model estimates incremental cost–utility and EVPI for an endoscopic surveillance regimen compared with no surveillance. The base case uses costs for 2004 and takes the perspective of the UK's NHS. A cohort of 1000 55-year-old men with a diagnosis of Barrett's oesophagus is modelled for 20 years. Cycle length is 4 weeks.

The influence diagram for the model is shown in *Figure 1*. The whole cohort starts at the initial endoscopy, when they are diagnosed with Barrett's oesophagus and may also have dysplasia. The model does not include patients diagnosed with ACO at the initial endoscopy as this is not relevant

TABLE 16 *Modelled disease states and their codes*

Model code	Disease state
STA	Initial endoscopy at which all modelled patients are found to have Barrett's oesophagus with or without dysplasia
REG	Barrett's oesophagus initially diagnosed, now Barrett's oesophagus regressed
BwB	Diagnosed state non-dysplastic Barrett's oesophagus. Actual state non-dysplastic Barrett's oesophagus
BwL	Diagnosed state non-dysplastic Barrett's oesophagus. Actual state Barrett's oesophagus with LGD
BwH	Diagnosed state non-dysplastic Barrett's oesophagus. Actual state Barrett's oesophagus with HGD
BwA	Diagnosed state non-dysplastic Barrett's oesophagus. Actual state Barrett's oesophagus with ACO
LwB	Diagnosed state Barrett's oesophagus with LGD. Actual state non-dysplastic Barrett's oesophagus
LwL	Diagnosed state Barrett's oesophagus with LGD. Actual state Barrett's oesophagus with LGD
LwH	Diagnosed state Barrett's oesophagus with LGD. Actual state Barrett's oesophagus with HGD
LwA	Diagnosed state Barrett's oesophagus with LGD. Actual state Barrett's oesophagus with ACO
HwB	Diagnosed state Barrett's oesophagus with HGD. Actual state non-dysplastic Barrett's oesophagus
HwL	Diagnosed state Barrett's oesophagus with HGD. Actual state Barrett's oesophagus with LGD
HwH	Diagnosed state Barrett's oesophagus with HGD Actual state Barrett's oesophagus with HGD
HwA	Diagnosed state Barrett's oesophagus with HGD. Actual state Barrett's oesophagus with ACO
ACD	ACO diagnosed through endoscopic surveillance
ACS	ACO diagnosed owing to symptoms instigating endoscopy
ACU	ACO not surgically treatable
SUR	Surgical treatment for ACO (oesophagectomy)
CMP	Complications during surgical treatment for ACO
WAS	Well after surgical treatment for ACO
DTT	Death due to surgery for ACO
DTA	Death from adenocarcinoma

to the comparison of surveillance versus non-surveillance, nor does it include those patients who do not receive a diagnosis of Barrett's oesophagus at endoscopy.

The solid-lined squares in *Figure 1* represent actual categories, whereas the dotted-lined squares represent diagnosed states. This allows the natural history of the disease to be modelled (movement between solid-line squares) while a new surveillance regimen or treatment is only instigated when the patient is reclassified at their next surveillance endoscopy. Patients then move between the dotted-line diagnosed states. Lines between the boxes indicate possible movement between states at the end of each cycle. This movement takes place in the direction of the arrow(s). Patients may stay in a state for more than one 4-week cycle where a circular arrow is shown. The proportion of patients moving in the model is based on available data for progression and regression.

The bold arrows show where patients move from a diagnosed state of Barrett's oesophagus with or without dysplasia to a diagnosed state of ACO. At this point, all those candidates who are suitable will receive treatment by oesophagectomy. For the non-surveillance arm, patients will be diagnosed with ACO only if symptoms lead to an investigative endoscopy being performed. Codes used in the influence diagram (*Figure 1*) are listed in *Table 16*. All modelled patients have Barrett's oesophagus initially and they may also be diagnosed initially, or at future endoscopies, as having no dysplasia, LGD, HGD or ACO. However, as the disease progresses and regresses independently of observation, patients have both a diagnosed and an actual disease state. See *Figure 1* and *Table 16* for further details.

In addition to the states shown, death from causes other than ACO is possible from any state and this is modelled as a time-dependent variable, related to the age of the patient.

The underlying pathological process is assumed to be that a proportion of the cohort will progress through increasingly severe dysplastic states and eventually develop ACO. True progression rates are unknown as the only estimates available are from diagnosed states detected at surveillance, which are subject to diagnostic error and limited by surveillance interval. The dysplastic states may also regress; regression rates may reflect both genuine pathological regression and diagnostic error. All rates are taken from the literature.

The model structure allows people to move between **actual** states even when they have not been observed to do so; their diagnosed state

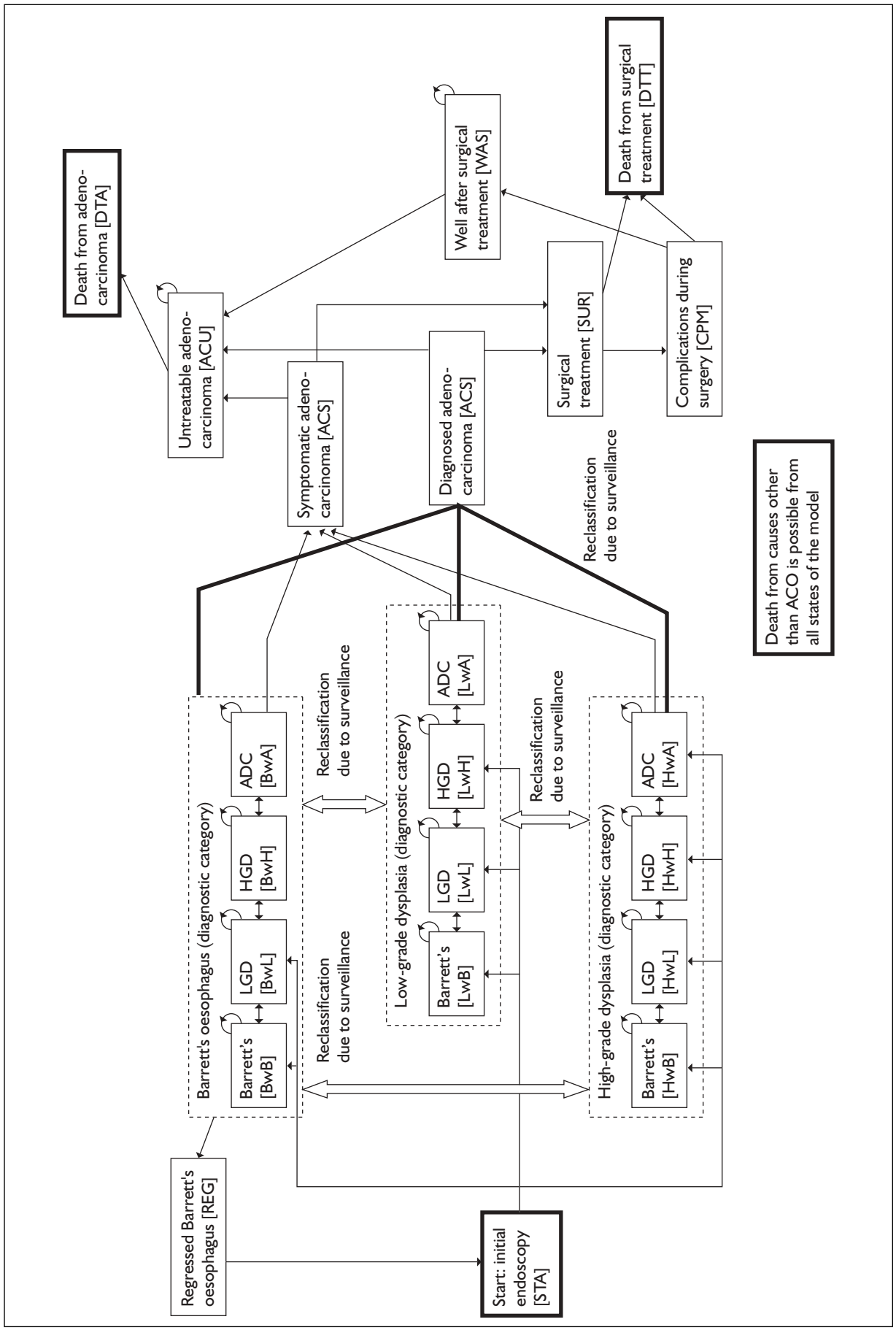

FIGURE 1 *Influence diagram for patients with Barrett's oesophagus*

remains the same until the next endoscopy. Endoscopic surveillance is observed in the model by taking a 'slice' across the model after the appropriate time and then recategorising patients on the basis of their newly diagnosed state. Until the time of the next endoscopy, when they will be reclassified, modelled patients incur the costs of their diagnosed, rather than their actual disease state (illustrated by the dotted line boxes in *Figure 1*), but will continue to move between states shown by the solid-line boxes within each diagnosed state.

The model does not **explicitly** account for less than perfect sensitivity and specificity of diagnostic tests (i.e. the tests are assumed to be 100% sensitive). However, the rates of progression and regression taken from the literature will contain both true progression and regression and corrections for misdiagnosis. To this extent, the model therefore accommodates some misclassification of disease state.

In each of the disease states – non-dysplastic Barrett's oesophagus, Barrett's oesophagus with LGD, Barrett's oesophagus with HGD, ACO – it is possible to continue in the same state for another cycle, progress to a more advanced disease state or regress to a less advanced state. Once ACO has bean diagnosed, either through endoscopic surveillance or through investigation due to symptoms, surgery is considered. ACO may be untreatable owing to advanced disease state or because the patient is unsuitable for surgery owing to concomitant illness or general frailty. Having surgical treatment may lead to the patient being well after surgery, having non-fatal complications due to surgery or dying following surgery. Following complications, patients may become well or may die as a result. It is assumed that complications last no longer than 4 weeks (one cycle). Patients may also die from causes unrelated to Barrett's oesophagus, ACO or surgery from any state in the model based on life tables for the relevant age group. These death rates alter with time as the cohort ages and have been taken from life tables adjusted to take account of death rates from adenocarcinoma.[65]

The model compared the following options:

- No surveillance – ACO is diagnosed only when it becomes symptomatic, leading to endoscopy. Treatment for ACO is oesophagectomy.
- Surveillance regimen once Barrett's oesophagus is diagnosed. Non-dysplastic Barrett's oesophagus is examined every 3 years, LGD annually and HGD every 3 months. Treatment for ACO is oesophagectomy.

The ICER between these options is calculated.

Uncertainty is explored through one-way sensitivity analysis and probabilistic sensitivity analysis, including EVPI and partial expected value of perfect information (PEVPI) calculations.

In one-way sensitivity analysis, each value is varied individually, keeping other inputs unchanged. This allows the variables having the greatest individual influence on the model output to be identified.

Probabilistic simulation analysis (PSA) is used to reflect parameter uncertainty in model outputs given the underlying uncertainty in model input data. This is achieved by running the model many times (for example, 1000) with input values sampled randomly from appropriate distributions. PSA provides outputs such as cost-effectiveness acceptability curves (CEACs), which give a means of assessing the likelihood that a particular intervention is cost-effective at varying 'willingness-to-pay' thresholds.

EVPI analysis uses PSA outputs to assess the likely costs of making a poor decision based on available data and hence provides a measure of the maximum monetary value of having perfect information. PEVPI examines the value that can be given to attaining perfect information for specific parameters within the model.

Model assumptions

The start point [STA] indicated in *Figure 1* is not a 'state' of the model – patients spend no time here, but pick up the cost of the endoscopy and are immediately categorised into one of the diagnostic states where they spend the first cycle. Patients with ACO at initial endoscopy are not included in the model, nor are patients without a diagnosis of Barrett's oesophagus.

At the first endoscopy, we take account of possible misdiagnosis, allowing modelled patients to be categorised to any of the solid-line boxes shown in *Figure 1*. From then on, as stated previously, we have not explicitly accounted for misdiagnosis. However, the use of progression and regression data from empirical studies means that some of the movement between states will take account of misdiagnosis.

In data taken from this systematic review, categories reported as ID and LGD have been grouped together as LGD.

By definition, information about the rates of progression comes from observed progression when endoscopic surveillance is undertaken. We have had to assume that the actual progression (natural history of Barrett's oesophagus) is equivalent to this. It is assumed that the actual disease progression is a linear function of the observed rate between states. This may lead to biases of unknown size and direction.

It has also been assumed that annual progression rates to cancer are constant. There is no published evidence on this point. This was considered a reasonable assumption by most of the expert advisory group. However, it was also suggested that the progression would show more cancers early and late. That is, that there are some high-risk patients whose cancers develop rapidly whereas others, if no progression is seen in the first year, have a lower risk of progression.

The model assumes that when patients progress, they do so sequentially through each state – from non-dysplastic Barrett's oesophagus to LGD to HGD to ACO.[66] This may not be observed by the surveillance regimen if progression occurs more quickly than the intervals between endoscopies. This may be a limitation of the model, but is a necessary simplification, given structural and data limitations. It is possible that in reality people may progress directly to ACO or may skip dysplastic states.

The model assumes that progression time, proportion of patients with ACO suitable for surgery and death associated with ACO are constant. In reality, these are likely to alter as the cohort ages, and the model may therefore bias in favour of surveillance.

Clinical assumptions – aspects of care

It was assumed that all patients entered into the surveillance programme comply with its demands. This may bias in favour of surveillance.

It is assumed that all endoscopies are carried out as hospital outpatient procedures.

Health state utility values are the same in the surveillance and non-surveillance arms. It was not known whether the possible discomfort and anxiety of being in a surveillance programme would be more or less than having a diagnosis of Barrett's oesophagus and no regular surveillance investigation. This also means that rare but potentially serious adverse effects from endoscopy have not been incorporated. This may bias the results in favour of surveillance.

Among those with Barrett's oesophagus but not ACO in the non-surveillance arm, we have assumed that 17.5% (based on expert opinion) will incur the cost of an additional endoscopy to investigate worsening or changing symptoms that are not due to malignancy. This has been added as a one-off cost and has no further implications in the model.

It is assumed that all patients in both arms receive PPIs at a maintenance dose. We have used an average of commonly used PPI costs – 20 mg omeprazole, 15 mg lansoprazole and 30 mg lansoprazole.

We have assumed that ACO in the non-surveillance arm is only detected when it becomes symptomatic. This means that cancers are at a more advanced stage and fewer are suitable for resection (50% compared with 95% detected through surveillance).[35,36]

If ACO recurs after resection it is considered inoperable, and patients move to the terminal state with 78% probability of death in 1 year.[35,36]

Data sources used in the cost-effectiveness models

Where possible, we have used published sources for inputs. We were hampered by the absence of RCT data, by the range of findings by case series studies of surveillance of Barrett's oesophagus and by the lack of reporting of some crucial data in these studies. Given the nature of the data used, results should be viewed with considerable caution.

Parameters included

The following parameters were included in the models:

- the proportion of patients who remain in their current state, progress to a more severe state or regress to a less severe state
- background death rate, from causes other than ACO, for men of the relevant age
- mortality rate from ACO
- mortality rate from oesophagectomy
- the ratio of treatable to non-treatable ACOs in both symptomatic and surveillance diagnosed ACO
- utility values associated with each state
- the costs associated with each state (costs of endoscopy, maintenance therapy and surgery).

Sources of estimates

Transitions

As there are no RCT data, we used the results from this systematic review of case series to estimate transition rates (see *Table 20*). Including only larger studies is likely to reduce the inflated cancer incidence rates from published smaller studies.[3]

The studies have a maximum follow-up of 3–4 years. An incidence per patient year follow-up was calculated and this was used as an annual progression rate. This assumes that progression to ACO is equal in each year of follow-up and can be extrapolated beyond the follow up of the studies. This assumes that an equal rate of progression is seen in each year and that this is the same in year one as year 20.

As the case series only report the Barrett's oesophagus or dysplasia state recorded by the final endoscopy, we assumed that patients progress sequentially through dysplastic states of increasing severity. Thus, for example, when a patient is recorded as having ACO at the final endoscopy after being initially diagnosed with non-dysplastic Barrett's oesophagus, we have assumed that they have passed through the states of LGD and HGD during the period between endoscopies. We therefore calculated the progression rates from Barrett's oesophagus to LGD, LGD to HGD and HGD to ACO taking this into account.

Other estimates have been take from the literature – using reviews of data (including where these have been undertaken for previous economic evaluations) where possible and relevant, recent case series where this is not available.

Utilities

The estimates of utility used in the model were obtained from the NHS Value of Health Panel, a pilot project being led by PenTAG in collaboration with the Universities of Southampton and Sheffield. The Value of Health Panel is a group of 64 people recruited from the general population who have been trained in carrying out the standard gamble method for preference elicitation. Panel members express their preference using this technique in relation to short descriptions of health states using the Internet. The health state scenarios are developed from disease-specific outcome measures and other relevant information and, where possible, checked for content validity with relevant clinicians and people with the conditions of interest prior to valuation. In the current project, the health states and their sources are described in *Table 17*. The health state scenarios are shown in Appendix 11. Given the short timescale available to obtain estimates for this project, it was not possible to check content validity prior to measuring preferences. As not all participants gave scores for all the scenarios, summary values are based on between 38 and 42 respondents.

Results from the Value of Health Panel are given in *Table 18*. We used median values in the model. We assumed that equal proportions of patients with Barrett's oesophagus experienced mild, moderate and severe GORD symptoms, giving an overall utility value for the cohort of 0.813. Those in the surveillance arm diagnosed with ACO were assumed to have mild symptoms of ACO and those diagnosed through symptoms were assumed to have severe symptoms.

Resource use and costs

Costs of endoscopy were taken from the National Schedule of Reference (NSR) costs 2002[46] using codes F04 (Oesophagus endoscopic or intermediate procedures with complications) and F05 (Oesophagus endoscopic or intermediate procedures without complications). Assuming the rate of complications stated in *Table 20*, we applied an adjusted cost to each endoscopy undertaken.

Costs of oesophagectomy were taken from the NSR costs 2003[46] using code F01 (Oesophagus – complex procedures.) In addition, the costs of preoperative assessments – blood tests, lung function tests and ECG – are added. Tumour staging investigation using computed tomography (CT) scan, endoscopic ultrasound or laparoscopy is added. We used the average cost of these staging investigations taken from NSR lists. Where costs were available only up to 2002, an inflation estimate was added to bring costs in line with 2004 levels. This was taken from Health Service Cost Index estimates for price inflation.[71]

Costs of PPIs were taken from the BNF No. 47 (March 2004) and are applied to all patients in both surveillance and non-surveillance arms at maintenance levels.

Associated with death from ACO are palliative care costs. These are assumed to include admission or day care in a hospice, stenting to relieve problems with swallowing (£1578 from HRG code F03, Oesophagus – major procedures or prostheses) 4 days in hospital (at £250 per day) and GP and community nursing costs, estimated to be about £1000.

TABLE 17 *Health states used in the model and source of their utility values*

Health state	Source and notes on preparation
Barrett's oesophagus on surveillance – mild GORD symptoms	The scenario uses data from a small study (n = 15) by Fisher *et al*.[67] of symptoms in people with Barrett's oesophagus on surveillance. The population is described as having mild symptoms of GORD using the QOLRAD instrument (Quality of Life in Reflux and Dyspepsia Patients), a validated tool for measuring the impact on QoL of symptoms of GORD.[68] This includes the following domains, each rated on a 7-point categorical scale: • emotional distress • sleep disturbance • food/drink problems • physical/social functioning • vitality The scenario depicts the mean domain scores reported in this sample
Barrett's oesophagus on surveillance – moderate GORD symptoms	The scenario was developed to reflect the mean domain scores on the QOLRAD in 759 patients with GORD.[68] A wide range of underlying diagnoses was present
Barrett's oesophagus on surveillance – severe GORD symptoms	Each of the domains of the QOLRAD score was described as being severely affected
Symptomatic adenocarcinoma – mild symptoms	The EORTC-QOL C30 (with oesophageal module) was used to describe symptoms. This is a generic instrument for measuring QoL in people with cancer, to which has been added a series of additional, site-specific questions In the time available, it was not possible to obtain data on patients presenting with ACO using this measure. Two scenarios were therefore developed. In the mild scenario, symptoms are described as mild or infrequent, with dysphagia predominating. Symptoms have limited impact on functional and social abilities. In the severe scenario, a wider range of symptoms of greater frequency and severity are included
Post oesophagectomy	This state was described using the Rotterdam Symptom Checklist (RSCL), a measure of QoL designed for use in all types of cancer. It has four subscales: • physical symptom distress • psychological distress • activity level • overall valuation of life Data from a group of 34 people at >2 years post-oesophagectomy were used to develop the scenario.[69] This was augmented by information on dumping syndrome taken from a patient information leaflet[70] The proportion of patients in the study population who complained of specific symptoms was calculated from data provided by De Boer *et al*.[69] and these used to indicate, crudely, how often the 'typical' patient might experience symptoms
Terminal adenocarcinoma	It is difficult to depict a health state of advanced cancer as the degree of symptoms experienced is likely to fluctuate on a short-term basis and will clearly, overall, worsen towards death. A brief search for relevant published information (i.e. description of QoL in the terminal stages of oesophageal cancer) was unproductive The scenario was therefore developed on the basis of clinical judgement with reference to general symptoms of advanced cancer and the specific symptoms of oesophageal cancer

Discounting

In accordance with HM Treasury guidance, costs were discounted at 6% and benefits at 1.5%.

Dealing with uncertainty

One-way sensitivity analysis

Extensive one-way sensitivity was performed to explore which of the inputs to the model have the greatest impact on the incremental cost–utility of surveillance for Barrett's oesophagus when varied in isolation. Based on this initial explanation, further analyses were carried out on the parameters found to have the most impact on the model:

TABLE 18 *Utility values for health states obtained from the Value of Health Panel*

Scenario	Mean	Median	Min.	Max.	Standard error	N[a]
Barrett's oesophagus – mild GORD symptoms	0.933	0.975	0.400	1.000	0.016	42
Barrett's oesophagus – moderate GORD symptoms	0.792	0.813	0.275	0.995	0.024	42
Barrett's oesophagus – severe GORD symptoms	0.625	0.650	0.100	0.995	0.036	42
ACO – mild symptoms	0.838	0.875	0.500	0.995	0.022	38
ACO – severe symptoms	0.654	0.675	0.050	1.000	0.032	42
Terminal ACO	0.395	0.400	0.000	0.925	0.042	39
Well after oesophagectomy	0.849	0.863	0.575	1.000	0.016	42

[a] *N* = number of respondents.

TABLE 19 *Distributions used in model*

Parameter type	Distribution used	Justification
Utility values	Beta	Ensures sampled values in the 0–1 range with variances not so high as to produce a distorted (i.e. U-shaped) distribution
Cost values	Log-normal	Positively skewed distribution with values above zero
Transition probabilities (except those below)	Beta	Returns values in the accepted 0–1 range
Transition probabilities for: 1. rate for adenocarcinoma becoming symptomatic 2. treatability ratio for adenocarcinoma 3. postsurgical recurrence rates in both arms	Uniform within 95% CIs	Clinical opinion gives widely varying estimates which are equally plausible. Uniform distribution reflects this wide variance given the underlying uncertainty in the data with no bias in favour of central values in the sampling

- rate of recurrence of ACO after initial surgery
- proportion of treatable cases of ACO in each arm
- transitions between the stages of Barrett's oesophagus, dysplasia and ACO and from ACO to symptomatic ACO
- costs of endoscopy
- utility values for Barrett's oesophagus and postsurgical state.

Probabilistic simulation

A probabilistic Monte Carlo simulation was developed to explore the impact on cost-effectiveness of parameter uncertainty in the underlying model inputs. In the stochastic approach, the Markov model is run for 1000 trials with key input values randomly drawn from probabilistic density functions in each model run. In these simulated trials, values were sampled for utilities, costs and transition probabilities using the distributions shown in *Table 19* and results were presented graphically.

Input data

Tables 20–22 show the data used in the base case of the model, together with how this value was obtained and why this method was used. Where appropriate, the costs in *Table 22* were inflated to reflect costs in 2004.

Transition probabilities per cycle were derived from stated annual rates using the following formula:

$$1 - \exp[\ln(1 - \text{yearly rate})/\text{cycles per year}]$$

In our model, cycles per year = 13 (i.e. 4-week cycle duration).

Ranges for data and sources used in the probabilistic sensitivity analyses are also shown. For the probabilistic sensitivity analyses, these ranges are assumed to be 95% CIS, and standard errors are derived from this assumption (= range/3.92).

TABLE 20 *Transition data used in the model base case and ranges*

Model input	Value	Source	Justification	Range	Source
Proportion of cohort diagnosed as non-dysplastic Barrett's oesophagus at initial endoscopy	0.8341	*Table 4* – mean of proportions in included studies. Not including incomplete data from Schnell[57] and excluding ACO at initial endoscopy	This systematic review (see Chapter 4)	0.394 0.936	Reid *et al*. (2000)[58] Murray *et al*. (2002)[53] Both large recent studies – minimum and maximum values in this systematic review (*Table 4*)
Proportion of cohort diagnosed as LGD at initial endoscopy	0.1205	*Table 4* – mean of proportions in included studies. Not including incomplete data from Schnell[57] and excluding ACO at initial endoscopy	This systematic review (see Chapter 4)	0.027 0.159	Ferraris *et al*. (1997)[55] Hillman *et al*. (2003)[54] Both large recent studies – minimum and maximum values in this systematic review (*Table 4*)
Proportion of cohort diagnosed as HGD at initial endoscopy	0.0454	*Table 4* – mean of proportions in included studies. Not including incomplete data from Schnell[57] and excluding ACO at initial endoscopy	This systematic review (see Chapter 4)	0.0 0.232	Ferraris *et al*. (1997)[55] Reid *et al*. (2000)[58] Both large recent studies – minimum and maximum values in this systematic review (*Table 4*)
Annual progression rate Barrett's oesophagus to LGD	0.0289	*Table 8* – assumed that progression from Barrett's oesophagus to LGD annually is the combined values of Barrett's oesophagus to LGD, Barrett's oesophagus to HGD and Barrett's to ACO in this table. Mean per 100 patient years of follow-up	This systematic review (see Chapter 4)	0.0185 0.05	Hurschler *et al*. (2003)[59] Minimum reported in *Table 4* of this systematic review. Recent large study Inadomi *et al*. (2003)[30] Previously published cost–utility analysis, based on literature
Annual progression rate LGD to HGD	0.0345	*Table 8* – assumed that progression from LGD to HGD annually is the combined values of LGD to HGD and to ACO in this table. Mean per 100 patient years of follow-up	This systematic review (see Chapter 4)	0.013 0.05	Sontag (1999) (abstract only)[139] Report on 848 LGD patients. 6% progress after an average of 2.3 years – PenTAG assume a linear progression rate Inadomi *et al*. (2003)[30] Previously published cost–utility analysis, based on literature
Annual progression rate HGD to ACO	0.1187	*Table 9* – mean progression value per 100 years of patient follow-up from included studies	This systematic review (see Chapter 4)	0.018 0.1362	Schnell (2001)[57] Report on 79 HGD patients, progression 9% at 5 years – assumed linear by PenTAG Weston *et al*. (2000)[72] Report on progression of 8/15 HGD patients after a median of 23.5 months, assumed half of patients had progressed by this time and linear rate of progression.

continued

TABLE 20 *Transition data used in the model base case and ranges (cont'd)*

Model input	Value	Source	Justification	Range	Source
Annual regression from Barrett's oesophagus to regressed Barrett's oesophagus	0.0243	*Table 6*. Hurschler *et al*. (2003)[59]	This systematic review (see Chapter 4)	0.0175 0.075	Inadomi *et al*. (2003)[30] Previously published cost–utility analysis, based on literature Provenzale *et al*. (1999)[42] Author estimate of normal mucosa diagnosed as Barrett's oesophagus
Annual regression from LGD to non-dysplastic Barrett's oesophagus	0.1291	*Table 7*. Mean Hurschler *et al*. (2003)[59] and Hillman *et al*. (2003)[54]	This systematic review (see Chapter 4). Only two studies reporting regression rates from LGD	0.0 0.63	Author assumption, lower confidence level assumed to be zero Inadomi *et al*. (2003)[30] Previously published cost–utility analysis, based on literature
Annual regression from HGD to LGD	0.0476	*Table 8*. Mean Hurschler *et al*. (2003)[59] and Hillman *et al*. (2003)[54]	This systematic review (see Chapter 4). Only two studies reporting regression rates from LGD	0.0405 0.0889	Levine *et al*. (1996) reported in Weston (2000)[72] on 16/58 patients with HGD regressed after mean of 40 months – assumed linear, and half had regressed by 40 months. Weston (2000)[72] Report 7/15 HGD patients regressed after a median of 31.5 months – assumed linear and that half had regressed by 31.5 months
Annual regression from ACO to HGD	0	Assumption		Not varied	
Annual progression from ACO to symptomatic ACO	0.143	Provenzale *et al*. (1999)[42,64] estimate that the average time for ACO to become symptomatic was 4–5 years PenTAG calculated an annual rate assuming linear rate and that 50% of the ACO population were symptomatic by 4.5 years	Previously published cost-effectiveness studies using values taken from Chinese study. No UK data identified	0.0455–0.240	Ferguson and Durkin (2002)[73] Retrospective survey of 80 patients undergoing resection for ACO (12 after surveillance, 68 non-surveillance) average age at surgery 53 vs 64 years, i.e. 11 years. Annual progression calculated by PenTAG Symmetry assumed around central value
Annual death rate from unresectable ACO	0.78	Corley (2002)[35] and Streitz and Henry (1993)[36]	Recent study of survival in surveillance detected vs non-surveillance detected ACO cases (n = 23), and same figure in earlier study of 77 ACO patients, non-surveillance and surveillance detected cases compared	0.7 0.88	Kellokumpu-Lehtinen *et al*. (1990)[74] Mortality in 106 patients with inoperable ACO in Finland Savage *et al*. (1994)[75] UK study of 211 patients with inoperable ACO.

continued

TABLE 20 *Transition data used in the model base case and ranges (cont'd)*

Model input	Value	Source	Justification	Range	Source
Background rate death rate from other causes	Variable	Life table mortality for relevant age group. Adjusted as cohort ages and for rate of ACO death	Age-specific UK data	Not varied	
Proportion of symptomatic ACOs treatable	0.5	Corley (2002)[35]	Recent study of surveillance detected vs non-surveillance detected ACO cases (n = 23)	0.26–0.74	US medical records study of 777 ACO cases (1999)[76] Symmetry around central value assumed
Proportion of ACO diagnosed through surveillance treatable	0.95	Steitz and Henry (1993)[36]	Study of 77 ACO patients, non-surveillance and surveillance detected cases compared	0.44–1.0	US medical records study of 777 ACO cases (1999)[76] Upper limit assumed to be 1.0.
Proportion of surgical procedures with non-fatal complications	0.30	Average proportion reported by van den Boogert *et al*. (1999)[15]	Recent review of the literature	0.0013–0.4	Inadomi *et al*. (2003)[30] and Provenzale *et al*. (1999)[42] Complications not requiring surgery Post-operative complications (bleeding, small bowel infarction, sepsis, respiratory failure, chest infection, thoracic duct fistula) in study of 17 patients resected for ACO[77]
Mortality from surgery	0.065	Average proportion reported by van den Boogert *et al*. (1999)[15]	Recent review of the literature	0.04–0.11	Enzinger and Mayer (2003)[78] Recent review of literature Perioperative mortality rate in 781 oesophageal cancer patients in SW England 1996–7[5]
Rate of ACO recurrence after surgery: Non-surveillance arm	0.26	Danish registry study of 578 ACO cases (1999)[79]	As this records patients going back to the 1970s prior to formal surveillance, this has been assumed to be the recurrence rate in the non-surveillance arm of the model	0.142–0.402	De Manzoni *et al*. (2003)[81] Recent study of 92 resected patients Symmetry around central value assumed
Surveillance arm	0.0928	Ratio of recurrence based on survival data for surveillance and non-surveillance detected cancers in Fountoulakis *et al*. (2004)[80]	Expert opinion is that most death after surgery is due to recurrence of ACO	0.0507–0.1435	Calculated as ratio from central value

TABLE 21 *Data used in the model base case – utility values*

Health state[a]	Utility value: base case (standard error)	Source	Justification
Well after regression from Barrett's oesophagus	0.8 (0.02)	Population norm at age 55–64 years from utility values derived from EQ5D[43]	General population values in the UK used
Barrett's oesophagus	0.8125 (0.025)	Value of Health Panel. Assume that equal number of patients have mild, moderate and severe GORD symptoms (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
LGD	0.8125 (0.025)	Value of Health Panel. Assume that equal number of patients have mild, moderate and severe GORD symptoms (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
HGD	0.8125 (0.025)	Value of Health Panel. Assume that equal number of patients have mild, moderate and severe GORD symptoms (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
Diagnosed with ACO	0.875 (0.025)	Value of Health Panel. Assume that surveillance diagnosed cases have mild ACO symptoms. (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
Symptomatic ACO	0.675 (0.032)	Value of Health Panel. Assume that ACO cases diagnosed cases due to symptoms have severe ACO symptoms (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
Untreatable ACO	0.400 (0.042)	Value of Health Panel for terminal ACO (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
Surgical treatment	0.55 (0.002)	Author assumption	One cycle state assumed to be worse than disease symptoms but quickly resolved
Surgical complications	0.5 (0.002)	Author assumption	One cycle state assumed to be worse than simple operation but quickly resolved.
Well after surgery	0.863 (0.016)	Value of Health Panel (*Table 18*)	Median and standard error from UK general public values from systematically derived health state scenarios
Death	0	Standard data	

[a] The values for Well after regression from Barrett's oesophagus and HGD and ACO states are counterintuitive, being slightly higher for the disease states than the well state. This is due to the different sources for these two data items and different methods of deriving them (standard gamble versus EQ5D). The number of patients moving into the former state is small and its impact is not likely to be important; however, the impact of changing this parameter was examined in sensitivity analysis (see *Figure 2*).

TABLE 22 *Data used in the model base case – costs*

Health state	Cost (£): base case (standard error)	Source	Justification
Barrett's oesophagus, LGD, HGD	22 (5.50)	BNF	Average of costs for commonly used PPIs
Endoscopy (including biopsy)	170 (10.78)	Codes F045 and F05 HRG (2002)[46]	National average costs
Presurgical tests	189 (30.02)	HRG codes for blood tests, heart and lung function plus CT scan or endoscopic ultrasound to stage tumour	National average costs
Surgical treatment of ACO	5753 (913.92)	Code F01 NSRC (2003)[46]	Cost for elective complex oesophageal procedure
Treatment of complications of surgical treatment of ACO	1541 (239.03)	Code F01 NSRC (2003)[46] – difference between average cost and upper quartile cost	Cost for elective complex oesophageal procedure
Untreatable ACO	3578 (894.50)	Costs for stenting HRG code F03 – major procedures for prostheses, 4 days in hospital at £250 per day and £1000 GP and nursing costs	National average costs

TABLE 23 *Baseline results for cost-utility of surveillance of Barrett's oesophagus patients compared with no surveillance*

	Cost (£)	QALYS	Incremental costs (£)	Incremental QALYS	ICER
Endoscopic surveillance	3,869,048	11,982	–	–	–
No surveillance	2,951,230	12,029	–917,818	48	Dominates

Baseline results of cost-effectiveness

Baseline results from the cost-effectiveness model are shown in *Table 23*. The surveillance programme confers 48 fewer QALYs to the whole cohort for an additional cost of £917,818, giving an ICER of –£19,318. In other words, surveillance causes more harm, giving fewer QALYs than non-surveillance and also costs more, i.e. it is dominated by non-surveillance. The absolute difference in QALYs, 48 over the whole cohort of 1000 people over 20 years is, however, small.

There are fewer QALYs in the surveillance arm because patients with ACO in this arm are detected sooner than those in the non-surveillance arm. They are therefore at risk of potential harm (disbenefits) related to surveillance – operative complications and mortality and early recurrence. In contrast, the benefits of surveillance are the avoidance of the consequences of cancers which would be detected later – worse stage at presentation, increased inoperability and higher rates of recurrence. The model's time horizon is therefore important as the consequences of the options explored occur at different times. However, in sensitivity analysis, extending the time horizon did not affect the direction of the results. Furthermore, the result is highly sensitive to plausible changes in single parameter values.

The model predicts that ACO will develop in a total of 9.5% of the modelled cohort during 20 years (*Table 24*). This is in line with an estimated 0.5% annual cancer incidence among those with Barrett's oesophagus in the literature.[82] As would be expected, different numbers of cases are actually detected in the two arms; 70% of cases are detected in the non-surveillance arm (i.e. from

TABLE 24 *Number of cancers predicted by the model*

ACOs	Non-surveillance	Surveillance
Number of detected ACOs	67.00	94.92
Number of undetected ACOs at end of model run	19.01	0.35
Undetected ACOs dying of other causes	9.18	0.35
Total	95.19	95.62

TABLE 25 *Number of detected cases of ACO treated with oesophagectomy*

ACOs	Non-surveillance	Surveillance
Number of detected ACOs treated	33.54	88.73
Number of detected ACOs untreated	33.46	6.19
Total	67.00	94.92

TABLE 26 *Number of deaths in the model*

ACOs	Non-surveillance	Surveillance
Deaths from surgical treatment	2.82	7.41
Deaths from ACO	55.90	55.10
Deaths from other causes	320.92	319.26
Total	379.64	381.76

symptoms alone) and 99% in the surveillance arm (*Table 24*). By the end of the model run, there are an additional 19 cases of ACO still undetected and not yet symptomatic or fatal in the non-surveillance arm. The consequences for these undetected cases of cancer represent further benefits that might have been accrued by surveillance. Many more of the detected cancers in the surveillance arm have been treated, owing to earlier stage of detection (*Table 25*). Although we may have introduced some bias in cost-effectiveness against surveillance by modelling the cohorts only to 20 years, extending the time horizon until the majority of people in the cohorts die would bias in favour of surveillance as the proportion of people who would be ineligible for surgery due to presence of co-morbidity would increase.

Up to 20 years, the surveillance programme detected an extra 28 cases of ACO and total endoscopy costs were £1,288,795 compared with £30,391 in the non-surveillance arm. This gives a cost of £44,943 per additional detected cancer. It should be noted that we have assumed perfect concordance with surveillance, resulting in an average of 7.4 endoscopies per participant. In practice, this may be high as drop-out and non-compliance have not been included in the model. For these reasons, which are expanded further in the sensitivity and value of information analyses, we believe that the current iteration of the model is insufficient to inform policy. It does, however, highlight the major drivers for cost-effectiveness and, by supporting value of information analysis, indicates the ceiling for investment in research which could be considered acceptable value for money in this area.

The total number of deaths after 20 years is very similar in both arms of the model (*Table 26*) and total numbers of deaths from ACO are also very similar. The majority of deaths from ACO in the surveillance arm come from recurrent ACO after oesophagectomy, whereas in the non-surveillance arm most are from first manifestation of ACO. There are also a larger number of deaths from surgery in the surveillance arm, reflecting an increased number of surgical interventions in this arm. The time to events is therefore clearly important. An analysis of time spent in the ACO states in the model suggests that there is no survival advantage due to surveillance. In fact, given assumptions made in the model, life expectancy is higher for those whose cancers are detected in the non-surveillance arm. It is critically dependent on specific model parameters, especially the rate at which ACO becomes

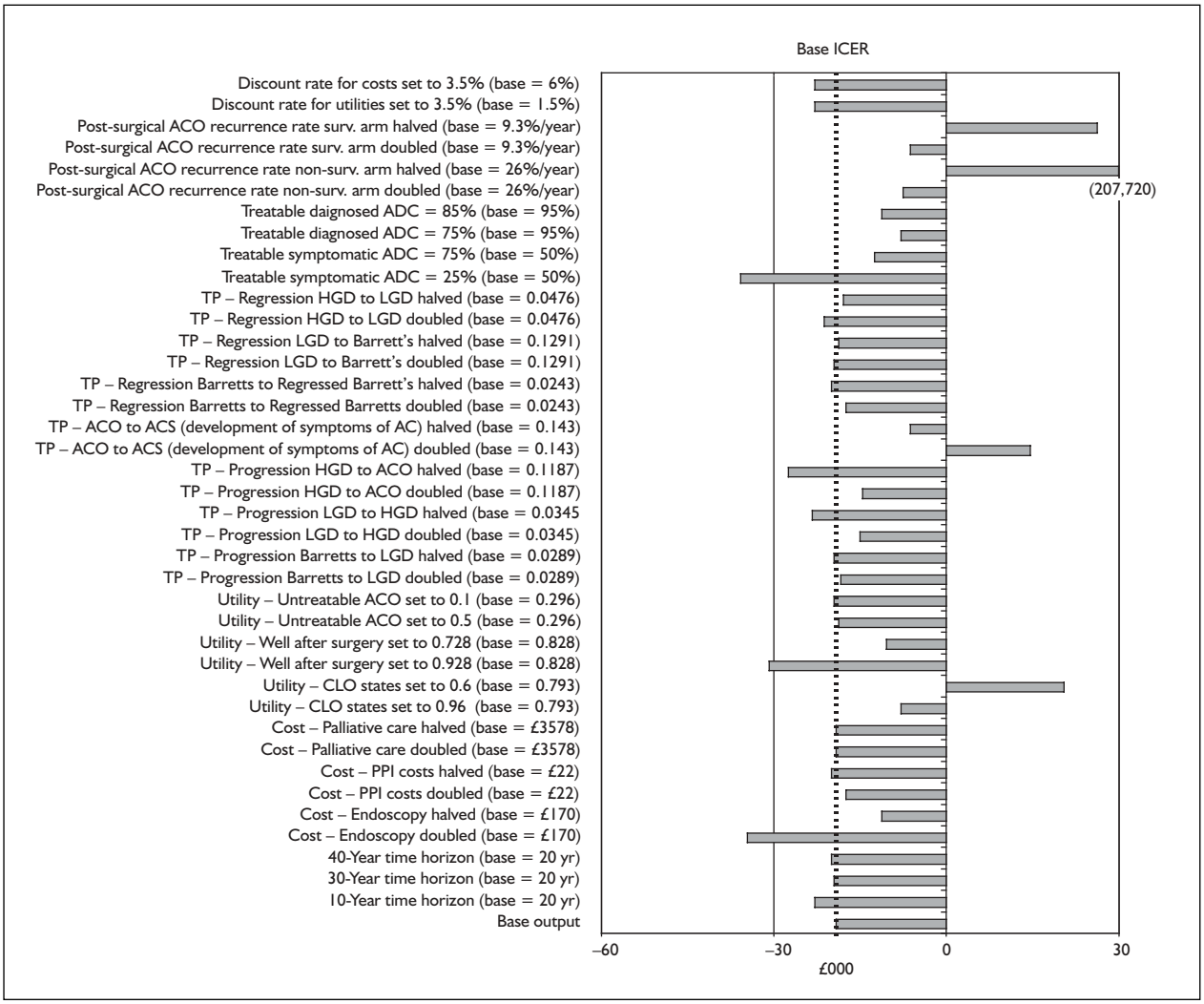

FIGURE 2 *ICER values from one-way sensitivity analyses (TP, transition probability)*

symptomatic and is detected. We thought that the time horizon may also affect this finding but extending the model to 30 and 40 years made no difference to the direction of the results. However, given the uncertainty in the data for the rate at which ACO becomes symptomatic, this result should be viewed with caution.

Sensitivity analyses

A key aspect of this evaluation, given the inherent uncertainties in this area, is extensive sensitivity analysis to explore the relationship between input parameters and model outputs. A range of techniques were used, including one-way sensitivity analyses and probabilistic sensitivity analysis, which employs Monte Carlo simulation to estimate the impact of the uncertainty on decision-making.

One-way sensitivity analyses

Figure 2 shows the effect of changing specific data parameters within the deterministic model on the ICER between the surveillance and non-surveillance arms. Each parameter is varied independently, so that the change in ICER shows what happens when a single parameter is altered and the rest of the model inputs remain fixed at the base case. The bar at the bottom of the chart shows the baseline ICER and the dotted line marks this level across the graph. The other bars show the effect on the ICER of raising or lowering the values used in the model base case. These are exploratory, and in most cases are investigated here by halving or doubling inputs.

From this initial analysis, the parameters that have a strong influence on the output of the model are identified. Inputs that potentially take the ICER to the right of the axis, in this case where

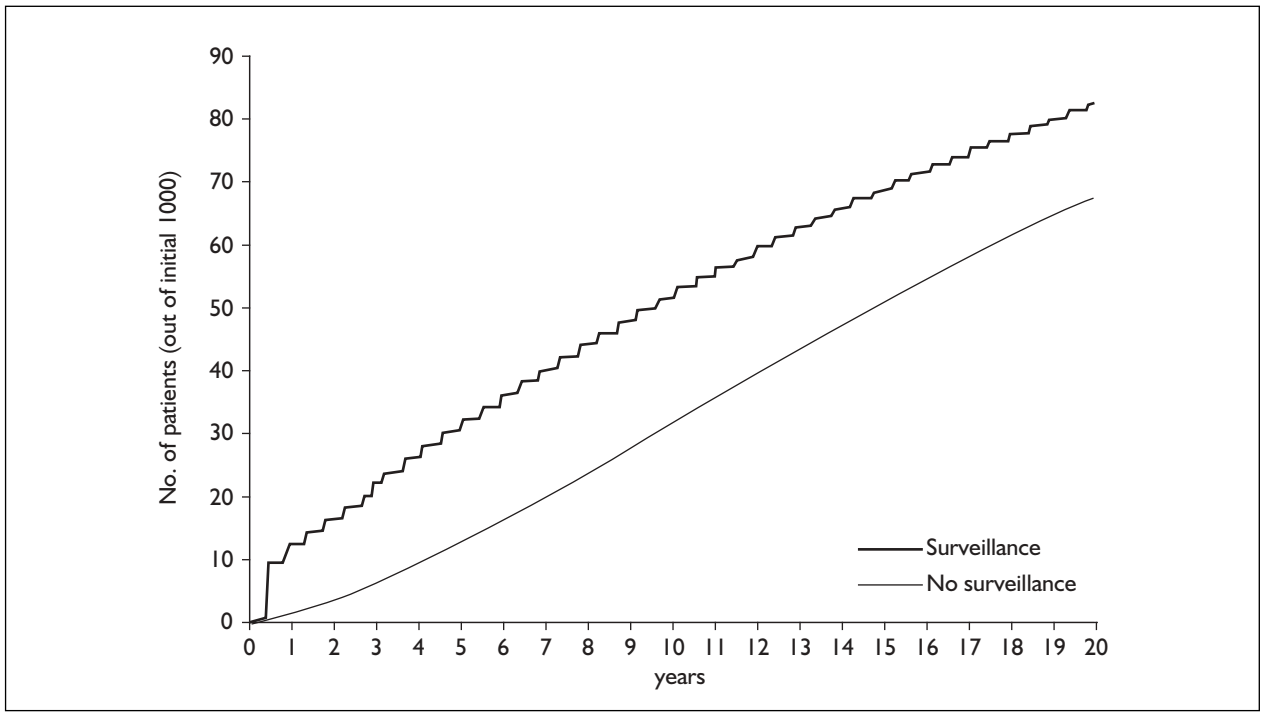

FIGURE 3 *Total number of ACO cases detected in the surveillance and non-surveillance arms of the model: total adenocarcinomas (symptomatic + diagnosed) (non-surveillance: diagnosed ACO = 0)*

surveillance no longer causes more harm than good, are of particular interest. These are:

- the recurrence of ACO (after oesophagectomy) in the surveillance arm
- the recurrence of ACO (after oesophagectomy) in the non-surveillance arm
- time taken for ACO to become symptomatic
- utility value for Barrett's oesophagus health states.

These are explored further in the following section with more detailed one-way sensitivity analysis.

In addition, we explored threshold values (values required for surveillance to become cost-effective) for:

- Proportion of patients whose cancer was detected owing to symptoms and who are treatable.
- Cost of endoscopy.
- Progression rates for Barrett's oesophagus states.
- Proportion of treatable ACOs detected through surveillance.
- Change in the ratio of proportion of recurrent ACOs detected in surveillance versus non-surveillance arms.
- Utility value for patients who are well following oesophagectomy.

Model time horizon

The time period of the model, set at 20 years in the base case, affects the number of adenocarcinomas which are detected, especially in the non-surveillance arm. In this arm, the associated disutilities of ACO (i.e. QoL associated with symptoms, untreatable ACO or treatment for ACO) only manifest once the ACO becomes symptomatic. In contrast, earlier detection of ACO in the surveillance arm produces more detected cancers in the early years of the model (with associated disutilities), hence shorter model runs are likely to bias against surveillance. This may have important implications for the interpretation of data from clinical studies with short periods of follow-up.

Figure 3 shows the number of ACO cases detected through surveillance or by investigation of symptoms over the 20-year time horizon. This shows the differential rate of cancer detection in each arm of the model, with the gap between them showing the number of undetected ACO cases in the non-surveillance arm. In the surveillance arm, the stepped nature of the curve reflects the impact of the modelled endoscopy protocol. The large initial jump in detection

number is due to the detection of ACO cases misclassified as HGD at initial endoscopy being identified at the first surveillance endoscopy.

Although cases are detected earlier, any benefits of surveillance for (quality-adjusted) survival do not become apparent until the non-surveillance arm is allowed to follow the natural history of progression to symptoms. However, we explored this by extending the model horizon to 30 and 40 years and found that surveillance continued to be dominated by non-surveillance (*Figure 2*).

Rate of ACO recurrence after treatment in surveillance and non-surveillance arms

After oesophagectomy, cancer may recur. In most cases, this will not be amenable to treatment. Less advanced cancers are less likely to recur after surgery. In the surveillance arm, 9.3% of resected cancers are assumed to recur each year in the base case and 26% in the non-surveillance arm since it is assumed that more advanced cancers are found through symptomatic presentation. Surveillance ceases to be dominated (i.e. it confers more benefit and costs more) if cancer recurrence falls to 6% in the surveillance arm (*Figure 4*) or to 14% in the non-surveillance arm (*Figure 5*). If the number of recurrent ACOs in the surveillance arm falls to 4.5% and the non-surveyed arm stays at 26%, the ICER drops to usually acceptable levels of willingness to pay (*Figure 4*). This is also the case if the percentage of cancers that recur in the non-surveillance arm falls to 7% and the surveillance arm stays at 9.3% (*Figure 5*).

Progression rate from undetected ACO to symptomatic ACO

The rate at which undetected ACO becomes symptomatic ACO is a highly significant parameter within the model. This data point determines how long patients in the non-surveillance arm with ACO remain in a diagnosed Barrett's oesophagus state before moving to the **symptomatic** ACO state, which is associated with a much lower utility level (QoL) owing either to surgery or to an untreatable ACO state. In the surveillance arm, in contrast, patients will generally move from ACO states to the **diagnosed** ACO state sooner as a result of surveillance. Hence the model output is extremely sensitive to the value of this parameter. This is illustrated in *Figure 6*, which plots ICER levels for different values of this progression rate. The value used in the base case model is 14.3% annual progression from ACO to symptomatic ACO. If this is increased to 19% per year, surveillance is no longer dominated. If the rate were 23% per year, the ICER is reduced to levels which may be considered cost-effective (*Figure 6*).

Utility value for Barrett's oesophagus states

Within the model, all Barrett's oesophagus states, with or without dysplasia, are assigned equivalent utility (QoL) levels since it is assumed that the patient experience is broadly comparable between these states. It is uncertain whether the anxiety provoked by entering a surveillance programme would be more or less than the anxiety of not entering a surveillance programme, despite a Barrett's oesophagus diagnosis. The generic level of the utility for these states, however, impacts on the ICER since, in general, patients will spend more time in these states in the non-surveillance arm compared with the surveillance arm (where detection of ACO occurs more quickly), moving patients into ACO states and associated utilities. Hence higher utility levels for Barrett's oesophagus states will be associated with dominance by the non-surveillance arm, or high ICER values. *Figure 7* shows the relationship between this utility value and the output ICER. The base case value is 0.8125. Any increase in this value and non-surveillance continues to dominate. However, at 0.72, the ICER becomes positive. If the utility value for the health state of Barrett's oesophagus falls as low as 0.63, the ICER drops below usual levels of willingness to pay. The more detrimental to QoL that symptoms experienced by those with Barrett's oesophagus are, the more possible it becomes that surveillance could be cost-effective.

Endoscopy costs

The cost of endoscopy is the major additional component of the cost of surveillance regimens compared with no surveillance. However, as shown in *Figure 8*, the cost of endoscopy is not important in assessing the cost-effectiveness of surveillance; even it were cost free, surveillance continues to be dominated. Note that as for other analyses in this section, this is assuming that all the other values in the model remain the same as the base case. It is possible that cost would be relevant if the base case ICER were closer to zero than is currently the case.

Utility value for the well after surgery state

Since many more patients are surgically treated for ACO in the surveillance arm of the model than in the non-surveillance arm, the utility level for the 'well after surgery' state may impact on the eventual cost–utility of surveillance. Higher levels of utility for the health state 'well after surgery' will therefore be associated with

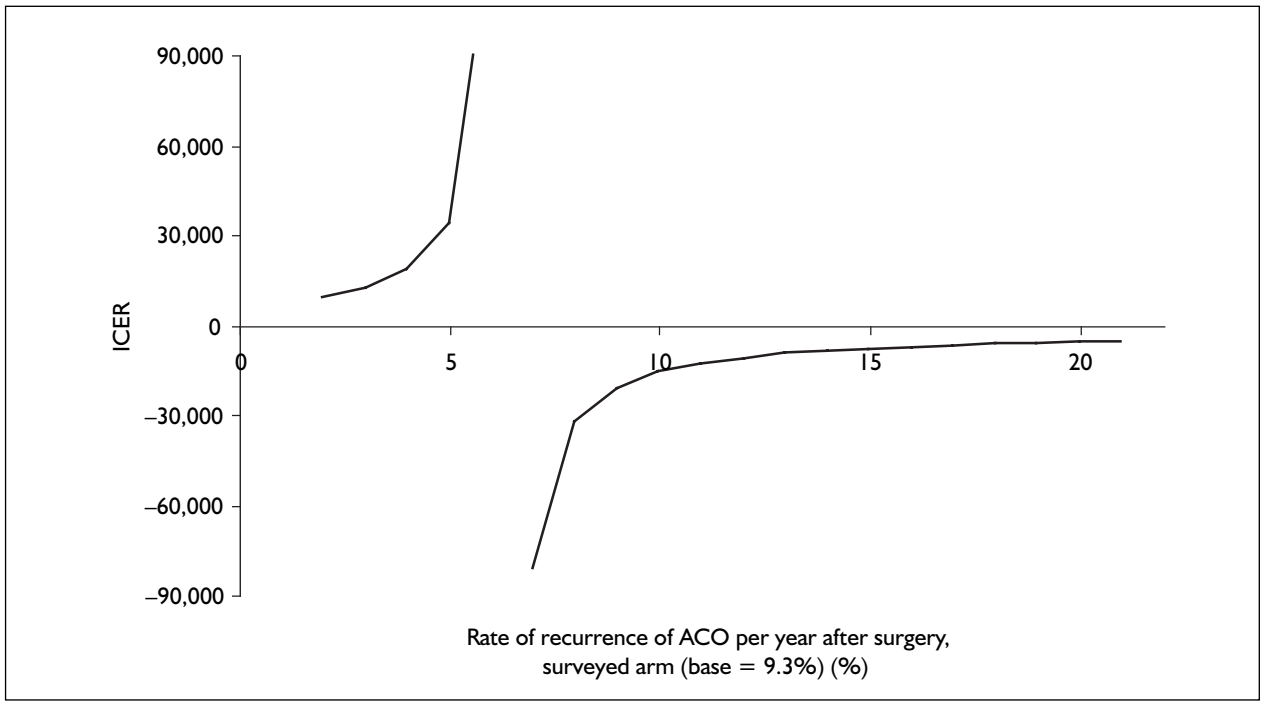

FIGURE 4 *Effect of altering ACO recurrence post-oesophagectomy in the surveillance arm: ICER (surveillance versus non-surveillance)*

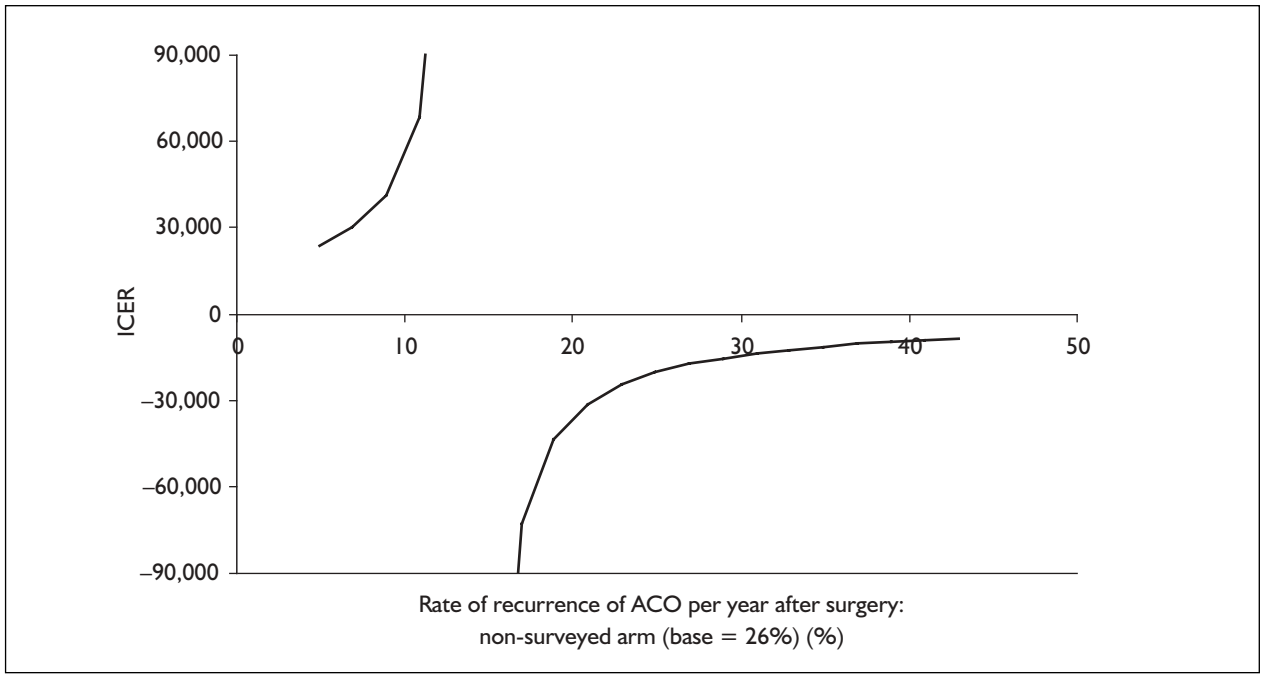

FIGURE 5 *Effect of altering ACO recurrence post-oesophagectomy in the non-surveillance arm: ICER (surveillance versus non-surveillance)*

lower ICER values (greater cost-effectiveness). *Figure 9* shows the relationship between this utility value and the resultant model ICER. The base case value is 0.863; if this is any lower, non-surveillance continues to dominate and the same is true for higher values, even full health (utility = 1.0).

Progression rates between Barrett's oesophagus states with and without dysplasia

The rate at which Barrett's oesophagus progresses through dysplastic states to ACO affects the rate at which surveillance is able to detect ACO and hence the efficacy of surveillance in identifying treatable ACO. Data used in *Figure 10* increase the value of

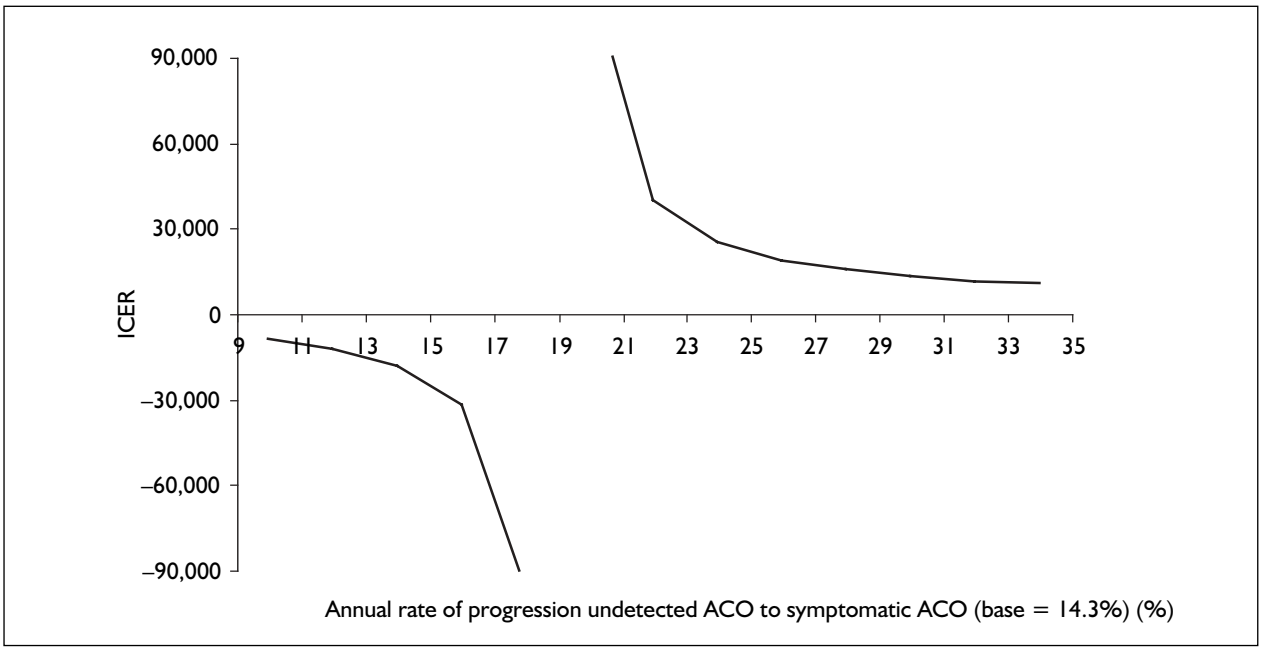

FIGURE 6 *Effect of altering time taken for ACO to become symptomatic on ICER values: ICER (surveillance versus non-surveillance)*

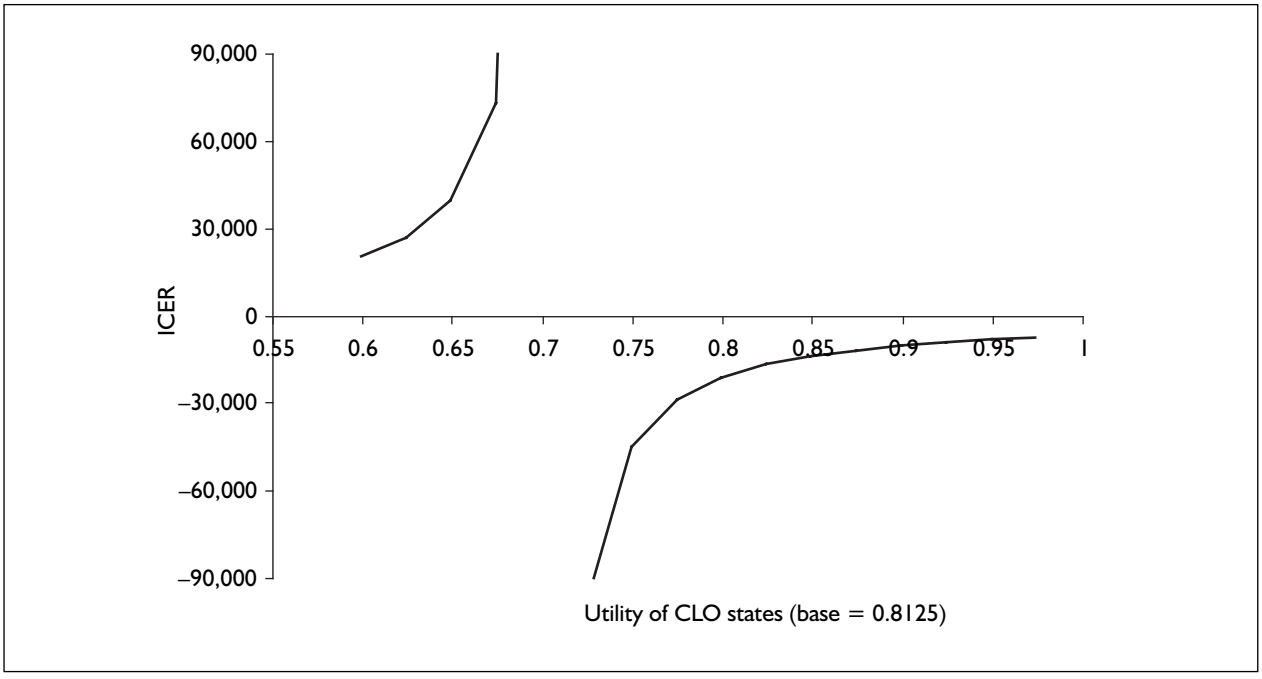

FIGURE 7 *Effect of altering utility value for Barrett's oesophagus on ICER values: ICER (surveillance versus non-surveillance)*

each of the progression rates (non-dysplastic Barrett's oesophagus to LGD, LGD to HGD and HGD to ACO) by the same amount and plot the effect of this combined increase on the ICER. Even if these values are doubled or halved, surveillance continues to confer less benefit and cost more.

Percentage of treatable symptomatic cases of ACO

In the non-surveillance arm of the model, ACO patients are detected only when the cancer becomes symptomatic, whereas in the surveillance arm almost all ACO patients are detected through surveillance. The ratio of treatable to untreatable ACO in the symptomatic ACO state may be important in determining the ICER of the model. This is because untreatable patients experience a much lower utility and are likely to die early. However, *Figure 11* shows that the percentage of symptomatic patients treatable does not dramatically affect the model ICER and

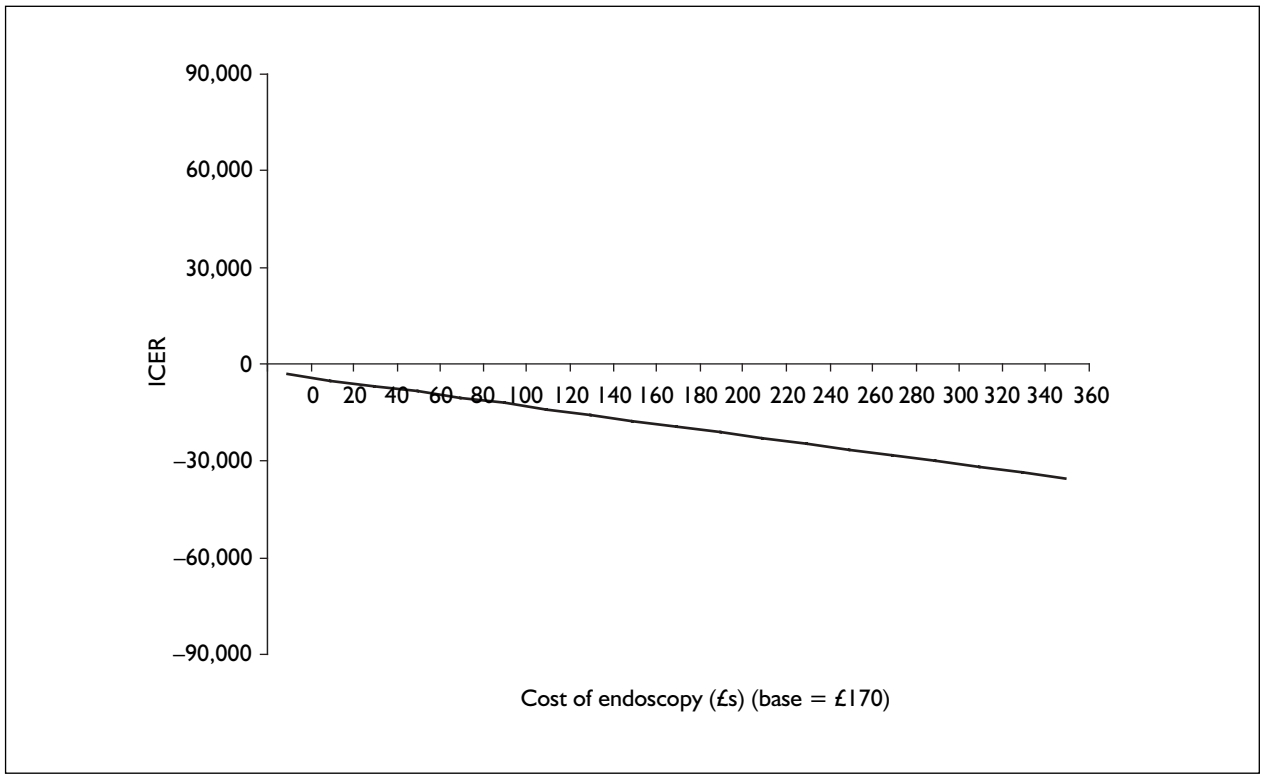

FIGURE 8 *Effect of altering the cost of endoscopy on ICER values: ICER (surveillance versus non-surveillance)*

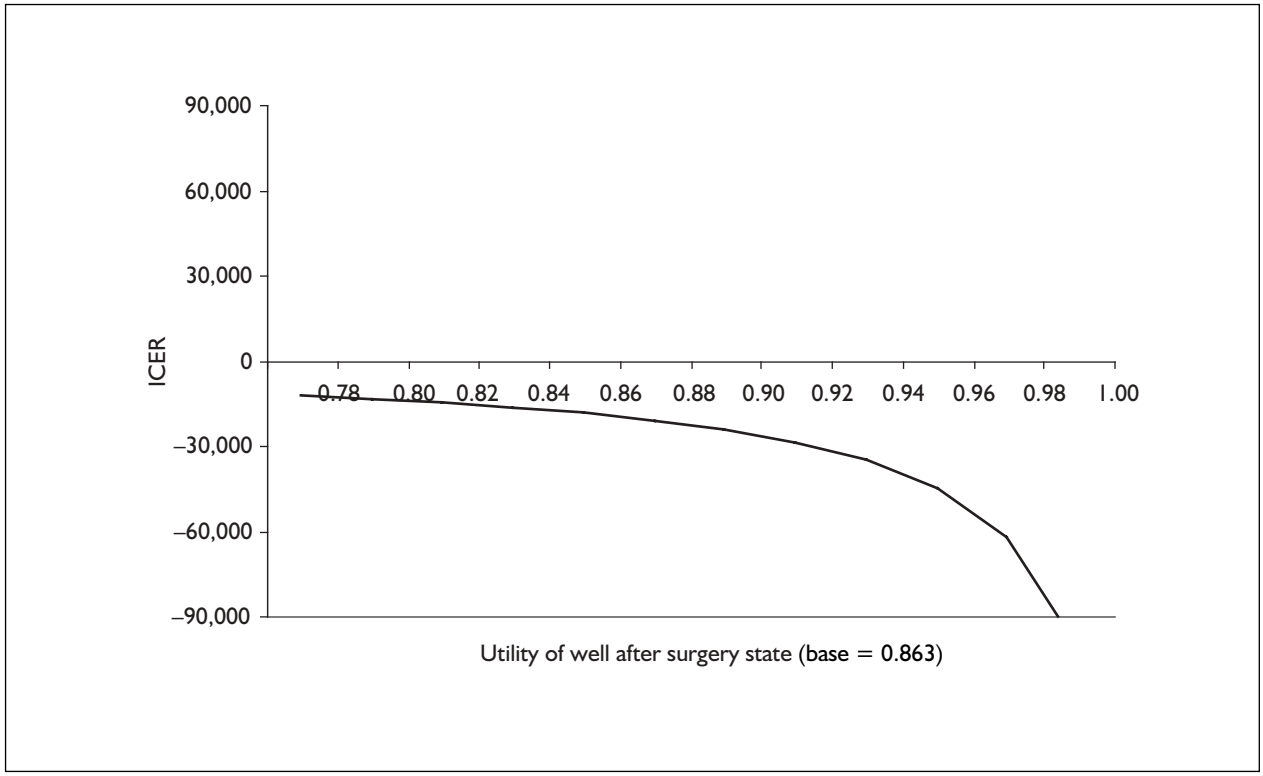

FIGURE 9 *Effect of altering the utility value for the health states 'well after surgery': ICER (surveillance versus non-surveillance)*

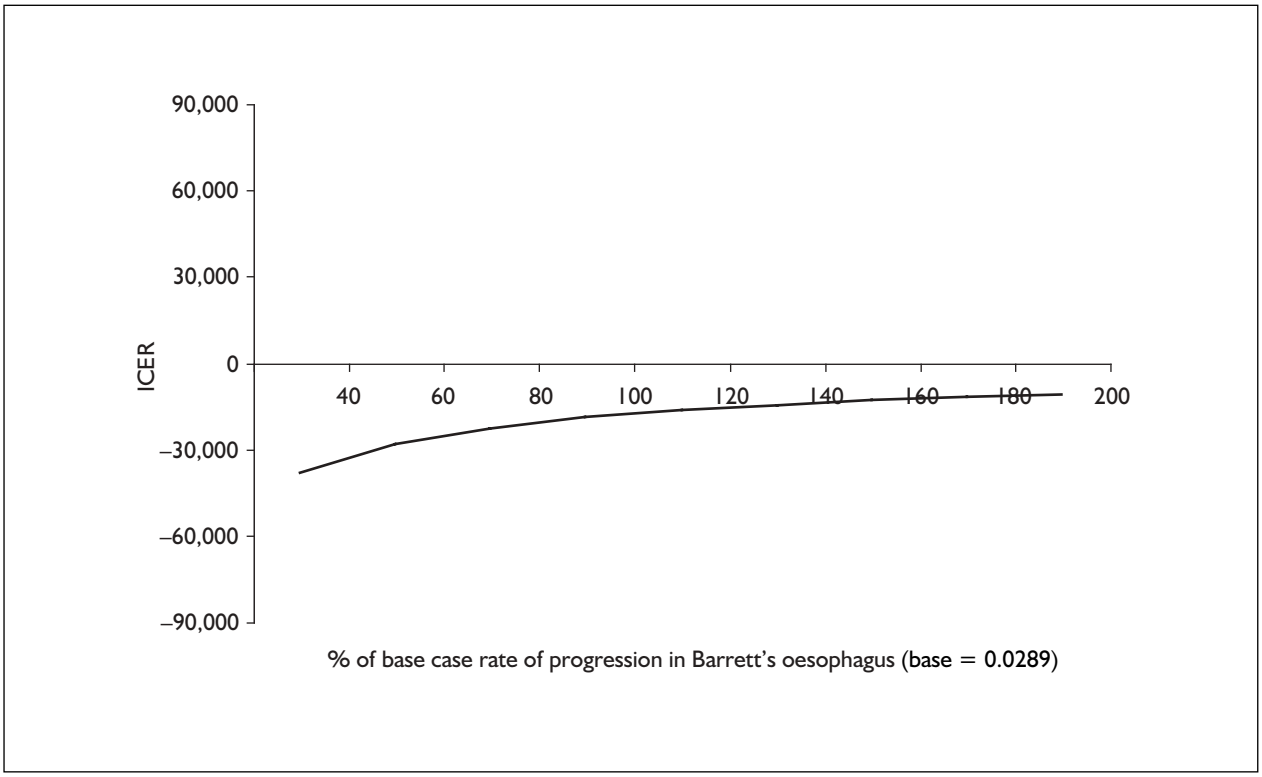

FIGURE 10 *Effect of altering the progression rates between Barrett's oesophagus, LGD, HGD and ACO on ICER: ICER (surveillance versus non-surveillance)*

surveillance confers less benefit and costs more at all points.

Percentage of treatable cases of ACO diagnosed through surveillance

For similar reasons to those outlined above, the model may be sensitive to the ratio of treatable to untreatable ACO in patients whose ACO has been detected through surveillance. *Figure 12* shows the relationship between this ratio and the output ICER. Non-surveillance confers more benefit and costs less in all shown cases.

Effect of varying surveillance intervals

We also ran the model with the baseline variables with three different surveillance patterns:

1. non-dysplastic Barrett's oesophagus surveyed every 5 years, LGD every year and HGD every 6 months
2. non-dysplastic Barrett's oesophagus surveyed every 3 years, LGD every 6 months and HGD every 3 months
3. non-dysplastic Barrett's oesophagus surveyed every 5 years, LGD every 6 months and HGD every 3 months.

Surveillance continued to confer less benefit and cost more than non-surveillance in all these scenarios.

Effect of varying treatment threshold

We also ran the model with patients in the surveillance arm receiving treatment by oesophagectomy when they were diagnosed with HGD. This slightly altered the structure of the model and one data point was also changed with the rate of ACO recurrence after surgery falling to 4.4% (from base case 9.3%). Despite this, non-surveillance continues to dominate. The new values show that this option both costs more and confers fewer QALYs than the base case of surgery for ACO only. This is because more people are operated on and so more patients spend time in states with low utility values due to surgery.

Probabilistic analyses

Outputs from a Monte Carlo simulation are shown graphically in *Figure 13*. For the modelled cohort, these illustrate the ICER values of 1000 simulated trials. A CEAC was also calculated (*Figure 14*) showing, at different levels of willingness to pay for an additional QALY, the probability that surveillance or non-surveillance is the most cost-effective option.

The simulation (*Figure 13*) shows that, in most cases, surveillance confers less benefit and costs more than non-surveillance (shown by all points to

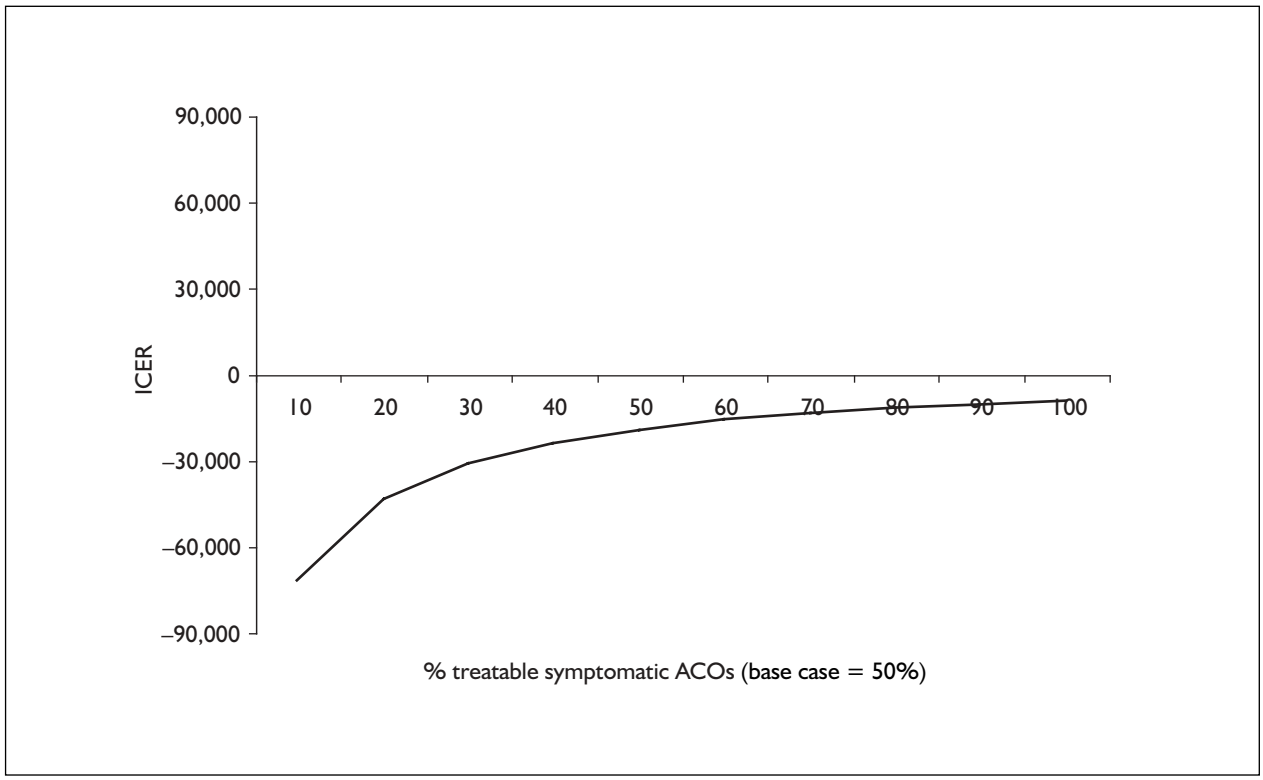

FIGURE 11 *Effect of altering the percentage treatable symptomatic ACOs on ICER: ICER (surveillance versus non-surveillance)*

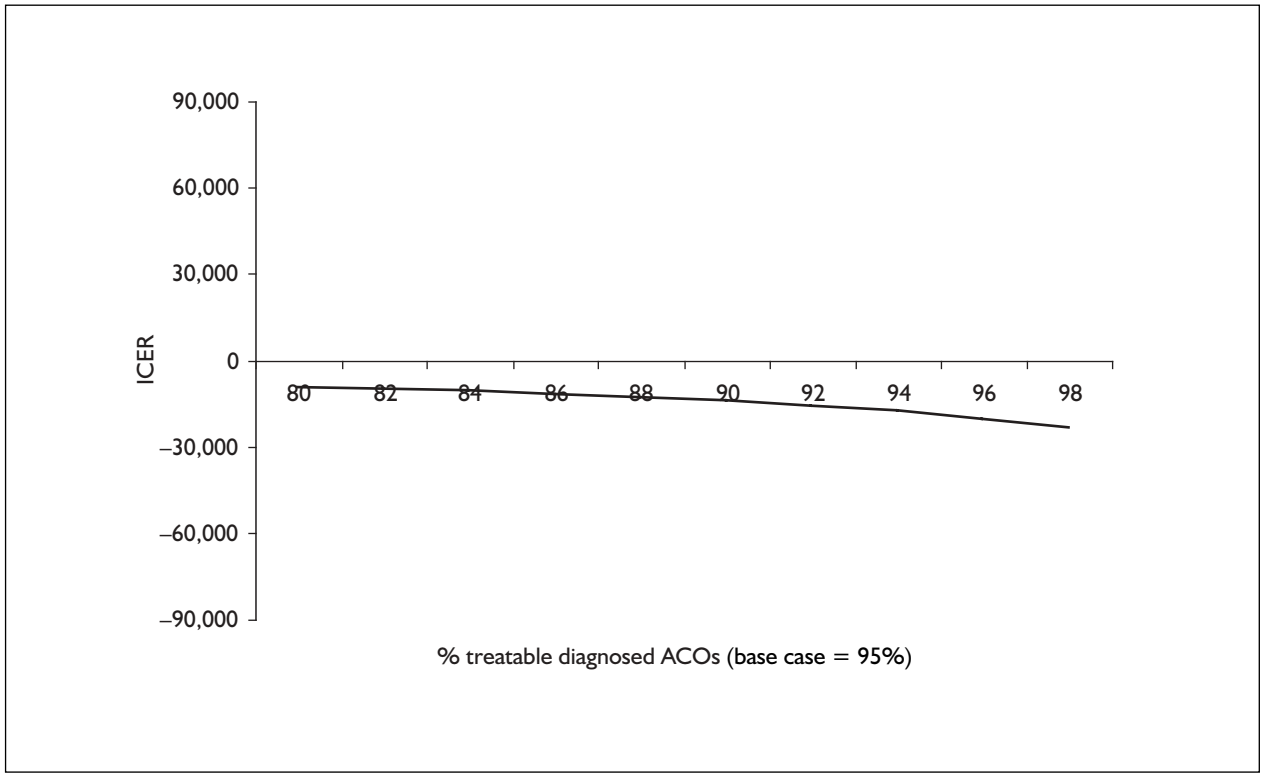

FIGURE 12 *Effect of altering the percentage of treatable to untreatable ACOs detected through surveillance: ICER (surveillance versus non-surveillance)*

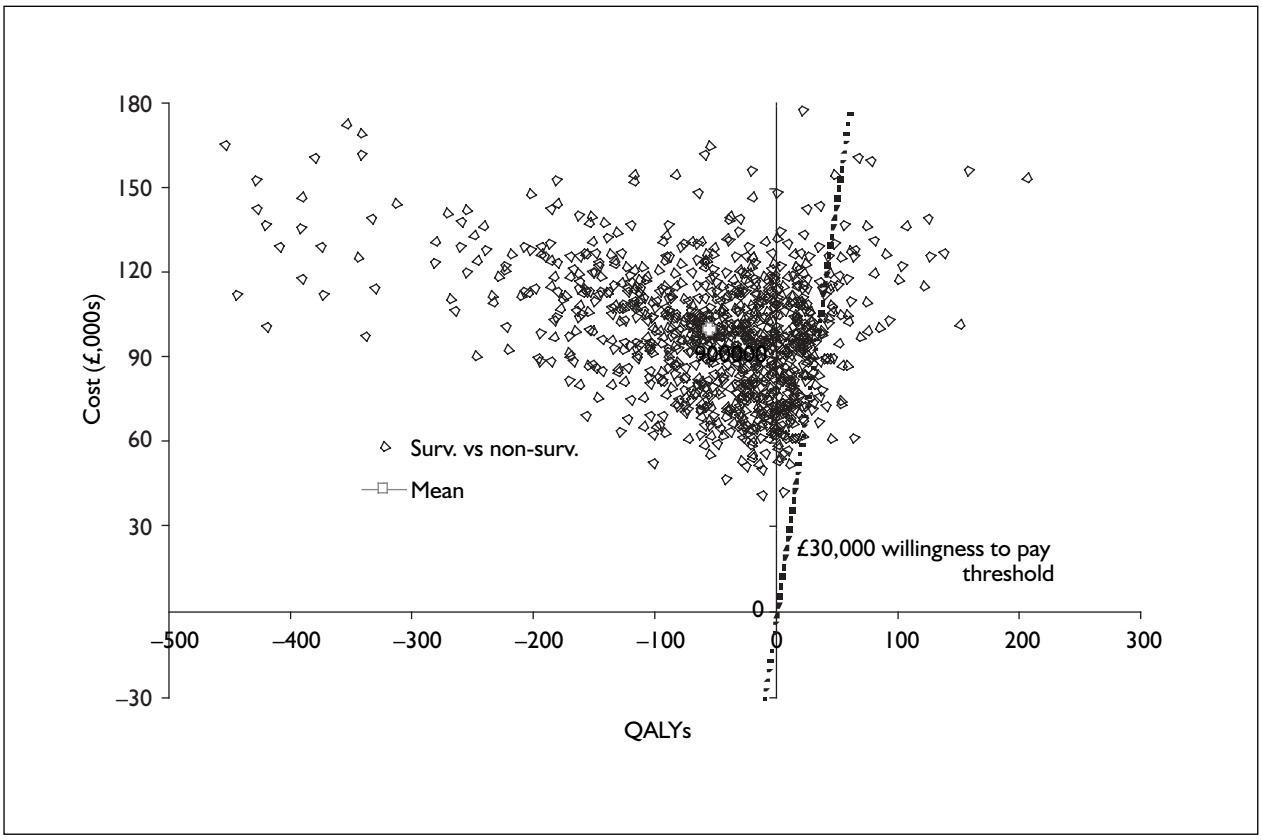

FIGURE 13 *Simulation output (1000 trials) for cost-effectiveness for surveillance of Barrett's oesophagus: ICER (surveillance versus non-surveillance)*

the left of the *y*-axis). In all cases, surveillance is more costly, and very few cases show it to be cost-effective at usual levels of willingness to pay (shown to the right of the dotted willingness to pay threshold).

The CEAC (*Figure 14*) shows that, at 20 years from an average age at entry of 55 years, and given the point estimates for parameters and associated distributions for the Monte Carlo simulation, surveillance is unlikely to be considered cost-effective at usual levels of willingness to pay. There is an 11% probability of surveillance being the most cost-effective option assuming a willingness to pay of £30,000 per additional QALY. Under this set of assumptions, surveillance is unlikely to be cost-effective, even at much higher levels of willingness to pay (up to £50,000 per QALY shown on the graph).

Analysis of trials from Monte Carlo simulation

Analysis of the simulation output in *Figure 13* shows that in one-quarter of the trials the model returned a positive ICER (shown as points to the right of the *y*-axis), whereas in the other 75% of trials non-surveillance dominates surveillance (costs less and accrues more benefit). In other words, surveillance does more harm than good, and costs more, in three-quarters of simulations. Of those 25% of trials which did produce a positive ICER output (suggesting it may be a cost-effective intervention), less than half (11.2% of the total) gave an ICER below a threshold of £30,000.

Figure 15 quantifies the distribution of simulation outputs shown in *Figure 13* across a range of ICER categories from having a low ICER (being cost-effective) to being dominated. Around one in nine simulations return a value for cost-effectiveness which would be considered acceptable value for money.

In order to investigate further the plausibility of combinations of inputs which could result in an ICER which would be considered cost-effective, we selected three simulation outputs for closer examination. These illustrate combinations of parameter values that resulted in the model showing surveillance as very cost-effective at normal levels of willingness to pay, as cost-effective

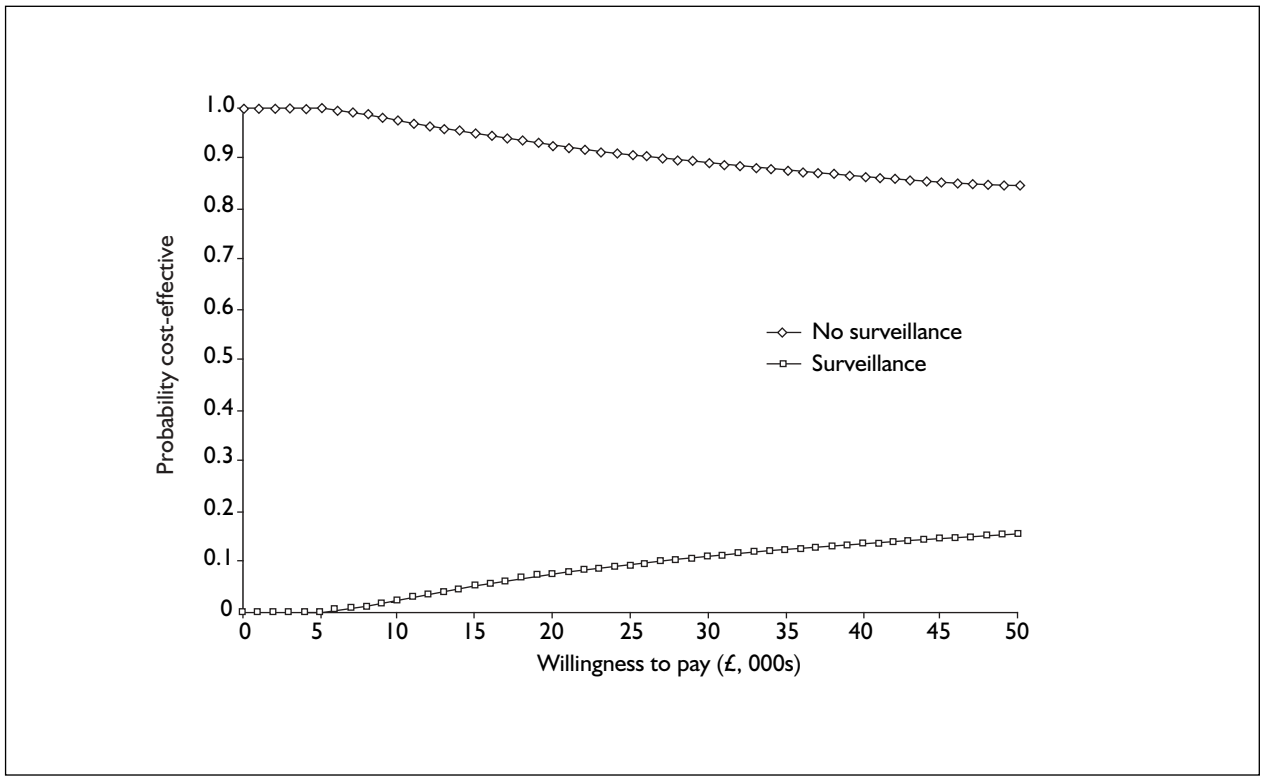

FIGURE 14 *Simulation output (1000 trials) showing the probability that surveillance of Barrett's oesophagus is cost-effective at various levels of willingness to pay (CEAC)*

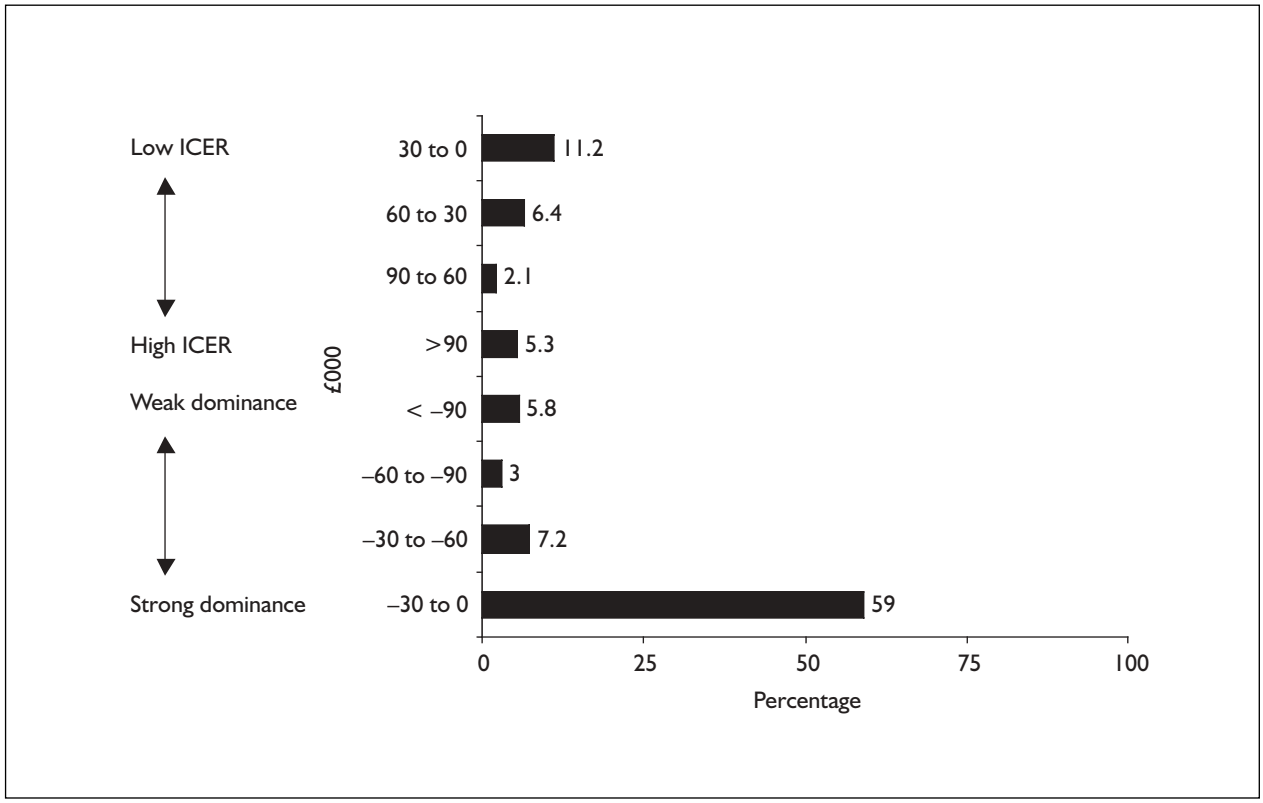

FIGURE 15 *Distribution of ICERs from Monte Carlo simulation*

TABLE 27 *Scenarios in which surveillance is cost-effective, not cost-effective and dominated*

Scenario	Baseline (dominated)	Highly cost-effective	Cost-effective	Strongly dominated
ICER (£/QALY)	–19,318	3,987	30,108	–2,315
Utility of regressed state	0.800	0.837	0.805	0.801
Utility of Barrett's oesophagus states	0.813	0.865	0.864	0.824
Utility of diagnosed ACO	0.875	0.781	0.815	0.773
Utility of symptomatic ACO	0.675	0.659	0.710	0.670
Utility of untreatable ACO	0.440	0.369	0.333	0.496
Utility of surgical state	0.55	0.631	0.546	0.477
Utility of surgical complications	0.5	0.398	0.567	0.512
Utility of the well after surgery state	0.863	0.885	0.918	0.796
Cost of endoscopy	170	170	156	161
Cost of Barrett's oesophagus states	22	18	20	30
Cost of surgery	5942	4858	5467	5292
Cost of complications	1352	1845	1165	1291
One-off cost of palliative care	3578	2818	2629	3202
Proportion of initial endoscopies showing LGD	0.121	0.162	0.129	0.148
Proportion of initial endoscopies showing HGD	0.045	0.382	0.073	0.090
Incidence of Barrett's oesophagus from normal state	0.008	0.101	0.102	0.100
Incidence of LGD from normal state	0.001	0.010	0.010	0.010
Incidence of HGD from normal state	0.001	0.007	0.007	0.007
Progression rate Barrett's oesophagus to LGD	0.029	0.028	0.024	0.030
Progression rate LGD to HGD	0.345	0.032	0.038	0.017
Progression rate HGD to ACD	0.119	0.179	0.147	0.161
Progression rate non-symptomatic ACO to symptomatic ACO	0.143	0.223	0.183	0.047
Regression from Barrett's oesophagus to normal state	0.024	0.009	0.007	0.030
Regression from LGD to Barrett's oesophagus	0.129	0.117	0.015	0.000
Regression from HGD to LGD	0.048	0.037	0.051	0.053
Proportional rate of deaths year from untreatable ACO	0.780	0.829	0.735	0.753
Percentage treatability for symptomatic ACO non-surveillance arm	0.500	0.412	0.498	0.616
Percentage treatability for diagnosed ACO surveillance arm	0.950	0.918	0.941	0.930
Proportion of complications from surgery	0.030	0.269	0.240	0.341
Proportion of deaths from surgery	0.065	0.058	0.041	0.067
Proportional rate of recurrence of ACO post-surgery non-surveillance arm	0.260	0.247	0.144	0.143
Proportional rate of recurrence of ACO post-surgery surveillance arm	0.093	0.065	0.068	0.136

and as strongly dominated (costing more for fewer QALYs conferred). These, together with the base case inputs for comparison, are shown in *Table 27*.

The two extreme cases come from the highest and lowest ICER outputs from the simulation. However, although these combinations of values are the least likely to appear in the simulation, the values for individual parameters are not, in our view, implausible and are, in most cases, very close to the central values used in the base case analysis. This reflects the relatively narrow distributions used in the probabilistic analysis.

The choice of distributions has a potentially important effect on the model outputs and in several cases we used a uniform distribution as there was no evidence that one value was more likely than others in a plausible range. This has increased the uncertainty in the model.

Expected value of perfect information analyses

Total expected value of perfect information

EVPI analysis is derived from the Bayesian approach to modelling. Levels of uncertainty are incorporated into the Monte Carlo simulation by sampling key parameters from prior statistical distributions. The resultant distributed range of cost–utility outputs for the two arms in the simulation is a function of the levels of uncertainty in the input parameters. EVPI analysis assigns a value to the reduction in output variance that results when key input parameters can be determined with precision. This value will depend on both the willingness to pay threshold adopted by the decision-makers and the extent to which

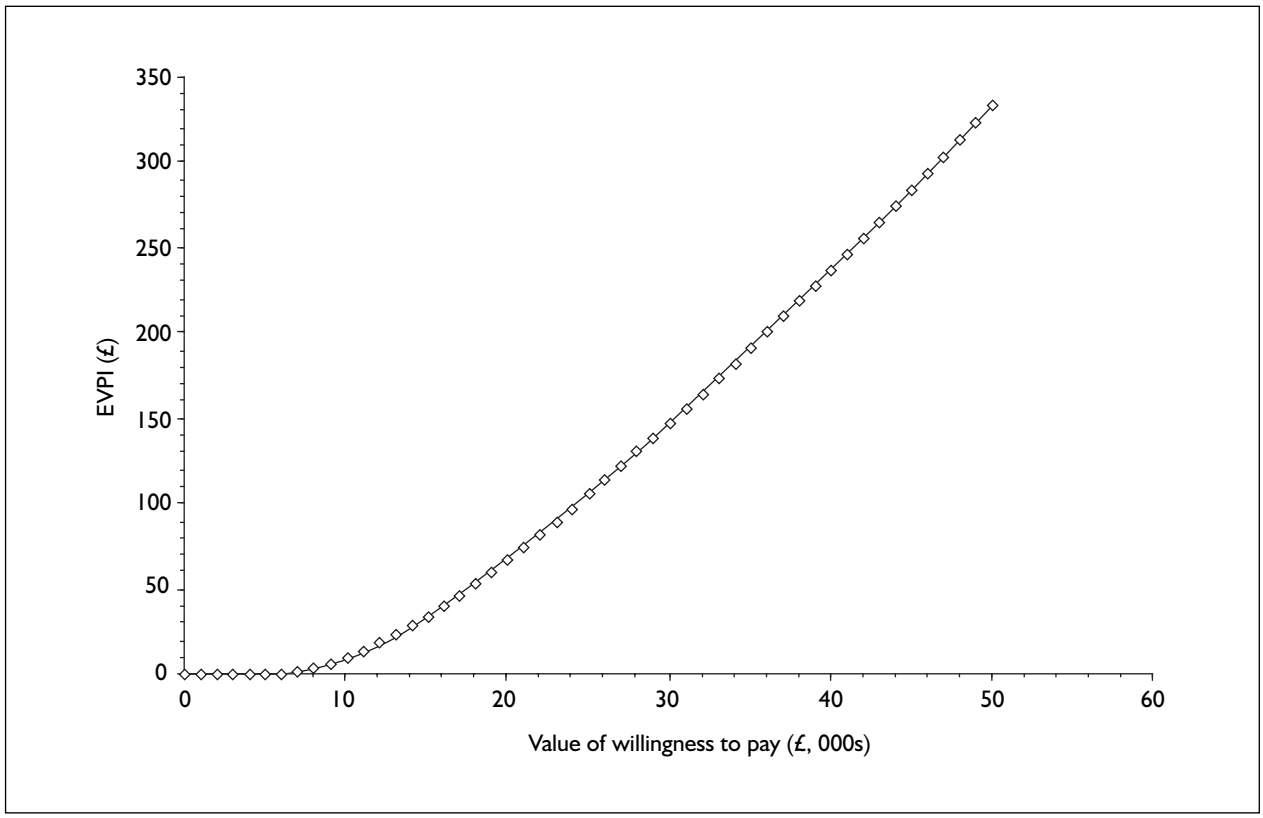

FIGURE 16 *Total expected value of perfect information at the patient level*

'perfect information' about a particular input parameter (or set of parameters) reduces the variance in the model outputs.

By using probabilistic simulation in the Markov model, it is possible to calculate the total value of information estimate for differing levels of willingness to pay.[83,84] These are shown in *Figure 16* at the patient level.

Patient level

Figure 16 depicts, for each willingness to pay threshold, the maximum value that could be gained by acquiring perfect information about all the input parameters per patient intervention. In our model, the intervention consists of the implementation of the Barrett's oesophagus surveillance programme. At a willingness to pay threshold of £30,000, for instance, the model predicts that the upper limit of value that could be obtained from acquiring perfect information on all input parameters would be around £148 per patient based on the levels of uncertainty recorded for the initial model parameters.

Population level

The initial assessments of value of information from the model have been calculated at the patient level. To calculate the overall value of information for the total population of patients likely to be affected by a decision to implement surveillance of Barrett's oesophagus, it is necessary to multiply this value by the total number of patients who would be affected annually, as defined in the bullet-pointed list below, over the estimated lifetime of the technology. The population EVPI is therefore derived by multiplying the patient-level EVPI by the number of patients affected per year and the number of years over which the technology is likely to apply (applying the appropriate cost discount rate to future years). The equation for this calculation is

$$\text{total EVPI} = \text{patient-level EVPI} \sum_{n=1}^{N} \frac{(\text{no. of incidents})_n}{(1+\text{discount rate})^n}$$

where n = year and N = total number of years over which the information would be useful.

In calculating the total value of information, the following assumptions were used:

- 12.5 per 1000 of the population present annually for upper GI endoscopy.[85]

TABLE 28 *Total EVPI*[a]

	Patient-level EVPI (£)	Population-level EVPI (£)
EVPI of base case model	147.58	6,553,619

[a] All values calculated at a willingness to pay threshold of £30,000 per QALY.

- Of the above numbers presenting, 1.75% will be diagnosed with Barrett's oesophagus.[86,87]
- Current census population estimate for England and Wales is 52,041,916.[47]
- This figure gives a newly diagnosed population with Barrett's oesophagus of 11,384 annually.
- Of these, we have assumed that 50% will be eligible for surveillance (5692).
- It is assumed that the technology would apply for 10 years: assuming that current guidelines for surveillance would remain in effect for this period.
- An annual discount rate of 6% is applied.

Using the above figures, the results of the value of information analysis suggest a total EVPI at the patient level of around £148 per patient given a willingness to pay threshold of £30,000 per QALY. Making the assumptions outlined above, the total EVPI at the population level is calculated as £6,553,619. This places an upper limit on the potential benefit of extra research aimed at reducing the uncertainty in the model. Using a similar equation to calculate the total value of information for the partial EVPI analysis, the results obtained for the value of research aimed at reducing the levels of uncertainty for particular parameters within the model are presented in *Table 28*, which gives the value of information levels for each of the three types of data within the model (costs, utilities, transition probabilities) and for specific parameters identified as critical in the one-way sensitivity analysis.

The EVPI depends on the size of the population affected and the expected lifetime of the technology. We have assumed a 10-year horizon for the technology and have based our calculation on current activity levels for diagnostic endoscopy. It is possible that the technology will have a longer lifetime and that, with initiatives to promote definitive diagnosis of upper GI symptoms, a larger number of people might be considered for surveillance. More importantly, the value of information is dependent on the willingness to pay for an additional QALY, which we have taken, in this case, as £30,000. This figure may not reflect actual willingness to pay in this context, as there is currently no clear policy-making process for this technology in the UK which takes explicit account of cost-effectiveness.

Interpretation of the EVPI from the perspective of a commissioner of research depends on the cost of possible research approaches to reducing uncertainty and attitude to the role of research as a means of influencing practice. It may be that there are differences in the role of further research where a technology is extensively used, or where there is significant pressure from society for its adoption for reasons other than clinical or cost-effectiveness, compared with where the technology is new and little used in current practice. The value of information (£6.5 million) in this case may be considered relatively high if further research were to be confined to small observational studies or further research synthesis or relatively low if commissioners were to proceed with a large RCT running over many years.

The EVPI is lower than our estimate of the cost of endoscopies being carried out for surveillance. This may seem counterintuitive since a decision to stop surveillance would, it might be presumed, release these costs. However, two points should be noted. First, any savings to the NHS from stopping surveillance would be offset by an increase in the number of endoscopies carried out for the development of symptoms. Second, the EVPI is derived from the net benefit statistic, which combines the assumed willingness to pay for an additional QALY with estimates of cost-effectiveness to express benefit in financial units. It describes, given the assumptions modelled, the financial impact of net costs and net benefits (assuming, in this case, that a QALY is worth £30,000 to decision-makers).

Partial EVPI

Patient level

In addition to the calculation for the overall EVPI shown above, an analysis based on the maximum value per patient that could be obtained by acquiring perfect information about **specific** parameters of interest was carried out (commonly referred to as a partial expected value of perfect information or PEVPI).

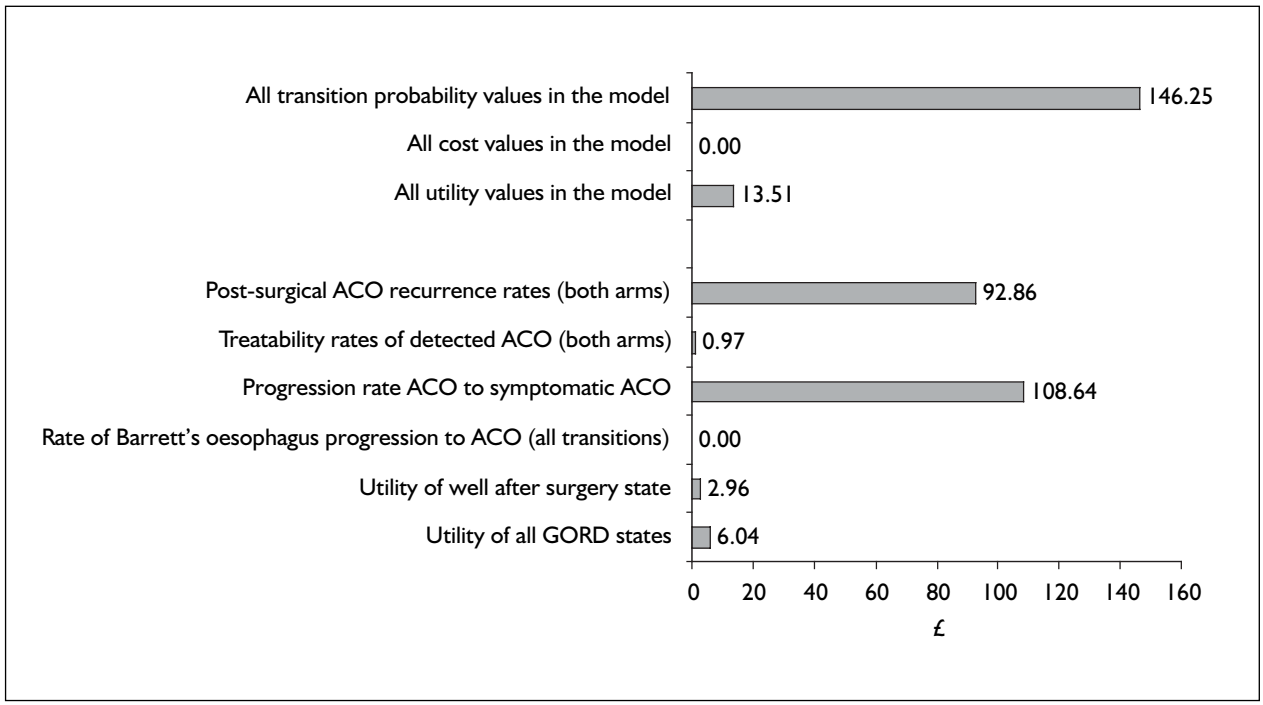

FIGURE 17 *PEVPI calculated at a willingness to pay threshold of £30,000 per QALY (patient level)*

The output from the PEVPI provides a probabilistic measure of model sensitivity to specific input parameters (or set of parameters) and the relative benefit of this reduction in uncertainty in terms of the value of this extra information in the decision context.[90] It therefore offers an alternative, arguably more multi-dimensional, perspective to the one-way sensitivity analysis presented earlier. It should be stressed, however, that the PEVPI results depend critically on the variance recorded for each input parameter (which is based in many cases on very limited evidence). These outputs should therefore be interpreted with some caution.

The results for the PEVPI are presented in *Figure 17* as a bar chart, representing the PEVPI values for a range of parameters (identified from the previous one-way sensitivity analysis) at the patient level.

The high levels of PEVPI for the progression rate from ACO to symptomatic ACO relative to other progression rates and the high PEVPI value for post-surgical ACO recurrence within the model confirm the importance of these variables as identified in the previous one-way sensitivity analysis.

Population level

As before, these calculations can also be applied to the population level using equation (p. 68) and applying the same assumptions as for the total EVPI (p. 69) (*Table 29*).

TABLE 29 *EVPI calculated at a willingness to pay threshold of £30,000 per QALY (population level)*

	Patient-level PEVPI (£)	Population-level PEVPI (£)
Type of data		
All transition probabilities with the model	146.25	6,494,558
All cost values within the model	0	0
All utility values within the model	13.51	599,942
Specific parameters		
Post-surgical recurrence rates (in both arms)	92.86	4,123,656
Treatability rates for detected ACO (in both arms)	0.97	43,075
Progression rate ACO to symptomatic ACO	108.64	4,824,402
Utility of well after surgery state	2.96	131,445
Utility of GORD states	6.04	268,220

The results from the value of information analysis as outlined above suggest that there is a high level of uncertainty within the model inputs and that considerable benefit could be derived from research which could reduce this uncertainty, even though the Monte Carlo simulation produces a large majority of outputs which suggest dominance of non-surveillance over surveillance. Costs are not important areas of uncertainty, and transitions have a much greater impact than utility data. The PEVPI highlights the same two critical parameters (recurrence of ACO after surgery and time taken for ACO to become symptomatic) as the one-way sensitivity analyses shown in the section 'One-way sensitivity analyses' (p. 57).

Summary of model uncertainty

We explored uncertainty using both one-way sensitivity analyses and probabilistic analyses. *Table 30* summarises and quantifies the importance of the various uncertainties. Within the model, variables that have both a high level of uncertainty about the correct value to use and which affect the model outputs highly are:

- levels of ACO recurrence after surgery for those diagnosed through surveillance versus patients presenting symptomatically
- time taken for ACO to become symptomatic
- utility value for the health state of Barrett's oesophagus.

Currently, levels of ACO recurrence are known after surgery, but the literature does not report on how the patients were initially identified as having ACO – through surveillance, at first endoscopy, or with a known diagnosis of Barrett's oesophagus but without being under surveillance. Given the structure of the model, this is crucial information.

It is clearly difficult to estimate the time taken for ACO to become symptomatic, as many cancers are only diagnosed because the patient presents with symptoms. Expert opinion was divided, with some feeling that our estimate of a mean of 4–5 years was too long, whereas others felt that it was about right and that some cancers may take much longer to manifest symptomatically. It is also possible that there may be distinct groups of cancers, with some aggressive cancers developing rapidly whereas others take longer.

The health state of Barrett's oesophagus may combine a number of factors: symptoms of GORD or other complaints, uncertainty about risk of cancer, the impact of either undergoing regular endoscopic surveillance or, conversely, if not in a surveillance programme, no regular endoscopic investigation. Within the time constraints of the project, we obtained the views of a small non-representative sample of the public, and assumed that the surveillance and non-surveillance arms have similar disutility associated with the rigours of surveillance and the uncertainty without surveillance. This assumption has not been validated and the results are taken from a limited number of people using the standard gamble technique.

In addition, the percentage of treatable cancers among those diagnosed through surveillance and through symptoms, and the ratio between these, were also important. Again, there are few published data providing information in this form and expert opinion was divided. The base case gave treatable percentages as 50% in the symptomatic group and 95% in those detected by surveillance. Some thought that these were reasonable assumptions, whereas others thought that either the surveillance or the symptomatic figure was too high.

A summary of previous cost-effectiveness findings is given in *Box 3* and a summary of PenTAG's cost-effectiveness model findings in *Box 4*.

- Three previous cost–utility studies of surveillance for Barrett's oesophagus were identified. All were from the USA.
- Incomplete reporting means that it is not clear for all parameters what data were used, how they were derived and how the models function.
- All report a rapidly increasing ICER above usual levels of willingness to pay with increasing intensity of surveillance. The most recent study finds that even with surveillance intervals of 5 years, surveillance of non-dysplastic Barrett's oesophagus is not cost-effective.
- Owing to limitations and uncertainties in existing economic models, a new model of surveillance in the UK was developed.

BOX 3 *Summary of previous cost-effectiveness model findings*

TABLE 30 *Rating of model uncertainties*

Issue	Source of variable	Level of uncertainty in data	Impact of uncertainty on model	Overall rating of importance
Levels of ACO recurrence after surgery for those diagnosed through surveillance vs those presenting symptomatically	Poor published evidence plus expert opinion	High	Very high	Very important
Time ACO takes to become symptomatic	Poor published evidence plus expert opinion	High	Very high	Very important
Health state utility – Barrett's oesophagus	Value of Health Panel	Moderate	Very high	Very important
% of ACO diagnosed through surveillance that are treatable	Poor published evidence plus expert opinion	Moderate	High	Important
% of ACO diagnosed due to symptoms that are treatable	Poor published evidence plus expert opinion	Moderate	High	Important
Utility value – well after surgery	Value of Health Panel	Moderate	High	Important
Progression rate LGD to HGD	Poor published evidence plus expert opinion	High	Moderate	Moderately important
Progression rate HGD to ACO	Poor published evidence plus expert opinion	High	Moderate	Moderately important
Discount rate for costs and utilities	Treasury advice	Moderate	Low	Not important
Regression of Barrett's oesophagus	Poor published evidence plus expert opinion	High	Very low	Not important
Regression rate LGD to Barrett's oesophagus	Poor published evidence plus expert opinion	High	Very low	Not important
Regression rate HGD to LGD	Poor published evidence plus expert opinion	High	Very low	Not important
Progression of Barrett's oesophagus to LGD	Poor published evidence plus expert opinion	High	Very low	Not important
Utility value untreatable ACO	Value of Health Panel	Moderate	Low	Not important
Cost palliative care	National schedule of costs	Low	Very low	Not important
Cost endoscopy	National schedule of costs	Low	Very low	Not important
Cost PPIs	Fixed – BNF	Low	Very low	Not important
Model time horizon	Author assumption	High	Very low	Not important

- Most key variables in the model are subject to considerable uncertainty.
- In addition, model outputs are found to be highly sensitive to a number of key parameters.
- The base case suggests that surveillance confers less benefit and costs more than non-surveillance, i.e. surveillance is dominated by non-surveillance. However, this is based on very uncertain data and is subject to change based on small changes in some key inputs.
- Surveillance confers fewer QALYs for a combination of reasons: cancers are diagnosed earlier; a small number will be untreatable and are associated with a low utility value; those who are treated will have a short, low utility value state due to surgery; after oesophagectomy successful recovery results in a high utility value state; recurrence is relatively high, and patients then move into a terminal health state with associated low utility. In the meantime, those in the non-surveillance arm have undiagnosed and non-symptomatic cancer for a much longer time, and the utility associated with this state is the same as for Barrett's oesophagus. Only when the cancer becomes symptomatic do they pick up the associated lower utility values.
- One-way sensitivity analyses showed high uncertainty in the following inputs, in some cases having the potential to prevent domination by non-surveillance, or bring values to levels that may be considered cost-effective:
  - rates of recurrence of ACO after oesophagectomy in the two arms
  - time taken for ACO to become symptomatic
  - utility value for 'Barrett's oesophagus' health state
  - utility value for 'well after oesophagectomy' health state.
- Probabilistic analyses suggested that surveillance is unlikely to be cost-effective even at high levels of willingness to pay given base case estimates.
- EVPI showed a high value at the population level when making the decision about whether or not to enter patients with Barrett's oesophagus into the surveillance programmes.

BOX 4 *Summary of PenTAG's cost-effectiveness model findings*

Chapter 7

Discussion and conclusions

Strengths and limitations of the report

The purpose of this study was both to assess the effectiveness, safety, affordability, cost-effectiveness and organisational impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus and to identify the important areas of uncertainty. The questions were addressed through a rapid systematic review of the literature, an expert workshop and the construction of a cost–utility model.

The assessment has several strengths. The systematic review brings together current evidence on the effectiveness of surveillance of Barrett's oesophagus. The workshop held to identify current issues for research was well attended and included many of the UK's opinion leaders in this field. The model takes a more sophisticated approach than previous studies and is the first to evaluate surveillance in the UK's NHS. It is also the first to include a value of information analysis.

There are, however, some limitations in the assessment which should be considered in interpreting the findings.

The systematic review

The systematic review was necessarily rapid, given the time constraints of the study. It is therefore not exhaustive and has been confined to identifying and reviewing previous studies of surveillance programmes. *Figure 18* shows the whole patient pathway relating to screening due to suspect symptoms, endoscopic investigation, treatment and possible progression to ACO. Surveillance, our focus, forms just one part of this overall picture. Even within this restricted focus, unknowns around areas such as epidemiology, natural history and the impact of treatment remain. Ideally, separate reviews should also be performed around each element of a surveillance programme, particularly as no RCTs of surveillance were identified. However, it seems unlikely that this would have added to the findings of the review. Extensive consultation with experts in the field both formally, through the workshop, and informally, through the expert advisory group, has shown that there is uncertainty throughout many of these areas and exhaustive systematic reviews would not have reduced the uncertainty.

The systematic review does not provide enough information to assess the effectiveness of surveillance of Barrett's oesophagus. Owing to prior expectation that no RCT data were available, time limitations and the unusual focus of this report on identifying uncertainty rather than quantifying the known, we chose to exclude case series containing <300 participants from the systematic review. This strategy was also used to try to restrict the review to better quality studies, for which we used size as a proxy indicator. This may be considered a weakness of the review. Other criteria, such as length of follow-up or definition of Barrett's oesophagus, would also be relevant and should ideally also be used. We found that the reporting was generally poor even in these larger case series and we have clearly not included the whole evidence base. However, we do not believe that relaxing the inclusion criteria would have provided different, or better, information and would have been unlikely to have changed the conclusions of the review. The major limitation is the lack of RCT or well-designed comparative evidence.

Case series are subject to considerable bias. In addition, there are crucial gaps in the reporting of the included studies that hamper the drawing of conclusions about the effectiveness of surveillance. Most important is the poor reporting of deaths from ACO and other causes among all participants. In addition, it is not possible in most studies to tell whether identified ACOs are the result of scheduled surveillance endoscopies or additional investigations resulting from symptoms. Other gaps in reporting include a lack of detail about the study populations and the progression of the disease through dysplasia and ACO.

The expert workshop

The workshop, held early in the study's time span, proved useful in bringing together a range of experts. The output confirmed the findings of the systematic review in identifying a wide range of questions, covering most elements of a

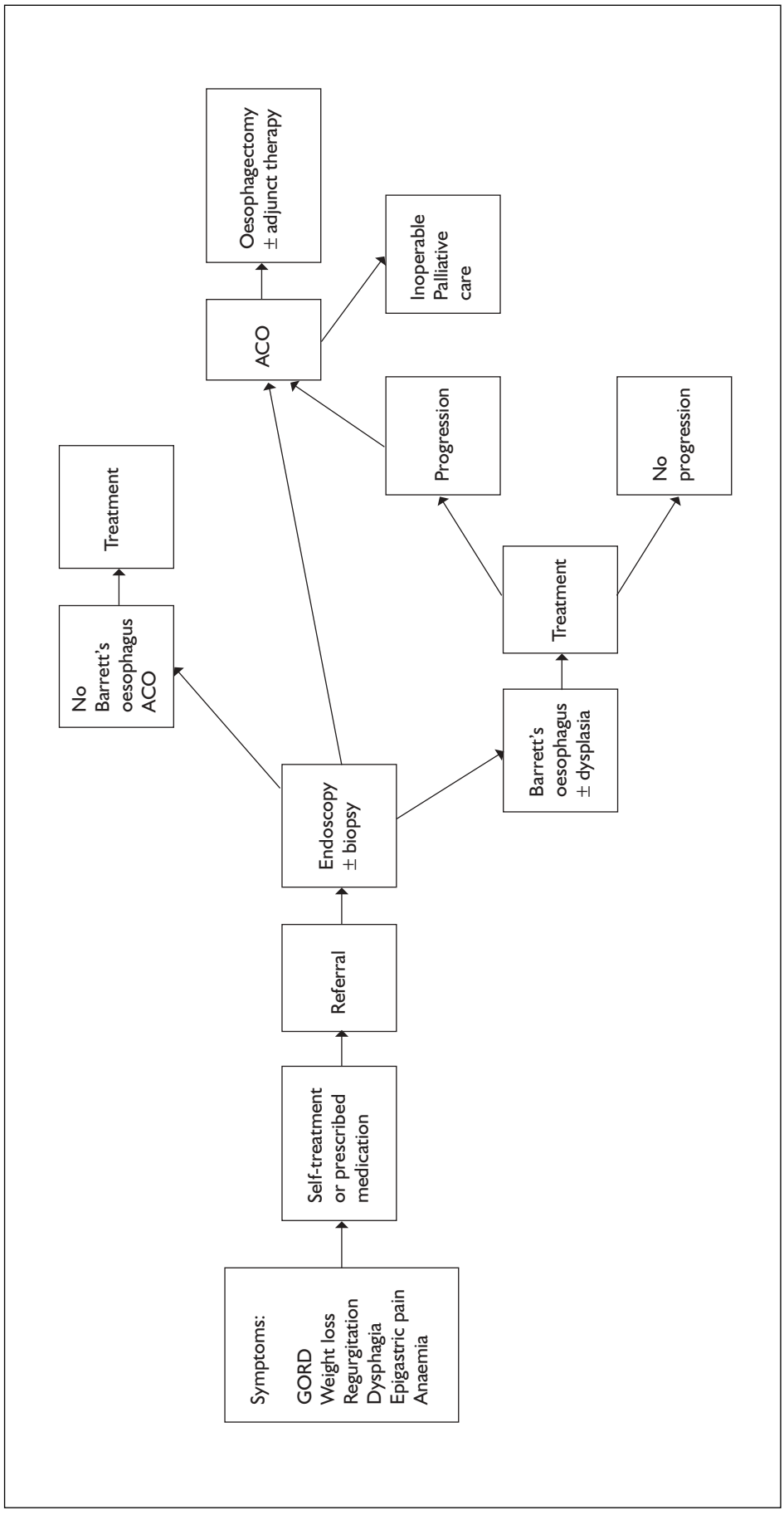

FIGURE 18 *Diagrammatic representation of patient pathway for diagnosis and treatment of Barrett's oesophagus and ACO*

surveillance programme and the overall impact of surveillance, and in highlighting variations in clinical practice, due to varying interpretations of the evidence. The format of the workshop, in identifying questions in several small groups predetermined by the organisers, may have encouraged this diversity and a future workshop in a similar study might usefully consider a more extended plenary or other methods of achieving some consensus after small group work.

The workshop was conducted using a recognised method, the NGT, to structure group interaction and to identify areas of agreement and disagreement. This allowed all participants to bring their ideas to the group and to rate independently the priority of all raised issues. We are not aware of the method being used in this way previously.

Although we tried to involve as many experts in the field as possible, it was clearly not possible to include everyone with an interest in surveillance of Barrett's oesophagus, and the time frame of the project meant that not all those who wished to be involved were available. It is not known whether the inclusion of different or additional participants would have substantially changed the outputs.

It was considered important to involve people with Barrett's oesophagus in the discussion and several patient representatives attended. It was hoped that the use of the NGT would allow equity in the contributions made by clinicians and patients in the small group work. However, their contribution has not been particularly highlighted and, in retrospect, it might have been more effective to bring together a separate group of patients that could focus specifically on patient issues and concerns. Alternatively, a different mechanism for obtaining and using user and patient perspectives might be considered.

Despite these limitations, the workshop confirmed the findings of the systematic review in highlighting global and specific uncertainties in the evidence base.

The model

The model is the first UK-based assessment of cost-effectiveness and the first to use probabilistic analyses. However, it is limited by many gaps and uncertainties in the available data. Transition values are uncertain for several reasons. First, the estimated progression rates are based on evidence from endoscopic surveillance and are limited both by the accuracy of diagnosis and the surveillance intervals. We had to assume that observed rates of progression are the same as actual natural history. They are also based on a limited number of studies from different populations using various surveillance and biopsy protocols. In addition, the rate of recurrence after oesophagectomy, a key value in sensitivity analysis, is reported in the literature relating to stage of tumour, which we had to assume relates to whether the cancer has been detected through surveillance, or not through surveillance.

A number of assumptions were made in order to produce a functioning model, summarised in *Table 31*.

We used a 20-year time frame for the model. At the end of the run, there are 19 cancers still undetected and non-fatal in the non-surveillance arm. The time to events is critical in modelling ACO and the impact of surveillance. When we ran the model for the extended time of 40 years, non-surveillance continued to dominate. However, if the model were to be extended fully, a number of parameters would become increasingly time dependent. For example, increasing numbers of patients would become unsuitable for surgery in both arms, owing to increasing frailty in the ageing cohort. We were not able to accommodate these changes in this iteration of the model. For this reason, it is unclear if, in selecting the 20-year time horizon, we have introduced bias into the model.

Utility (QoL) values do not appear to be consistent in all cases. For example, we have taken the 'well after surgery' value (0.863) from the Value of Health Panel whereas the 'well after regression of Barrett's oesophagus value' (0.8) uses the EQ5D assessments from the general population for the relevant age group. It is not logical that the 'well after surgery' state would have a higher utility than that for the general population of the same age. This is not likely to have a large influence on the model as the number of patients in the regressed Barrett's oesophagus health state is small, but it does indicate some lack of consistency.

Gaps in the evidence base

Gaps in the evidence base are discussed under the headings listed by the National Screening Committee for appraising the viability, effectiveness and appropriateness of a screening programme[91] and adapted for surveillance

TABLE 31 *Assumptions in the model and likely direction of bias*

Assumptions and limitations	Direction of bias likely to favour	Comments
All patients comply with surveillance programme	Surveillance	
Progression rates linear	Unknown	
100% specificity and sensitivity assumed	Surveillance	We assumed that figures for progression and regression reported in clinical studies will include misdiagnosed cases due to lower specificity and sensitivity. If this underestimates true rates, then surveillance may become less efficient
Those diagnosed with ACO at index endoscopy are excluded	Surveillance	
Observed progression rates reflect true progression rates	Surveillance	Length time bias as surveillance may tend to detect slower developing cases
Progression occurs sequentially through states.	Surveillance	Skipped states mean surveillance is less likely to detect critical illness early
Model assumes that progressions and treatment are the same at all stages of the model (i.e. does not accommodate cohort ageing)	Surveillance	
Endoscopy carried out as outpatient procedure	Unknown	
Adverse effects of endoscopy not incorporated	Surveillance	
All patients receive maintenance PPIs	None	It is likely that a substantial proportion of patients receive much more medication than this, but it would probably affect each arm similarly
ACO in the non-surveillance arm only detected if symptomatic	Surveillance	It is possible that change or worsening of other symptoms (relating for example to GORD) will prompt further endoscopy and early, non-symptomatic ACO may be detected
Recurrent ACO is terminal	None	
There is no assumed disutility (reduced QoL) associated with being in a surveillance programme	Unknown	All are diagnosed with Barrett's oesophagus – those not given surveillance may have reduced QoL in addition to those enduring regular endoscopy. No published accounts of this are available
Transitions are taken from larger studies of Barrett's oesophagus; however, this means that data about progression from those diagnosed with LGD and HGD initially come from a smaller sample	Unknown	
Utility value for well after surgery is the same in both arms	Non-surveillance	As in general the ACO detected outside surveillance programmes is more advanced, subsequent QoL in the non-surveillance arm may be lower
No account is currently taken of complications due to endoscopy	Surveillance	The effect is likely to be small, but there are more endoscopies in the surveillance arm
Model horizon 20 years	Unknown	Using other current inputs, extending the time horizon does not appear to influence results. However, bias may be introduced owing to the increasing time dependence of other parameters which have not been accounted for – see above

programmes (see Appendix 12 for details). No such framework is available specifically for surveillance programmes, although many features, such as the relevance of an effective treatment, enhanced outcomes with early detection of a condition and knowledge of the disease natural history, will be identical. The main difference for a surveillance programme is the selected nature of the population who have already been identified as particularly at risk. Participants' expectations of a surveillance programme may therefore be different. A schematic representation of the progression from GORD symptoms to Barrett's oesophagus and ACO and the possible interventions involved in a surveillance programme are shown in *Figure 18*.

The condition

The purpose of surveillance of Barrett's oesophagus is to reduce the morbidity and mortality from ACO. However, most ACO cases are currently diagnosed at an endoscopy performed for the investigation of symptoms and not as part of a Barrett's oesophagus surveillance programme. The incidence of ACO has been increasing over recent years.[8] Stage at presentation varies, but may be late, when operative treatment is frequently ineffective or not appropriate, owing to the frailty of the patients. Consequently, 1- and 5-year survival remains poor (see background, p. 3). GORD is considered a risk factor for ACO, but there is little evidence that any primary prevention measures reduce the incidence of ACO.

One main gap in the evidence base is lack of knowledge of the natural history of Barrett's oesophagus. This was highlighted in all three streams of the current investigation – the systematic review, expert workshop and economic modelling.

The systematic review found that few studies give details of the study population beyond age and sex. Further clinical details are essential, as no studies are population based and all studies start with those patients who present with symptoms that are deemed to require endoscopy. Many other factors besides the underlying pathology determine whether an endoscopy is performed for upper GI symptoms and on whom. Patient factors, access to health services and clinical practice will all influence the population that is investigated by endoscopy and all vary both within and between countries. The lack of detail means that there are no reliable estimates of the prevalence of Barrett's oesophagus either in people with GORD symptoms or in the general population. With few data available on the prevalence of Barrett's oesophagus in the general population, the relationship between GORD symptoms, Barrett's oesophagus and ACO remains uncertain.

The systematic review noted limited reporting of the findings at initial endoscopy and very variable reporting of the presence of dysplasia subsequently. Coupled with lack of detail on, and variation in, the diagnostic methods used, this lack of information results in substantial uncertainty about the rate at which Barrett's oesophagus progresses to dysplasia and ACO and the extent to which dysplastic states may regress. It is also unclear if all patients with Barrett's oesophagus inevitably progress to dysplasia or whether any particular patients can be identified clinically as being at greater risk of progression.

The systematic review identified few studies that follow up patients for more than 5 years. The majority of cases of ACO are identified at initial endoscopy and removed from follow-up and the population under surveillance will take some time to develop dysplasia and incident cancers. Reported follow-up may therefore be too short as yet to give reliable estimates of rates of progression from Barrett's oesophagus to dysplasia and ACO.

Few studies in the systematic review systematically attempt to follow up non-participants in the surveillance programme, and so fail to report morbidity and mortality in this group from either ACO or other causes. Without this information, it is impossible to determine whether there is any benefit from inclusion in a surveillance programme.

The expert workshop identified natural history as a key area for further research. Linked to this were questions about risk factors and risk groups for ACO, both within the population with Barrett's oesophagus and within the general population, and possible treatments for Barrett's oesophagus that might alter the progression to ACO.

The PenTAG economic model is particularly sensitive to one aspect of the natural history: the rate at which ACO becomes symptomatic. Other disease progression rates do not have such an impact on the model outputs, and regression rates have extremely little impact. It may be a weakness of the model that this aspect of natural history appears so important, when in clinico-pathological terms it is part of the continuum from the

development of Barrett's oesophagus, through stages of dysplasia, to cancer and then the development of symptoms. The PEVPI highlights both the transition rates and the rate at which ACO progresses to symptomatic ACO as the most important areas in which it would be valuable to pursue more accurate information. These are areas for which existing data are very uncertain. In addition, the end-point in practical terms is the presentation of the patient to health services; the decision and action to seek healthcare for symptoms depends on factors such as access to healthcare and patient concerns and also pathological features such as size and situation of the tumour. Determining the rate at which ACO becomes symptomatic would logically need to include the investigation of these factors also.

The test

All studies in the systematic review use endoscopy and biopsy to diagnose Barrett's oesophagus. They also agree that, although the appearance on endoscopy is characteristic, histological confirmation is necessary. Studies included in the systematic review vary in the number of biopsies taken and the protocol followed in taking them and many do not state precisely what was done. Definitions of Barrett's oesophagus also vary and studies do not always state which definition has been used in their inclusion criteria.

The expert workshop also identified several areas related to diagnosis as important for further investigation. However, they were particularly interested in identifying biomarkers in the general population that would identify those at most risk of developing ACO. In addition, participants were interested in identifying alternative biomarkers for ACO – this may involve new tests, which may or may not be linked to endoscopic surveillance.

As the nature of dysplastic change and the development of ACO is patchy across the whole segment of the oesophagus affected by Barrett's oesophagus, there remains a sampling problem when using endoscopy and biopsy to detect such changes, and this was also noted by the workshop participants. Other diagnostic techniques have been tried, which could potentially be used to examine the whole of the oesophageal mucosa, but they have yet to be validated rigorously.

A gap in the evidence base is the lack of data on the performance of the usual diagnostic procedure of endoscopy and biopsy, which is not standardised and for which no sensitivity and specificity data are available. The effect of this lack of knowledge is to increase uncertainty over the progression and regression rates between the diagnosed states of Barrett's oesophagus, LGD, HGD and ACO, as diagnostic misclassification cannot be identified or quantified. Uncertainty could be reduced by first establishing the performance of endoscopy/biopsy and then working to improve it, if possible, or by examining the performance of alternative tests to see if their performance is superior. The data on some transition states are very uncertain, although their impact on the model is only moderate.

The treatment

Various treatment options are available for GORD. The main one is medical treatment with PPIs and other acid suppressants. Anti-reflux surgery is an alternative. There are a number of studies, including a few small RCTs, on the effect of PPIs on the presence of Barrett's oesophagus, but most report disappointing results in terms of regression of Barrett's oesophagus.[92] None report any effect on the risk of developing ACO.[92] Workshop participants highlighted the lack of knowledge surrounding any treatments for Barrett's oesophagus, and identified this as a key area for further research.

A large trial of chemoprevention in Barrett's oesophagus began recruiting in 2005 (AspECT), using aspirin and PPIs to suppress acid and reduce cancer risk. If recruitment is successful, then further evidence on alteration of cancer risk by treatment will become available. The potential of this trial was noted by the workshop participants.

Oesophagectomy is accepted as an effective treatment for ACO in those patients who are able to undergo such a radical operation, although this effect has not been tested in RCTs. Treatment at an early stage is also accepted as leading to improved survival compared with operation at a later stage, although again this observation has not been tested formally in RCTs. Current practice is not yet standardised across the UK and the extent to which cancer units and centres provide adjuvant chemotherapy and chemoradiation to patients with ACO is not clear.[25] Various trials of treatment for ACO are in progress or planned (such as the MRC OE05 trial and REAL-2), but the extent to which they are likely to improve survival is limited by the stage at presentation. Surveillance programmes at present have limited ability to alter the overall profile of stage at presentation owing to the small numbers of people included in them.

Alternative treatment options to oesophagectomy are available, but they have not yet been tested through RCTs and their long-term effectiveness in reducing cancer risk is unknown. These alternatives, if effective, would enable many patients, who are currently unsuitable for operation due to co-morbidity, to be treated successfully.

The current evidence base suggests that there is no good method yet identified for reducing cancer risk in patients with Barrett's oesophagus. For patients with ACO, the evidence supports the use of oesophagectomy as an effective treatment in those able to undergo the procedure. However, this current evidence base does not provide any evidence for other effective means of either reducing cancer risk or for treating ACO in patients not suitable for surgery, thus limiting the effectiveness of current treatments in reducing morbidity and mortality from ACO.

The cost–utility model proved sensitive to the extent to which patients with ACO detected by surveillance or presenting with symptoms are treatable by oesophagectomy. Altering the proportion of people who can be treated requires either that a greater proportion of people with ACO are picked up at an early stage or that the treatment is less invasive and therefore accessible to more people.

Gaps in the evidence base are the identification of effective means of reducing cancer risk in patients with Barrett's oesophagus and less radical methods of treating ACO. These were noted in the workshop.

The model does not identify the effectiveness of treatment of Barrett's oesophagus as a specific element to be adjusted. One aspect of its effectiveness is assumed to be the extent to which it reduces cancer risk, which translates in the model into the progression/regression rates of Barrett's oesophagus through the dysplastic states to ACO. The more effective the treatment, the lower are the progression rates, thus increasing the likelihood that surveillance is either not cost-effective or does more harm than good.

Another aspect of treatment of Barrett's oesophagus is the effect it may have on QoL, particularly that of associated with GORD/Barrett's oesophagus. The utility value (QoL) of this health state is a parameter to which the model is sensitive. Effective treatment of Barrett's oesophagus (which is assumed to be about relieving the symptoms of GORD in addition to reducing cancer risk) should alter the proportions of the population with GORD in each of the mild, moderate and severe categories and therefore improve QoL. As this utility value impacts in the model, a higher value due to improved treatment will also tend to increase the likelihood of surveillance not being cost-effective or causing more harm than good. In addition, QoL after oesophagectomy also has a major impact on the model. Improved treatment of ACO at first diagnosis may reduce recurrence rates, which will favour surveillance. However, it may mean that patients spend longer in a 'treatment' health state as they are receiving adjuvant or other treatment besides surgery which will lengthen their treatment time beyond the four weeks allowed for in this model.

Levels of recurrence of ACO after surgery in the surveillance compared with the non-surveillance arm are uncertain and have a major impact on the model.

The surveillance programme

In addition to the above elements of surveillance, the overall picture of surveillance is also uncertain. A major gap in the evidence base is the lack of RCT data on the effectiveness of surveillance programmes in reducing morbidity and mortality from ACO. This was identified by all three strands of the project's inquiry: systematic review, workshop and identifying inputs for the model. The lack of standard diagnostic criteria, diagnostic methods and surveillance intervals, seen in studies included in the systematic review, all hamper comparison between studies of surveillance programmes.

Possible harms of surveillance of Barrett's oesophagus are not generally reported in the studies identified here. In general terms, harms can be considered as due to the investigation, the treatment offered and psychological harms. For Barrett's oesophagus surveillance, harms due to endoscopy and biopsy could include the effects of sedation, transient pain or discomfort from the procedure and, rarely, bleeding or perforation of the oesophagus. Treatment of Barrett's oesophagus may cause some adverse effects from drugs, but PPIs and other acid suppressants have a good safety profile, although if higher doses are prescribed, adverse effects may increase. Harms from oesophagectomy may be substantial, with a considerable minority of patients suffering postoperative morbidity and mortality. Persistent postoperative symptoms include 'dumping' and other gastrointestinal disturbances related to the alteration in GI anatomy.

Psychological harms include the effect of regular attendance for follow-up and associated loss of time from other activities and the effect on QoL if oesophagectomy is performed when the patient has few, if any, symptoms. It is also possible that there may be an adverse impact on QoL if a diagnosis of Barrett's oesophagus is made and no provision is made for surveillance, although this is unknown.

If oesophagectomy is confined to those with ACO on biopsy, then harm to patients without disease is minimised, but if oesophagectomy is offered to those with HGD at biopsy, there is far more potential for harm to those who will not benefit as they are very unlikely to develop the disease.

This model produced similar outputs to the US models published previously. There is a historical trend from the earliest study[64] which found surveillance to be cost-effective for all patients with Barrett's oesophagus at 2- and 3- yearly intervals, to Provenzale and colleagues' later study in 1999,[42] using better estimates of the data, which concluded that only 5-yearly surveillance was cost-effective, to Inadomi and colleagues' study,[30] the most recent, which found that any surveillance programme for all patients with Barrett's oesophagus was not cost-effective. Inadomi and colleagues concluded that only once in a lifetime screening of those with GORD symptoms and surveillance of patients with dysplasia were cost-effective. The PenTAG model similarly found that any surveillance programme for all patients with Barrett's oesophagus is unlikely to be cost-effective, but we have not modelled a scenario of only surveying those with dysplasia. However, owing to the discussed gaps in the evidence base, PenTAG's model is associated with considerable uncertainty, and relatively small changes in the model inputs, many of which may be within plausible ranges, can dramatically alter the outputs. The results must be viewed with extreme caution.

Addressing the evidence gap: areas of uncertainty

The natural history of Barrett's oesophagus and ACO and the population at risk of ACO

The first major gap is understanding the natural history of Barrett's oesophagus. Workshop participants identified this as a key question to be addressed and the systematic review found incomplete reporting of relevant data on most aspects of it. However, progression rates from Barrett's oesophagus through dysplastic states to ACO have only a moderate effect on the economic model. In contrast, the model is very sensitive to the rate at which undetected ACO becomes symptomatic. This parameter determines the potential effectiveness of surveillance as it reflects the 'window of opportunity' for surveillance to identify an occult cancer. Where cancers rapidly become symptomatic, then a high proportion will be identified as 'interval' cancers in the surveillance programme and, in comparison with non-surveillance, the surveillance programme will achieve less benefit. In contrast, if a tumour remains asymptomatic (but detectable given the limits of endoscopic examination) for some time, and particularly if it undergoes asymptomatic progression, then surveillance may lead to identification at an earlier stage with the consequent potential for improved operability and survival.

Important aspects of this area of uncertainty include the possible existence of subgroups of the population at high risk of progression, the prevalence of Barrett's oesophagus in the general population and whether all patients who present with ACO have had a preceding state of Barrett's oesophagus.

Surveillance and diagnostic tests for Barrett's oesophagus and dysplasia

The next major area of uncertainty concerns the performance of endoscopy and biopsy as a surveillance and diagnostic test for Barrett's oesophagus and dysplasia. This was a problem in interpreting the data from the systematic review for incorporation into the model. Concerns with better ways to identify risk groups were also raised by the workshop participants. Without reliable data on the performance of an agreed standard protocol of this investigation, estimates of the prevalence of Barrett's oesophagus and progression rates to dysplasia and ACO remain uncertain. There is a requirement for the test to perform to high levels of sensitivity and specificity for such estimates to be reliable, but there is real uncertainty that endoscopy and biopsy can ever be shown to perform to the required standard, either for the purposes of surveillance or diagnosis. Development of alternative diagnostic tests is therefore desirable.

Treatment of Barrett's oesophagus and ACO

There is another area of uncertainty around the effectiveness of any treatment to alter risk of progression of Barrett's oesophagus to ACO. This was highlighted by the workshop. Although several treatment options have been tested in

small trials, further evidence is awaited that any treatment induces regression of Barrett's oesophagus and that that regression results in reduction of risk. It is also possible that it is not necessary for Barrett's oesophagus to regress to normal oesophageal mucosa for the cancer risk to be reduced.

Another area of uncertainty highlighted by the economic model concerns the proportion of people who are treatable by oesophagectomy depending on the way in which the ACO was detected – through surveillance or endoscopy for symptoms prior to or after a diagnosis of Barrett's oesophagus. In addition, the model is sensitive to the recurrence rate of ACO after oesophagectomy. This variable would be influenced by the stage at which ACO is detected in each arm. Alternative treatment options for ACO need rigorous evaluation, as do studies maximising the benefit from current treatment options.

Surveillance programmes

The preceding points show that there is considerable uncertainty around the benefit and harm to patients in participating in a surveillance programme. The individual elements listed above all require addressing before the overall question about the impact of a surveillance programme on morbidity and mortality from ACO can be addressed. The question as to whether surveillance should be undertaken at all was highlighted by the expert workshop.

Conclusions

The systematic review failed to find proof of the effectiveness of surveillance. Although the absence of RCT data concerning the benefits and harms of surveillance is crucial, other major areas of uncertainty were also identified. These areas were the lack of knowledge concerning the natural history of Barrett's oesophagus, the performance of surveillance and diagnostic tests for Barrett's oesophagus, the effectiveness of treatment for Barrett's oesophagus in terms of reducing cancer risk and improving health-related QoL, the effectiveness of treatment for ACO in terms of reducing recurrence rates and improving health-related QoL after surgery.

The economic model developed by PenTAG shows that surveillance at 3-yearly intervals for non-dysplastic Barrett's oesophagus does more harm than good compared with non-surveillance (costs more and confers fewer QALYs). However, there is much uncertainty around the inputs and the results are critically dependent on variables for which there is little reliable evidence.

The total EVPI is around £148 per patient. The EVPI is driven by the number of people affected and the expected lifetime of the technology. The PEVPIs show that the main uncertainty concerns the transition probabilities in the model, not the costs or the utilities (QoL).

The high degree of uncertainty in the model makes it unwise to place too much reliance on the outputs. We have incorporated this uncertainty as far as possible in the probabilistic analysis. However, although surveillance is unlikely to be cost-effective, it is possible using clinically plausible inputs.

Despite this lack of conclusive evidence for the effectiveness of surveillance for Barrett's oesophagus, most UK practitioners believe it to be worthwhile and some form of surveillance is usual current practice [see the section 'Current UK practice' (p. 10)]. It may be more difficult to influence practitioners to stop using an existing technology than to encourage them to start using a new one, especially in the absence of an obvious alternative strategy.

Further research is required before the question of the effectiveness and cost-effectiveness of surveillance of Barrett's oesophagus in reducing morbidity and mortality from ACO can be answered with confidence. In addition, such evidence may form a vital part of any education programme for clinicians to support the decision to continue or cease surveillance. Future research should target both the overall effectiveness of surveillance and the individual elements that contribute to a surveillance programme, particularly the performance of the test and the effectiveness of treatment for both Barrett's oesophagus and ACO. In addition, of particular importance is the clarification of the natural history of Barrett's oesophagus. More detailed research proposals will be discussed separately with the HTA programme to inform their commissioning process.

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About PenTAG

The Peninsula Technology Assessment Group (PenTAG) is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Contribution of authors

Ruth Garside (Research Fellow) provided overall project management, commented on the protocol, checked abstracts and papers for inclusion, checked data extraction, drafted the background, systematic review and modelling chapters of the TAR, edited other chapters and identified model inputs. Martin Pitt (Research Fellow) designed and ran the economic model and contributed to and commented on the economic sections of the Technology Assessment Report (TAR). Margaret Somerville (Director of Public Health Learning and Principal Lecturer) drafted the protocol, edited the TAR, drafted conclusions and discussion sections and read and edited the report. Ken Stein (Senior Lecturer in Public Health) commented on the protocol, contributed to the design of the model and read and edited the report. Naomi Gilbert (Research Assistant) coordinated the workshop, checked abstracts and papers for inclusion, extracted data and tabulated results of the systematic review. Alison Price (Information Scientist) undertook literature searches for the project and commented on a draft of the report.

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Appendix 1

Expert advisory group

Members of the advisory group:

Professor Hugh Barr, Consultant General and Gastrointestinal Surgeon, Gloucestershire Royal Hospital, Gloucester.

Professor Janusz A Jankowski, Professor of Medicine, Gastroenterology and Academic Head, University Department of Cancer Studies and Molecular Medicine, Leicester Medical School, Leicester Royal Infirmary.

Dr Laurence Lovat, Consultant Gastroenterologist and Senior Lecturer in Laser Medicine, University College Hospital, London.

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen.

Professor Tony Watson, Director of UK National Barrett's Oesophagus Registry, Department of Surgery, University College London, and Royal Free Hospital, London.

Appendix 2

Search strategy

Database: MEDLINE, 1966 to February week 4, 2004. Searched 10 March 2004

1 exp Barrett Esophagus/ (2624)
2 exp Esophageal Stenosis/ (5230)
3 exp Esophagitis, Peptic/ (3243)
4 (barrett$ adj5 (oesophag$ or esophag$)).mp. [mp=title, abstract, name of substance, mesh subject heading] (3089)
5 ((long adj5 segment$) or LSBO).mp. [mp=title, abstract, name of substance, mesh subject heading] (3406)
6 ((short adj5 segment$) or SSBO).mp. [mp=title, abstract, name of substance, mesh subject heading] (3246)
7 (column$ adj5 (epithelium$ or esophag$ or oesophag$)).mp. (2016)
8 ((esophag$ or oesophag$) adj5 adenocarcinoma).mp. (4543)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (21086) **Total Population** (condition)
10 exp Mass Screening/ (62219)
11 surveill$.mp. (36966)
12 exp Population Surveillance/ (21486)
13 endoscopy/ or exp endoscopy, gastrointestinal/ or endoscop$.tw. or chromoendoscop$.tw. (91768)
14 exp BIOPSY/ (120864)
15 or/10-14 (312697) **Total Intervention**
16 metaplas$.mp. [mp=title, abstract, name of substance, mesh subject heading] (11924)
17 (goblet adj4 cell$).mp. [mp=title, abstract, name of substance, mesh subject heading] (3962)
18 pre?cancer$.mp. (17812)
19 (biomarker$ or bio$ marker$).mp. (54970)
20 or/16-19 (86282) **Total outcome**
21 9 and 15 (4161) **First set**
22 20 and 21 (765) **Final set (PIO)**
23 limit 22 to english language (652) **Final set Limited to English downloaded**
24 exp "Costs and Cost Analysis"/ (107219)
25 exp ECONOMICS/ (314037)
26 exp Value of Life/ (4231)
27 exp ECONOMICS, PHARMACEUTICAL/ or exp ECONOMICS, HOSPITAL/ or exp ECONOMICS, NURSING/ or exp ECONOMICS, MEDICAL/ or exp ECONOMICS, DENTAL/ (29616)
28 exp "Fees and Charges"/ (20452)
29 exp BUDGETS/ (8229)
30 cost$.mp. (188631)
31 (economic$ or pharmacoeconomic$ or price$ or pricing).mp. [mp=title, abstract, name of substance, mesh subject heading] (107278)
32 or/24-31 (436062)
33 (letter or editorial).pt. (654827)
34 32 not 33 (410109) **Total economics filter**
35 34 and 23 (48) **Final set economics/costs**
36 from 35 keep 1-48 (48) **Costs downloaded**
37 exp INCIDENCE/ (80174)
38 exp PREVALENCE/ (69723)
39 incidence.mp. (294486)
40 prevalence.mp. [mp=title, abstract, name of substance, mesh subject heading] (165227)
41 or/37-40 (435576)
42 exp Risk Factors/ (231330)
43 exp Time Factors/ (629668)
44 exp Cohort Studies/ (482497)
45 epidemiol$.mp. or Epidemiology/ (135525)
46 (aetiolog$ or etiolog$).mp. [mp=title, abstract, name of substance, mesh subject heading] (120040)
47 or/42-46 (1430858)
48 ((natural$ or disease$) adj3 (progress$ or course$ or histor$)).mp. [mp=title, abstract, name of substance, mesh subject heading] (95596)
49 or/41,47-48 (1762605) **Epidemiology filter**
50 49 and 9 (5089) **Epidemiology of total population**
51 limit 50 to english language (4087)
52 49 and 23 (365) **Final set of epidemiology (limited to surveillance)**
53 exp DIAGNOSIS/ (3198639)
54 exp "Sensitivity and Specificity"/ (153804)
55 exp Mass Screening/ (62219)
56 predictive value$.mp. (70209)
57 roc curve$.mp. (7821)
58 (sensitivit$ or specifit$).mp. [mp=title, abstract, name of substance, mesh subject heading] (322039)
59 false negative$.mp. (21598)
60 accuracy.mp. (79910)
61 screening.mp. (135607)
62 likelihood ratio$.mp. (2370)
63 diagnos$.mp. (988670)
64 false positiv$.mp. [mp=title, abstract, name of substance, mesh subject heading] (31915)
65 or/53-64 (3813692) **Sensitive diagnosis filter**

66 or/54,56-60,62-64 (1337384) **More specific, low recall, high precision filter**
67 65 and 9 (9456) **Diagnosis total condition**
68 66 and 9 (3539) **Higher precision total condition**
69 65 and 23 (541) **Sensitive diagnosis search of final set**
70 66 and 23 (267) **High precision diagnosis filter of final set**

Database: EMBASE, 1980 to week 12, 2004. Date searched: 24 March 2004

1 exp Barrett Esophagus/ (3200)
2 (barrett$ adj5 (oesophag$ or esophag$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (3254)
3 ((long adj5 segment$) or LSBO).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (2796)
4 ((short adj5 segment$) or SSBO).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (2757)
5 (column$ adj5 (epithelium$ or esophag$ or oesophag$)).mp. (1789)
6 ((esophag$ or oesophag$) adj5 adenocarcinoma).mp. (2331)
7 1 or 2 or 3 or 4 or 5 or 6 (10782)
8 screening/ or antibody screening/ or cell screening/ or mass screening/ or cancer screening/ (44681)
9 surveill$.mp. (30727)
10 endoscopy/ or exp endoscopy, gastrointestinal/ or endoscop$.tw. or chromoendoscop$.tw. (77720)
11 biopsy/ or esophagus biopsy/ (15166)
12 or/8-11 (161333)
13 metaplas$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (8821)
14 (goblet adj4 cell$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (3041)
15 pre?cancer$.mp. (5843)
16 (biomarker$ or bio$ marker$).mp. (16039)
17 or/13-16 (32494)
18 7 and 12 (2272)
19 17 and 18 (681)
20 limit 19 to english language (597) Final set
21 exp ECONOMICS/ (11189)
22 exp Health Economics/ (133457)
23 BUDGET/ (5094)
24 exp COST/ (78603)
25 (cost or costs or costly or costing).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (117751)
26 economic$.mp. (97108)
27 pharmacoeconomic.mp. (1334)
28 (price$ or pricing).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (7583)
29 exp Quality of Life/ (45176)
30 (qol or hrqol or qaly$ or lyg).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (4889)
31 (willing$ adj2 pay).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (658)
32 or/21-31 (300087)
33 (letter or editorial).pt. (382495)
34 32 not 33 (274532)
35 20 and 34 (52) Total costs
36 20 not 35 (545)
37 from 36 keep 1-545 (545) Surveillance downloaded
38 from 35 keep 1-52 (52) Costs download

Cochrane Library, 2004, Issue 1. Adapted from MEDLINE search strategy

1. BARRETT ESOPHAGUS
2. ((barrett* near oesophag*) or (barrett* near esophag*))
3. ((long near segment) or lsbo)
4. ((short near segment) or ssbo)
5. ((column* near epithelium*) or (column* near esophag*) or (column* near oesophag*))
6. ((adenocarcinoma* near esophag*) or (adenocarcinoma* near oesophag*))
7.(#1 or #2 or #3 or #4 or #5 or #6)
8. surveill*
9. (endoscop* or chromoendoscop*)
10. ESOPHAGOSCOPY
11. biopsy
12. (#8 or #9 or #10 or #11)
13. metaplas*
14. (precancer* or (pre next cancer*))
15. (biomarker* or (bio* next marker*))
16. (goblet near cell*)
17. (#13 or #14 or #15 or #16)
18. (#7 and #12)
19. (#18 and #17)

Record sheet for surveillance for Barrett's oesophagus

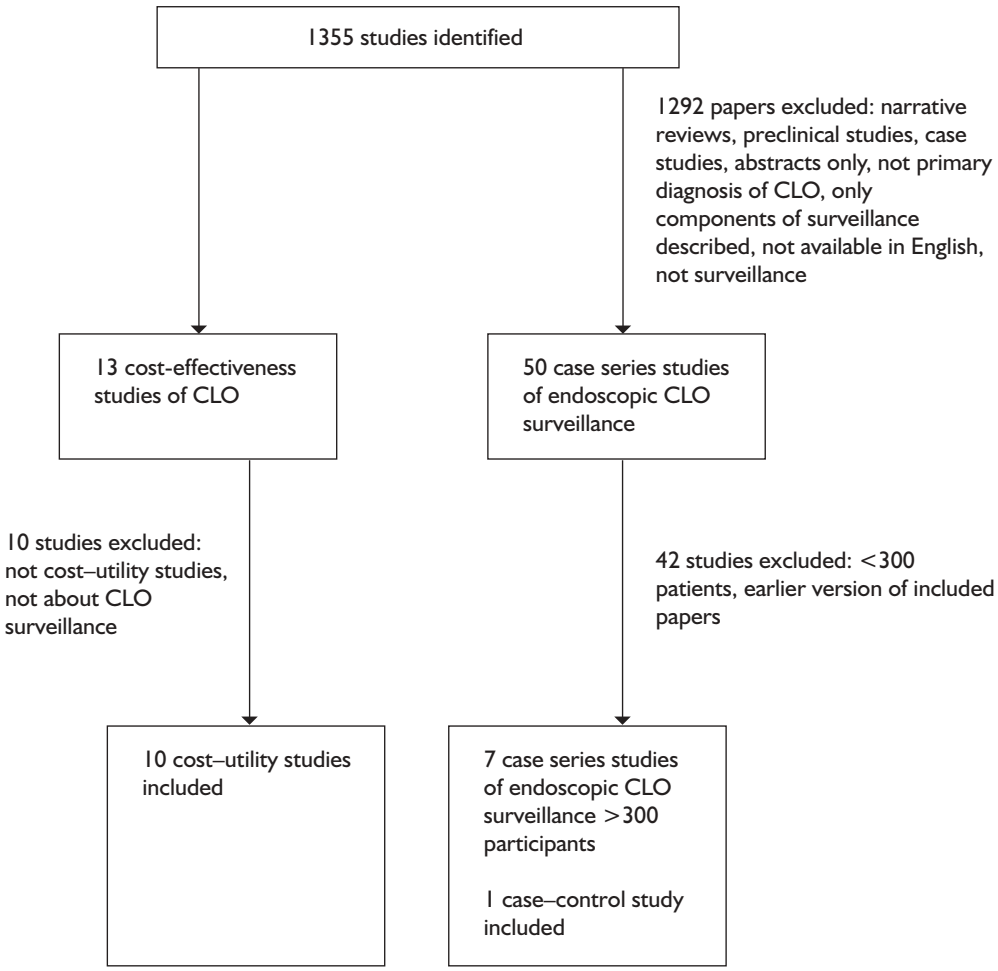
Database and years searched	Date searched and search files	Number retrieved	Download file
Cochrane Library – CDSR 2004 – Issue 1	24 March 2004 coch-srch-strat-txt (see MEDLINE search strategy)	6	6
Cochrane Library – CENTRAL – Issue	24 March 2004 coch-srch-strat-txt	50	50
MEDLINE (OVID), 1966 to week 4, February 2004	09 March 2004 med-surveillance-agreed	652	641
EMBASE (OVID), 1980 to week 12, 2004	16 March 2004 embase-barrett-all	597	597
PubMed, last 180 days	29 March 2004 Barrett* (esophag* or oesophag*) and surveill*	19	19
Web of Knowledge ISI Proceedings, 1990–present	Barrett* (esophag* or oesophag*) and surveillance	23	23
BIOSIS, 1985–2004	Barrett* (esophag* or oesophag*) and surveillance	301	201
DARE, 1995–2004	24 March 2004 coch-srch-strat-txt	1	1
NHS EED, 1995–2004 (on CRD databases)	24 March 2004 coch-srch-strat-txt	18	18
HTA database, 1998–2004 (on CRD databases)	24 March 2004 coch-srch-strat-txt	2	2
NRR, 2004/1 (National Research Register)	24 March 2004 Barrett* (esophag* or oesophag*) and surveillance	25	25
Total Refman records			1249

Economics searches

Database and years searched	Date searched and search files	Number retrieved	Number of hits (download file)
MEDLINE (OVID), 1966 to week 4,ß February 2004	10 March 2004	48	48
EMBASE (OVID), 1980 to week 12, 2004	23 March 2004	52	52
NHS EED, 1995–2004		18	18

Appendix 3

Flow of studies and excluded studies



Excluded studies – effectiveness

Study	Reason for exclusion	Summary of enquiry
Nanurkar and Talley *et al*. (1998)[48]	Superseded by DEC report	Systematic review but included in more recent DEC report so not included here. None of the included studies had >300 participants.
Atkinson *et al*. (1992)[93]	<300 participants	Non-systematic review of the surveillance plus review of practice in one UK centre. Not clear how many patients were followed up
Bartlesman *et al*. (1992)[94]	<300 participants	Report on surveillance of 50 patients for 5.2 years with CLO plus CLO histology in 115
Benipal *et al*. (2001)[95]	<300 participants	343 patients with Barrett's oesophagus, but 116 had SSBO and were focus of the paper and were followed up for an average of 64 months. Only 57 enrolled into surveillance programme
Beddow *et al*. (1999)[96]	<300 participants	Review of case notes of 38 children with Barrett's oesophagus. Mean follow-up 43 months
Bonelli *et al*. (1992)[97]	<300 participants	246 Barrett's oesophagus cases followed-up annually for 2 years
Buttar *et al*. (2001)[98]	<300 participants	Retrospective analysis of 134 patients with Barrett's oesophagus and HGD. 100 analysed, 4-year follow-up
Caygill *et al*. (1998)[99]	Not surveillance	Registry data from 2 centres on 268 patients with Barrett's oesophagus. Patient characteristics, incident ACO
Collins *et al*. (1991)[100]	Not surveillance	Retrospective analysis of 96 patients with Barrett's oesophagus
Conio *et al*. (2003)[101]	<300 participants	177 patients with Barrett's oesophagus. Surveillance every 2 years. Mean follow-up 5.5 years
Dolan *et al*. (2003)[102]	<300 participants	48 patients with Barrett's oesophagus. Mean follow-up 5 years
Drewitz *et al*. (1997)[103]	<300 participants	177 patients with Barrett's oesophagus. Mean follow-up 4.8 years
Hameeteman *et al*. (1989)[104]	<300 participants	50 patients with Barrett's oesophagus. Mean follow-up 5.2 years
Iftikhar (1992)[105]	<300 participants	104 patients with Barrett's oesophagus. Mean follow-up 54 months.
Katz *et al*. (1998)[106]	<300 participants	102 patients with Barrett's oesophagus. Median follow-up 4.8 years
Klump *et al*. (1999)[107]	<300 participants	41 patients with Barrett's oesophagus. Mean follow-up 46 months
Mills *et al*. (1989)[108]	<300 participants	26 patients with Barrett's oesophagus. Mean follow-up unclear
Miros *et al*. (1991)[109]	<300 participants	81 patients with Barrett's oesophagus. Mean follow-up 3.6 years
Montgomery (2001)[110]	<300 participants	138 patients with Barrett's oesophagus. Mean follow-up 38.2 months
Oberg *et al*. (2001)[111]	<300 participants	177 patients with Barrett's oesophagus. Mean follow-up unclear
O'Connor *et al*. (1999)[112]	<300 participants	136 patients with Barrett's oesophagus. Mean follow-up 4.2 years

continued

Study	Reason for exclusion	Summary of enquiry
Ovaska *et al*. (1989)[113]	<300 participants	32 patients with Barrett's oesophagus. Mean follow-up unclear
Rana and Johnston (2000)[114]	Not surveillance	70 patients with Barrett's oesophagus undergoing endoscopy when clinically indicated. Mean follow-up unclear
Reid *et al*. (1992)[115]	<300 participants	62 patients with Barrett's oesophagus. Mean follow-up 34 months
Sabel *et al*. (2000)[116]	<300 participants	Retrospective study of 66 patients with Barrett's oesophagus. Mean follow-up unclear
Schnell *et al*. (1992)[117]	Not surveillance	Analysis of 4 patients with ACO in SSBO
Sharma *et al*. (1997)[118]	<300 participants	59 patients with SSBO. Mean follow-up 36.9 months
Sharma *et al*. (2000)[119]	<300 participants	177 patients with SSBO. Mean follow-up 24 months
Spechler (1984)[24]	<300 participants	105 patients with Barrett's oesophagus. Mean follow-up 2.3 years
Van der Burgh and van Blankenstein (1996)[120]	<300 participants	166 patients with Barrett's. Mean follow-up 9.3 years
Van der Veen *et al*. (1989)[121]	<300 participants	166 patients with Barrett's oesophagus. Mean follow-up unclear
Van Sandick *et al*. (1998)[122]	Not surveillance	Comparison of 54 patients presenting with ACO and 16 with ACO detected through surveillance of Barrett's oesophagus
Weston (1999)[123]	<300 participants	99 patients with Barrett's oesophagus. Mean follow-up 48 months
Weston *et al*. (1997)[124]	<300 participants	152 patients with Barrett's oesophagus, 55 under surveillance. Follow-up 12-40 months
Weston (2000)[72]	<300 participants	15 patients with Barrett's oesophagus and HGD. Mean follow-up 36.8 months
Weston *et al*. (1999)[125]	<300 participants	108 patients with Barrett's oesophagus. Mean follow-up 39.9 months
Weston *et al*. (2001)[126]	<300 participants	48 patients with Barrett's oesophagus and LGD. Mean follow-up 41.2 months
Williamson (1991)[127]	<300 participants	176 patients with Barrett's oesophagus. Mean follow-up 2.8 years
Williamson (1992)[128]	<300 participants	212 patients with Barrett's oesophagus. 30 also had an ulcer – this group mean follow-up 3.6 years

Excluded studies – cost effectiveness

Study	Reason for exclusion	Summary of enquiry
Achkar and Carey (1988)[129]	Does not consider QALYs	Uses data from 72 cases at a single clinic in the USA to estimate the cost per cancer identified
Arguedas and Eloubeidi (2001)[130]	Review – not focused on cost–utility studies	Reviews six cost-effectiveness papers about GORD and Barrett's oesophagus
Hur (2003)[131]	Not surveillance. Not relevant to UK practice	Uses a Markov model to examine the cost–utility of photodynamic surgery compared with oesophagectomy for HGD. Based in USA
Ofman (2000)[132]	Not surveillance. Not relevant to UK practice	Uses data from a 2-year RCT comparing omeprazole and ranitidine in 95 patients with Barrett's oesophagus to model the cost impact of transitory dysplasia diagnoses (i.e. those diagnosed with dysplasia that was subsequently not confirmed). Based in USA
Soni (2000)[133]	Does not consider QALYs	Uses a decision tree analysis to assess the ICER of surveillance of patients with GORD as cost per life-year saved. Based in USA
Sonnenberg (1997)[134]	Not focused on surveillance of Barrett's oesophagus	Reviews previous cost-effectiveness studies of endoscopic surveillance (for colorectal cancer, ACO, gastric stump, ulcerative colitis and colon polyps). Based in USA
Sonnenberg (2002)[135]	Does not consider QALYs	Uses a Markov model to assess surveillance of Barrett's oesophagus every 2 years with no surveillance and ICERs are calculated. Based in USA
Sonnenberg and Fennerty, (2003)[136]	Not focused on surveillance vs non-surveillance of Barrett's oesophagus. USA based	Uses a Markov model to assess the cost-effectiveness of chemo-prevention (using NSAIDS, including aspirin) for patients with Barrett's oesophagus. This regimen alone was compared with it combined with surveillance and ICERs calculated. Based in USA
Streitz (1998)[137]	Does not consider QALYs	Compares cost per life-year gained of Barrett's oesophagus surveillance with mammographic surveillance for breast cancer. Based in USA
Wright (1996)[37]	Does not consider QALYs	Estimates the cost of screening to a UK hospital and the cost per detected cancer, based on data from 166 annually surveyed patients from two hospitals

Appendix 4

QUOROM quality checklist for DEC report[25]

1. Title: Identify the report as a systematic review?

No

2. Abstract: Uses a structured format?

No. Summary is in the form of a bullet-pointed list, but broadly covers the following headings:

- Background — Outlines the clinical problem.
- Objectives — To review the evidence that a surveillance programme for Barrett's oesophagus can reduce morbidity and mortality from oesophageal cancer.
- Data sources — Not described.
- Review methods — Not described.
- Main results — No RCTs located. Not clear how many, or what type of other data sources were identified or used. Results from one cost-effectiveness study from the US stated.
- Reviewers' conclusions — That effectiveness is not proven.

3. Introduction

Explicit clinical problem, biological rationale for surveillance and rationale for review described.

4. Methods

- Searching — Databases and search terms listed together with date of searches and list of expert informants. No restrictions stated.
- Selection — No details given.
- Validity assessment — No details given.
- Data abstraction — No details given.
- Study characteristics — One published systematic review, five retrospective surveys of surveillance programmes, two RCTs of treatments for Barrett's oesophagus (further three in abstract form only) and four economic analyses were identified. Summary table of study type, limited patient characteristics, intervention, definition of condition and main intervention given. Clinical heterogeneity not formally assessed.
- Quantitative data synthesis — Not attempted.

5. Results

- Trial flow — None given.
- Study characteristics — Main results summarised.
- Quantitative data synthesis — Not applicable.

6. Discussion

Key findings are summarised, clinical relevance is discussed but not in terms of validity of individual studies. Possible biases in the review process are not discussed. Further research recommended but detailed areas for research not specified.

Appendix 5

Data extraction tables

Reference and design	Surveillance programme	Outcome measures
Authors Fitzgerald *et al*. (2001)[50] **Country** UK **Setting** Havering Hospitals NHS Trust **Recruitment dates** 1992–8 **Surveillance period** Informal surveillance 1992–7 Rigorous protocol 1997–8 **Study design** Non-randomised comparison of informal (retrospective) vs rigorous (prospective) surveillance **Comparator groups** 1. Informal surveillance period 2. Rigorous surveillance period **Two cohorts within each group** Patients entering surveillance No surveillance (those presenting with *de novo* cancers) **Inclusion criteria** Unclear – diagnosis of Barrett's oesophagus? Surveillance cohorts defined as ≥3 endoscopies examining Barrett's oesophagus segment over ≥ 2 years **Exclusion criteria** Not stated	**Diagnostic methods** *Informal surveillance* No standardised biopsy protocol. Endoscopic diagnosis of Barrett's oesophagus without histological confirmation. Mean biopsies taken 4 (range 0–6) *Rigorous surveillance* Quadrantic 2-cm biopsy protocol. Histological confirmation of presence of SIM to diagnose Barrett's oesophagus Mean biopsies taken 12 (range 4–20) **Treatment** *Informal surveillance patients* 40% on PPIs 11% on H_2 antagonists *Rigorous surveillance patients* 60% on PPIs 3% on H_2 antagonists **Surveillance protocol** *Informal surveillance* No consistent selection for surveillance, 1–2 yearly endoscopy *Rigorous surveillance* Selection criteria – histologically proven Barrett's oesophagus, fit for surgical treatment. Annual endoscopy, 3–6 monthly if dysplasia	**Primary outcome measure** Progression to invasive cancer Progression to HGD **Secondary measures** Cost of detecting cancer under informal vs rigorous surveillance protocols **Method of assessing outcomes** Endoscopic follow-up and calculation of costs per case of cancer/HGD detected (based on a cost of £124.00 for one endoscopy and 12 biopsies) **Length of follow-up** *Informal surveillance (N = 96)* Total 375 patient years *Rigorous surveillance (N = 108)* Total 108 patient years

Subjects	Informal 1992–7	Rigorous 1997–8
Total number of patients	12,854 gastroscopies, 358 Barrett's oesophagus: 96 (27%) surveillance 262 (73%) no surveillance	2949 gastroscopies, 196 Barrett's oesophagus 108 (55%) surveillance 88 (45%) no surveillance
Reason initial endoscopy	Not stated	Not stated
Patient characteristics	Reported only for surveillance cohort Ratio males:females 2.8:1 Mean age 62 (range 28–89) years	Reported only for surveillance cohort Ratio males:females 3.5:1 Mean age 64 (range 34–83) years
Definition of Barrett's oesophagus	Endoscopic diagnosis sufficient (definition not stated)	Histological confirmation of presence of SIM
Average length Barrett's oesophagus	Mean 5 (1–15) cm	Mean 6 (1–15) cm
Concomitant illness	Not stated	Not stated
Dysplasia at initial biopsy	Not stated	Not stated

continued

Results	Informal 1992–7		Rigorous 1997–8	
	N	**Incidence per 100 patient years**	***N***	**Incidence per 100 patient years**
Progression to HGD				
Surveillance cohort	1/96	~0.28 (1/375 years)	3/108	~2.8 (1/36 years)
No surveillance (de novo)	0/262	–	0/88	–
Progression to ACO				
Surveillance cohort	0/96		2/108	~1.9 (1/54 years)
No surveillance (de novo)	10/262	0.0 (0/357 years)	9/88	–
Survival	**Group 1**		**Group 2**	
Non-ACO mortality	Not stated		Not stated	
ACO mortality				
Surveillance cohort	Not stated		0/5 with HGD/invasive cancer died	
No surveillance (*de novo*)	9/10 with invasive cancer died (cause of death not stated)		2/9 with invasive cancer died (cause of death not stated)	
Perioperative mortality	4/10 non-surveyed		3 received oesophagectomy – 0 deaths	
Treatment for ACO or HGD?	Oesophagectomy for ACO – $^{1}/_{4}$ curative		ACO oesophagectomy	

Methodological comments
Prospective? Formal surveillance arm prospective, historic comparison arm retrospective
Consecutive patients enrolled? Yes
Malignancies identified at initial endoscopy excluded? Yes – analysed separately
Malignancies identified early in follow-up excluded? No
Loss to follow-up Not stated
Statistical methods: χ^2 with Yates correction factor to compare ACO incidence and age between groups

General comments
Population sample drawn from: Patient records, consecutive case series
Changes in practice during study? Yes – as stated above

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Macdonald *et al*. (2000)[138] **Country** UK **Setting** University teaching hospital **Recruitment dates** 1984–4 **Surveillance period** 1984–9 **Study design** Observational – concurrent comparison group – surveillance compared with no surveillance **Inclusion criteria** Those with Barrett's oesophagus who are fit for major surgery (usually <70 years and no serious concomitant disease) **Exclusion criteria** Not stated **Reasons for not entering surveillance (of total cohort)** >70 years old 39% Serious coexisting illness 10%	**Total number of patients** 409 with Barrett's oesophagus 143 (35%) entered into surveillance programme **Reason for initial endoscopy** Of surveillance group Epigastric pain 33 (23%) GORD 30 (21%) Dysphagia 29 (20%) Anaemia 16 (11%) Haematemesis 10 (7%) **Patient characteristics** *Surveillance cohort* 86 (60%) male Mean age 57 (17–69) years Stricture 23 (16%) *Non-surveillance cohort* 125 (47%) male Mean age 69 (17–64) years Stricture 12 (5%) **Definition of Barrett's oesophagus** Endoscopic abnormality of ≥ 30 mm Biopsy confirmation of columnar metaplasia **Average length Barrett's oesophagus** 76 mm 81 mm in surveillance group **Concomitant illness** Present in 10% of total – no details **Dysplasia at initial biopsy** Not clear	**Diagnostic methods** Length of macroscopically affected area recorded together with details of stricture/ulcer Quadrantic biopsy samples taken from midpoint of affected mucosa plus multiple samples form areas showing abnormality Dysplasia recorded as mild, moderate or severe **Treatment** Not stated **Surveillance protocol** Annual	**Primary outcome measure** Mortality **Secondary measures** All-cause mortality Dysplasia Method of assessing outcomes Hospital records **Length of follow-up** Mean 4.4 (Range 1–11 years)

continued

Results	*N*	Incidence per 100 patient years	Survival
Progression to HGD	None 5 to mild dysplasia (3 regressed, 1 lost to follow-up, 1 LGD)		**Non-ACO mortality** *Surveillance group* 25 (30/143 by 2000, 23% – 6 ischaemic heart disease, 3 other vascular disease, 5 pneumonia, 1 stomach cancer, 11 other specified cancer, 2 other non-specified cancer, 2 other)
Progression to ACO	5	0.0079	*Non-surveillance group* 104 by 2000 (28–28 ischaemic heart disease, 15 other vascular disease, 19 pneumonia, 2 stomach cancer, 20 other specified cancer, 12 other non-specified cancer, 7 other) **ACO mortality** *Surveillance group* 2 (3/142 by 2000) *Non-surveillance group* 1 **Perioperative mortality** Not stated **Treatment for ACO or HGD?** Not stated

Methodological comments
Prospective? Yes
Consecutive patients enrolled? Not clear but likely – those fit for surgery entered onto surveillance, those not fit were monitored through hospital records, including details of illness and death from other local hospitals, GPs
Malignancies identified at initial endoscopy excluded? Yes
Malignancies identified early in follow-up excluded? Not clear
Loss to follow-up: Yes 88/143 by 1994, 135/143 by 1999. Death 27 (20%), development of serious co-morbidity 36 (27%), age and frailty 43 (32%), default from follow-up 14 (11%), moved away 13 (10%)
Statistical methods Descriptive statistics reported

General comments?
Population sample drawn from: Those with Barrett's oesophagus after endoscopic investigation for symptoms at one hospital.
Changes in practice during study? None stated

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Bani-Hani *et al*. (2000)[56] **Country** UK **Setting** Annual surveillance programme at Leeds General Infirmary **Recruitment dates** January 1984–January 1995 **Surveillance period** January 1984–January 1996 **Study design** Case series **Inclusion criteria** Confirmed diagnosis of Barrett's oesophagus **Exclusion criteria** Did not meet diagnostic criteria (*N* = 17) Lack of clinical records (*N* = 12) **Reasons for not entering surveillance:** Age >80 years (*N* = 71) Clinician did not offer surveillance (*N* = 41) Unknown (*N* = 36) Died before follow-up (*N* = 22) Failed to attend follow-up (*N* = 13) Not fit for surgery (*N* = 10) Other malignancies or other major disease (*N* = 9) Moved away (*N* = 3) Short segment (*N* = 3) Age <10 years (*N* = 1)	**Total number of patients** 597 with Barrett's oesophagus diagnosis 357 entered surveillance **Reason for initial endoscopy** Not stated **Patient characteristics** **Definition of Barrett's oesophagus** Presence of columnar epithelium for ≥ 3 cm above GOJ or SIM anywhere within tubular oesophagus **Average length of Barrett's oesophagus** Males 6.2 (2–20) cm Females 5.9 (2–17) cm Subgroups? **Concomitant illness** Not stated **Dysplasia at initial biopsy** 24 ACO at initial biopsy 7 ACO within 6 months	**Diagnostic methods** No mandatory biopsy protocol. No use of vital staining or other techniques **Treatment** Not stated **Surveillance protocol** No standardised protocol: recommendation to clinicians that patients fit for surgery should be considered for yearly surveillance	**Primary outcome measure** Progression to ACO **Secondary measures** Comparison of incidence rate in Barrett's oesophagus patients with cancer registry data for Leeds **Method of assessing outcomes** Retrospective review of surveillance programme **Length of follow-up** (*N* = 357 surveillance) 1207 surveillance endoscopies Mean 43 months 1293 patient years

continued

Results	*N*	Incidence per 100 patient years	Survival
Progression to HGD			**Non-ACO mortality**
Not stated			Not stated
Progression to ACO	12	~0.93 (1/108)	**ACO mortality**
Males	11	~1.45 (1/69)	Not stated
Females	1	~0.19 (1/537)	
			Perioperative mortality
Size of risk in comparison with general population			Not stated
			Treatment for ACO or HGD?
Males ×128			10/12 ACO patients oesophagectomy
Females ×25			(5 Stage I, 3 Stage II and 2 Stage III)
			2/12 unresectable

Methodological comments

Prospective? No

Consecutive patients enrolled? Yes – all patients with Barrett's oesophagus diagnosis

Malignancies identified at initial endoscopy excluded? Yes, 24 initial ACO excluded

Malignancies identified early in follow-up excluded? Yes, 7 ACO within 6 months excluded

Loss to follow-up: 85 patients left owing to death, age or co-morbidity, 96 missed periods of follow-up for non-medical reasons

Statistical methods: Descriptive. Kaplan–Meier survival analysis for ACO incidence

General comments

Population sample drawn from: Records of those with Barrett's oesophagus diagnosis at Leeds Royal infirmary. Referral for surveillance at individual clinicians' discretion

Changes in practice during study? Not known – no protocol

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Ferraris *et al*. (1997)[55] **Country** Italy **Setting** Multicentre study in upper GI endoscopy clinics **Recruitment dates** November 1987–June 1995 **Surveillance period** November 1987–April 1996 **Study design** Case series **Inclusion criteria** Histologically proven Barrett's oesophagus Age <75 years No invasive cancer No co-morbid life-threatening disease Geographic accessibility **Exclusion criteria** ACO at first follow-up	**Total number of patients** 344 eligible for surveillance 187 complied with follow-up (i.e. minimum 1year data) **Reason for initial endoscopy** Not stated **Patient characteristics** **Definition of Barrett's oesophagus** Endoscopic evidence of red gastric-like mucosa ≥ 3 cm between GOJ and Z-line. Histological confirmation of SIM, gastric fundic or gastric junctional epithelium **Average length of Barrett's oesophagus** Not stated **Subgroups?** Not stated **Concomitant illness** Not stated **Dysplasia at initial biopsy** (Surveillance *N* = 187) LGD 5 (2.7%) HGD 0	**Diagnostic methods** ≥ 4 biopsy samples every 2cm from GOJ. Biopsy from proximal fundic mucosa of stomach taken as a control sample. Haematoxylin–eosin and high iron diamine/Alcian blue staining Histological classification (Paull *et al*.) of Barrett's as intestinal specialised, gastric fundic or gastric junctional type. Dysplasia classified as negative, indefinite, LGD and HGD Slide sessions held prior to study to minimise interobserver variability. All biopsies evaluated at one pathology unit **Treatment** GORD treated with H_2 blockers or omeprazole by GP or gastroenterology clinic. 10 surveillance patients had a surgical anti-reflux procedure **Surveillance protocol** Endoscopic and histological follow-up at 1-yearly intervals	**Primary outcome measure** Incidence of ACO **Secondary measures** Clinical outcomes for 3 patients developing ACO **Method of assessing outcomes** Annual endoscopic and histological follow-up **Length of follow-up** (Surveillance *N* = 187) Median 3 (1–7.5) years Total 562 patient years

Results	*N*	Incidence per 100 patient years	Survival
Progression to HGD *NB: both progress to ACO* From status on entry: No dysplasia (*n* = 182?) LGD (*n* = 5)	2 1 1	During follow-up, (therefore years not stated)	**Non-ACO mortality** 1/3 ACO patients died of pancreatic cancer **ACO mortality** 0/3 ACO patients
Progression to ACO *From status on entry:* No dysplasia (*n* = 182?) LGD (*n* = 5)	3 2 1	0.53 (1/187)	**Perioperative mortality** Not stated **Treatment for ACO or HGD?** 2 ACO patients photodynamic laser ablation owing to poor general condition 1 radical oesophagectomy

Methodological comments
Prospective? Yes
Consecutive patients enrolled? Not stated
Malignancies identified at initial endoscopy excluded? Yes
Malignancies identified early in follow-up excluded? Yes, within 1 year of initial endoscopy
Loss to follow-up: 157/344 (46%) did not comply with follow-up
Statistical methods: Incidence of ACO calculated as ratio between *n* cancers detected and sum of follow-up for all patients with ≥ 1 follow up

General comments?
Population sample drawn from: Upper GI endoscopy clinic patients
Changes in practice during study? Not stated (Note: inconsistency in numbers eligible for surveillance from previously reported data – Bonelli *et al*. 1993)[140]

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Hillman *et al*. (2003)[54] **Country** Australia **Setting** Community-based gastroenterology clinics **Recruitment dates** January 1981–July 2001 **Surveillance period** Not specified **Study design** Case series **Inclusion criteria** Diagnosis of Barrett's oesophagus (SSBE or LSBE) At least one initial and one follow-up endoscopy **Exclusion criteria** ACO initially or <2 months HGD with immediate oesophagectomy Not suitable for surveillance (age/co-morbidity) Single endoscopy only (failed to return or recently diagnosed)	**Total number of patients** 433 Barrett's oesophagus diagnosis: 353 entered surveillance **Reason for initial endoscopy** Not stated **Patient characteristics** 249 (71%) male Mean age 59.2 (18–89) years **Definition of Barrett's oesophagus** Biopsy confirming SIM on at least one occasion and: SSBE <3 cm^2 segment of macroscopic Barrett's oesophagus LSBE >3 cm segment **Average length of Barrett's oesophagus** Not stated **Subgroups** Macroscopic markers at diagnosis: Severe oesophagitis Barrett's ulcer (within Barrett's oesophagus segment) Nodularity Stricture **Concomitant illness** Not stated **Dysplasia at initial biopsy** *Excluded patients* (n = *80*) HGD 1 ACO 17 ACO within 2 months: 2 *Surveillance* (n = *353*) LGD 56 (15.9%) HGD 3 (0.8%)	**Diagnostic methods** Oesophagitis graded using Savary–Miller/Los Angeles classification. Ulceration 'severe' if extending over more than 1 mucosal fold. Quadrantic biopsies from every 2 cm of Barrett's oesophagus segment. Biopsies from areas of nodularity and stricture Haematoxylin–eosin, Alcian blue and Giemsa staining. Presence of LGD/HGD evaluated by 2 independent pathologists **Treatment** GORD: 27 patients treated with anti-reflux surgery PPIs introduced from 1989 **Surveillance protocol** Annual surveillance. Severe oesophagitis 3–6 monthly review	**Primary outcome measure** Progression to ACO **Secondary measures** Progression to HGD/LGD **Method of assessing outcomes** Follow-up of surveillance records. **Length of follow-up** Median 42 months (3.5 years) (range 1–245 years) Total 19,056 patient months (1588 patient years) **Total 1465 endoscopies** Median 3 (1–40) per patient

continued

Results (*N* = 353)	***N***	**Incidence per 100 patient years**	**Survival**
Progression to HGD	4	0.25 (1/397 years)	**Non-ACO mortality**
From status on entry:			1/9 ACO patients
No dysplasia (*N* = 294)	3		1/4 HGD patients
LGD (*N* = 56)	1		
			ACO mortality
Progression to ACO	9	0.57 (1/176 years)	0/9 ACO patients
From status on entry:			Perioperative mortality
No dysplasia (*N* = 294)	3		
LGD (*N* = 56)	4		0/7 oesophagectomies
HGD (*N* = 3)	2		Treatment for ACO or HGD?
			ACO (n = 9) 7 oesophagectomy 1 photodynamic therapy 1 did not return for assessment
			HGD (n = 4) 2 oesophagectomy 1 anti-reflux surgery 1 died unrelated illness

Additional analysis: Cox proportional hazards

Likelihood of developing LGD
1 macroscopic marker vs no markers: HR 4.4 (95% CI 2.4 to 8.1)
≥ =2 macroscopic markers vs no markers: HR 3.0 (95% CI 1.0 to 8.8) (2 marker group small size and short follow-up)[a]

Likelihood of developing HGD/ACO
1 macroscopic marker vs no markers: HR 6.7 (95% CI 1.3 to 35)
≥ 2 macroscopic markers vs no markers: HR 14.1 (95% CI 2.0 to 102)

5-year LGD-free survival
No markers 92%[a]
1 marker 66%[a]
≥ 2 markers 70%[a]

10-year LGD-free survival
No markers 90%[a]
1 marker 54%[a]
≥ 2 markers 70%[a]

5-year ACO-free survival
No markers 99%[a]
1 marker 95%[a]
≥ 2 markers 92%[a]

10-year HGD/ACO-free survival
No markers 98%[a]
1 marker 92%[a]
≥ 2 markers 70%[a]

Methodological comments

Prospective? 220 patients evaluated retrospectively, 213 prospectively from May 1996
Consecutive patients enrolled? Not stated
Malignancies identified at initial endoscopy excluded? Yes, ACO at initial endoscopy
Malignancies identified early in follow-up excluded? Yes, ACO <2 months
Loss to follow-up: Unclear – 21 failed to return for surveillance after initial endoscopy
Statistical methods
Predictive value of macroscopic markers for progression to LGD and HGD/ACO assessed using Kaplan–Meier survival curves and Cox proportional hazards regression to adjust for age and sex
Patients with dysplasia at initial diagnosis excluded from survival analysis but included in text/tables

General comments

- *Population sample drawn from:* Community-based gastroenterology surveillance
- *Changes in practice during study?*

HR, hazard ratio.
[a] Extracted from Kaplan–Meier curves.

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Hurschler *et al.* (2003)[59] **Country** Switzerland **Setting** Oesophageal biopsies registered at St Gallen Institute of Pathology **Recruitment dates** 1989–9 **Surveillance period** Not specified **Study design** Registry case series **Inclusion criteria** Diagnosis of Barrett's oesophagus **Exclusion criteria** No diagnosis of Barrett's oesophagus Cardiac or fundic mucosa Squamous cell carcinomas	**Total number of patients** 842 of 3659 biopsy patients (742 Barrett's oesophagus (BE), 100 ACO) **Reason for initial endoscopy** Not stated **Patient characteristics** *Barrett's oesophagus (no ACO)* 65% male, 35% female. Mean age 64.4 (17–90) years *ACO* 78% male, 22% female. Mean age 67.6 (36–92) years. Ethnicity not stated **Definition of Barrett's oesophagus** Not stated **Average length of Barrett's oesophagus** Not stated **Subgroups** (A) 635 follow-up ≤ 1 year (B) 207 follow-up ≥ 1 year 6 subcategories: GERD (no BE initially) BE with SIM HistoSIM (no endoscopic specification of BE) EndoBE (no histological confirmation of SIM) Dysplasia (ID LGD HGD) ACO **Concomitant illness** Not stated **Dysplasia at initial biopsy** *Group A* ACO non-BE 56 (8.8%) Barrett's oesophagus present (n = 579): Dysplasia 36 (6.2%) ID 9 (1.6%) LGD 22 (3.8%) HGD 5 (0.9%) ACO 34 (~5.9%) *Group B* Dysplasia 19 (9.2%) ID 4 (1.9%) LGD 13 (6.3%) HGD 2 (1.0%) ACO 0 (0%)	**Diagnostic methods** 80% of biopsies followed 4-quadrant 2-cm protocol *Staining techniques:* Haematoxylin–eosin or periodic acid–Schiff (before 1994), Alcian blue–periodic acid–Schiff or van Gieson (from 1994). Biopsies with diagnosis of dyplasia reviewed by pathologist **Treatment** Not stated **Surveillance protocol** No standardised protocol ≤ 3-year interval between biopsies judged 'adequate'	**Primary outcome measure** Progression to ACO **Secondary measures** Incidence rates of Barrett's oesophagus, dysplasia and ACO in eastern Switzerland Rates of diagnosis of Barrett's oesophagus and ACO **Method of assessing outcomes** Comparison with Cancer Registry data **Length of follow-up** Mean 1.6 (1–11) years Group B mean 4.6 (1–11) years, total 966 patient years

continued

Results (Group B, *N* = 207)	***N***	**Incidence per 100 patient years**	**Survival**
Progression to HGD	3	0.3	**Non-ACO mortality**
From BE with SIM (*N* = 55)	2	Length of follow-up	**ACO mortality**
From EndoBE (*N* = 46)	1		Unclear: 4/6 ACO patients followed for >4 years died, but cause not reported
Progression to ACO	10	1.0	
From GERD (*N* = 67)	3		**Perioperative mortality**
From EndoBE (*N* = 46)	2	Length of follow-up	Not stated
From ID (*N* = 4)	2	not stated	
From LGD (*N* = 13)	1		**Treatment for ACO or HGD?**
From HGD (*N* = 2)	2		Not stated
Relative risk of ACO			
BE (*N* = 786) vs no evidence of BE (*N* = 2873)			
OR 2.97 (95% CI 2.0-4.4)			
Dysplastic changes vs no evidence of BE			
(*N* not stated)			
OR 4.4 (95% CI 2.2 to 8.8)			

Additional analysis of incidence
Barrett's oesophagus
1989–3: 8.5/10^5/year (95% CI 7.4 to 9.7)
1994–8: 15.5/10^5/year (95% CI 14.0 to 17.0)

ACO (Cancer Registry data)
1988–2: 1.24/10^5/year
1993–7: 1.78/10^5/year

Methodological comments
Prospective? No
Consecutive patients enrolled? Not stated
Malignancies identified at initial endoscopy excluded? Yes, excluded from group B
Malignancies identified early in follow-up excluded? Not stated
Loss to follow-up: Not stated
Statistical methods: Linear regression analysis of incidence data for Barrett's oesophagus and ACO, 1989 data as baseline
Incidence rates calculated for two 5-year intervals using newly identified cases/10^5 inhabitants/year (age adjusted and standardised for European Standard Population)
Relative risk calculated using χ^2

General comments
Population sample drawn from: All oesophageal biopsies in St Gallen Institute of Pathology during study period
Changes in practice during study? Yes, staining techniques changed in 1994, and surveillance intervals decreased during the study period.

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Murray *et al.* (2003)[53] **Country** Northern Ireland **Setting** Regional registry **Recruitment dates** January 1993–December 1999 **Surveillance period** January 1993–December 2000 **Study design** Registry case series **Inclusion criteria** All adult patients in Northern Ireland cancer registry with identified oesophageal columnar epithelium **Exclusion criteria** Malignancy at initial biopsy and within 6 months of initial biopsy, biopsies taken at oesophageal junction (10,715 biopsies excluded)	**Total number of patients** 15,670 biopsies 2969 Barrett's oesophagus (4955 biopsies) **Reason for initial endoscopy** Not stated **Patient characteristics** 1701 (57.3%) male; 1268 (42.7%) female. Age and ethnicity not stated **Definition of Barrett's oesophagus** Presence of columnar metaplasia **Average length of Barrett's oesophagus** Not stated **Subgroups** SIM present/absent Macroscopic Barrett's oesophagus (Barrett's mucosa present) **Concomitant illness** Not stated **Dysplasia at initial biopsy** LGD 171 (5.8%) HGD 19 (0.6%)	**Diagnostic methods** Not stated **Treatment** Not stated **Surveillance protocol** Routine clinical practice, therefore no specific protocol	**Primary outcome measure** Progression to ACO or histologically unspecified carcinoma/malignancy **Secondary measures** Not stated **Method of assessing outcomes** Matching identified patients with death records and Northern Ireland cancer registry database of incident cancers **Length of follow-up** Mean 3.7 (1–8 years) Total 11,068 patient years

Results (*N* = 2969)	*N*	Incidence per 100 patient years (95% CI)	Survival
Progression to HGD Not stated			**Non-ACO mortality** Not stated
Progression to ACO	29	0.26 (0.18 to 0.38)	**ACO mortality** Not stated
Men (*N* = 1701)	22	0.35 (0.21 to 0.52)	
Women (*N* = 1268)	7	0.14 (0.06 to 0.30)	**Perioperative mortality** Not stated
SIM present (*N* = 1670)	26	0.40 (0.26 to 0.59)	
Macroscopic (*N* = 1929)	22	0.29 (0.18 to 0.44)	**Treatment for ACO or HGD?** 4 patients oesophagectomy for HGD 2 laser ablation reason not stated
HGD (*N* = 19)	3	4.69 (0.97 to 13.7)	
Mild dysplasia (*N* = 171)	7	1.08 (0.43 to 2.23)	

Methodological comments
Prospective? No
Consecutive patients enrolled? Not stated
Malignancies identified at initial endoscopy excluded? Yes
Malignancies identified early in follow-up excluded? Yes, within 6 months initial biopsy
Loss to follow-up: Not stated
Statistical methods: Person years of follow-up calculated until diagnosis of malignancy, death or 31 December 2000
95% CIs estimated from Poisson distribution

General comments
Population sample drawn from: All oesophageal biopsies in Northern Ireland during study period
Changes in practice during study? Not stated – no specific biopsy protocol as data from routine clinical practice

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Reid *et al*. (2000)[58] **Country** USA **Setting** Seattle Barrett's oesophagus project **Recruitment dates** July 1983–June 1998 **Surveillance period** Not specified **Study design** Case series **Inclusion criteria** Metaplastic columnar epithelium present No history of oesophageal malignancy Baseline and ≥ 1 follow-up endoscopy **Exclusion criteria** Not stated	**Total number of patients** 327 Barrett's oesophagus patients (322 with baseline histology and flow cytometry) **Reason for initial endoscopy** Not stated **Patient characteristics** 265 (81.0%) male, 62 (9.0%) female Median age 62 (22–83) years. **Definition of Barrett's oesophagus** Presence of metaplastic columnar epithelium **Average length of Barrett's oesophagus** Not stated **Subgroups** Dysplasia at baseline: Negative (n = 129) Indefinite (n = 79) LGD (n = 43) HGD (n = 76) **Concomitant illness** Not stated **Dysplasia at initial biopsy** LGD 43 (13.1%) HGD 76 (23.2%)	**Diagnostic methods** Quadrantic biopsies with jumbo forceps ≥ 2-cm intervals (1985–1998). After 1992, 1-cm intervals if previous HGD. Multiple biopsies of endoscopic abnormalities. Histological analysis by single observer blinded to flow cytometric results Classified at highest level of abnormality present (negative, ID, LGD, HGD, cancer) Flow cytometry interpreted by single observer blinded to histological results. Anueploidy diagnosed if 2 discrete peaks observed on histogram, and aneuploid peak represented at least 2.5% of cells in the biopsy specimen. 4N fractions >6% classified as abnormal **Treatment** HGD patients informed of alternatives to surveillance, including surgery **Surveillance protocol** Not stated; however, median surveillance intervals reported: Negative 24.4 months ID 18.2 months LGD 15.7 months HGD 4.6 months Patients counselled about risks and benefits of surveillance and told alternatives	**Primary outcome measure** Progression to ACO **Secondary measures** Cumulative incidence of ACO **Method of assessing outcomes** Follow-up endoscopy with histological and flow cytometric analysis **Length of follow-up** Reported only for patients without cancer at last contact (N = 285): Median 2.4 years Mean 3.9 years Range 17 days–13 years Total 1200 patient years

Results (N = 327)	N	Incidence per 100 patient years	Survival
Progression to HGD Not stated	35	Within 5 years	**Non-ACO mortality** Not stated
Progression to ACO From negative (N = 129) From indefinite (N = 79) From LGD (N = 43) From HGD (N = 76)	42 5 1 3 33	Total follow-up not stated	**ACO mortality** Not stated **Perioperative mortality** Not stated **Treatment for ACO or HGD?** Not stated

continued

Additional analysis: 5-year cumulative cancer incidence
Negative ID LGD (combined for analysis) 3.8% (95% CI 1.6 to 9.0)
HGD 59% (95% CI 44 to 74)

RR risk of ACO in HGD vs negative/ID/LGD combined
RR 28 (95% CI 13 to 63) $p < 0.001$

Methodological comments
Prospective? Yes
Consecutive patients enrolled? Not stated
Malignancies identified at initial endoscopy excluded? Not stated
Malignancies identified early in follow-up excluded? Not stated
Loss to follow-up: Not stated
Statistical methods:
Kaplan–Meier curves used for cumulative cancer incidence, 95% CIs based on Greenwood standard error estimates or exact binomial confidence limits for groups without cancer incidence. Censored at time of last endoscopic follow-up.
RR calculated using Cox proportional hazards. Group comparison *p*-values based on Wald test.
χ^2 for comparison of proportions other than disease outcome

General comments
Population sample drawn from: Not stated
Changes in practice during study? Biopsy protocol changed after 1992, with introduction of 1-m quadrantic biopsies for HGD

RR, relative risk.

Reference and design	Subjects	Surveillance programme	Outcome measures
Authors Schnell (2001)[57] **Country** Illinois, USA **Setting** Outpatient endoscopy clinic (Veterans Affairs Hospital) **Recruitment dates** January 1979–July 1996 **Surveillance period** Jan 1979–June 2000 **Study design** Case series **Inclusion criteria** Not stated **Exclusion criteria** Not stated	**Total number of patients** 1125: 1099 Barrett's oesophagus, 26 non-Barrett's cancer of GOJ **Reason for initial endoscopy** Not stated **Patient characteristics** Only reported for subset of 75 HGD patients undergoing surveillance *12 progressed to ACO* 100% male, mean age 60 (SD 9) years, 100% white *63 remained HGD* 98% male, mean age 64 (SD 9) years, 98% white **Definition of Barrett's oesophagus** Presence of intestinal metaplastic epithelium in oesophagus or GOJ **Average length Barrett's oesophagus** Not stated **Subgroups** *Prevalent HGD/ACO* Diagnosed at initial biopsy or within 12 months *Incident HGD/ACO* Diagnosed >12 months after initial biopsy **Concomitant illness** Not stated **Dysplasia at initial biopsy** (% 1099 Barrett's oesophagus patients) **LGD not stated** Prevalent HGD 34 (3.1%) Prevalent ACO 42 (3.8%)	**Diagnostic methods** Standard 2.8-mm forceps Minimum 2 specimens if segment ≤ 1 m; minimum of 4 per segment if ≥2 months Hematoxylin–eosin staining Joint examination of specimen by endoscopist and pathologist **Treatment** *Severe oesophagitis* 3 months with H_2 blockers/PPIs *HGD* Given option of close follow-up/oesophagectomy *ACO* Surgery **Surveillance protocol** No dysplasia: 3-year interval LGD: repeat at 1 year, then at 2–3 year if no HGD HGD: every 3 months for 1 year; if no HGD on 2 consecutive endoscopies, every 6 months for 1 year; then every 12 months until HGD again noted If persistent HGD on 4 × 3-monthly biopsies, patient-led: continue 3-monthly or at 6–12 months, 2–3 years or cessation.	**Primary outcome measure** Progression to ACO **Secondary measures** Survival time until cancer Survival time until death **Method of assessing outcomes** Not clear **Length of follow-up** 75 HGD surveillance patients: mean 7.3 years (0.5–12.3 years) ~548 patient years

continued

Results (*N* = 1125)	***N***	**Incidence per 100 patient years**	**Survival**
Progression to HGD Not stated		Length of follow-up only reported for 75 HGD surveillance	Mortality data only reported for 75 HGD patients **Non-ACO mortality** 18/63 patients without cancer 2/12 patients with cancer
Progression to ACO From initial status: LGD (*N* not stated) HGD >12 months (*N* = 75) HGD <12 months (*N* = 79)	 10 12 4	 ~ 1.8	**ACO mortality** 1/12 unresectable **Perioperative mortality** 0/9 patients treated by resection
Highest level of dysplasia at most recent endoscopy Barrett's no dysplasia LGD HGD no progression (Prevalent ACO) (Prevalent cancer GOJ)	 230 738 63 (42) (26)		**Treatment for ACO or HGD?** *ACO* (*n* = 12) 9 resection 1 unresectable 1 electrocoagulation 1 refused treatment
Additional multivariate analysis: No variables exerted significant influence on survival time until cancer Age and smoking affected survival time until death ($p = 0.02$) Length of Barrett's oesophagus segment affected occurrence of ACO ($p < 0.001$)			**Survival rates (*N* = 75 HGD patients)** Taken from Kaplan–Meier curves *5-year survival* With cancer 100% Without cancer 98% *Survival at cut-off (8 years)* With cancer 90% Without cancer 91% **Survival time until cancer [mean (SD)]** Incident ACO: 5.7 (4.4) years **Survival time until death** Incident ACO: 10.1 (4.2) years HGD no progression: 12.3 (4.3) years
Methodological comments *Prospective?* Yes *Consecutive patients enrolled?* Not stated *Malignancies identified at initial endoscopy excluded?* Yes, excluded prevalent ACO or cancer of GOJ *Malignancies identified early in follow-up excluded?* Yes, 4 'unsuspected ACO' within 12 months *Loss to follow-up:* Not stated *Statistical methods:* Length of follow-up calculated from first endoscopy to most recent endoscopy/clinical evaluation, or occurrence of ACO or death χ^2 to compare ACO and HGD subjects, continuous variables compared with Student's *t*-test, 95% CI from exact binomial distribution Multivariate logistic regression for predictors of ACO, ORs (95% CI) for strength of predictors (NB: these were not reported in *Table 4* or text), significance levels with *t*-test Kaplan–Meier survival curves for death and time free of ACO, log-rank to compare survival. Cox proportional hazards to investigate the influence of predictor variables on survival Inconsistency in reporting of mortality rates: *Table 3* reports 32% death for incident ACO but text reports 3/12 (25%) **General comments** Population sample drawn from: Veterans Hospital Changes in practice during study? Yes, follow-up criteria modified during study and treatment of oesophagitis changed from H_2 blockers to PPIs			
SD, standard deviation.			

Appendix 6

List of workshop attendees

Workshop attendees:

12 Consultant gastroenterologists
8 Epidemiologists
5 Consultant pathologists
4 Patient representatives
2 Surgeons
1 Primary care specialist
1 Cancer specialist
1 Health economist
1 Observer from the HTA programme

Appendix 7

Workshop programme

Programme
HTA 03/49 Surveillance for Barrett's oesophagus workshop
24 May 2004 Senate House

9.45 REGISTRATION

10:00 Introduction from the Chair
➢ *Dr Robert Heading, Edinburgh*

10:15 Outline of the PenTAG project
➢ *Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School*

10:25 Perspectives from service users
➢ *Mr Robin Thomas and Mr Jonathan Turnbull, Barrett's Oesophagus Foundation*

Presentations summarising four key areas of uncertainty:

10:45 (1) Definition, natural history, epidemiology and prognosis
➢ *Professor Julian Little, Professor of Epidemiology, University of Aberdeen*

11:00 (2) Diagnostic methods and sampling
➢ *Dr Laurence Lovat, Consultant Gastroenterologist and Senior Lecturer in Laser Medicine, University College Hospital, London*

11:15 COFFEE BREAK

11:30 (3) Treatment of Barrett's oesophagus and adenocarcinoma
➢ *Professor Janusz Jankowski, Professor of Medicine, Gastroenterology and Academic Head, University Dept of Cancer Studies and Molecular Medicine, Leicester*

11:45 (4) Potential impact of surveillance programmes
➢ *Professor Raymond Playford, Professor and Head of Department of Gastroenterology, Imperial College School of Medicine, London*

12:00 Small group discussion – four groups on each of the key areas of uncertainty

1:00 LUNCH

2:00 Small group feedback and plenary discussion

3.00 COFFEE BREAK

3:30 Chair and PenTAG feedback of results

4:00 Close

Appendix 8

Workshop small group participants

Impact of surveillance – facilitated by Naomi Gilbert (PenTAG)

3 Gastroenterologists, 1 surgeon, 1 primary care specialist,1 patient representative, 1 HTA programme observer.

Treatment – facilitated by Margaret Somerville (PenTAG)

3 Gastroenterologists, 2 patients' representatives, 1 surgeon.

Diagnostics – facilitated by Ruth Garside (PenTAG)

3 Pathologists, 2 gastroenterologists, 1 health economist.

Epidemiology – facilitated by Ken Stein (PenTAG)

6 Epidemiologists, 1 gastroenterologist, 1 patient representative.

Appendix 9

Evaluation comments for the workshop

1. Were the aims of the workshop clear?

Very	4	Quite	9	Neutral	0
Not very	1	Not at all	0		

Comments:
In advance of the workshop, aims seemed clear, but themes that emerged suggested that a better focus might have been preventive strategies for AE.

I feel we would benefit from another update in 6 months and maybe another workshop.

It might have been better to make the aims clear before we arrived. As the day developed I got a much clearer idea as to aims.

I was not really clear about the ulterior aims for this workshop. The small groups came up with very diffuse objectives for further research and would have benefited but much more focused thinking. Also while it was very useful to have the input of patients and their comments, their views on research were generally rather unhelpful in specifics.

As a non-medical person, I probably didn't have a very specific understanding of the aims, but as we got into the workshop, the aims became clearer.

It wasn't clear (to me) until the small group sessions that the focus was very restricted to surveillance. There are much wider contextual questions relating to epidemiology of Barrett's and risk of ACO that need to be addressed at the same time as surveillance.

2. How well do you think the workshop met its aims?

Very	4	Quite	8	Neutral	2
Not very	0	Not at all	0		

Comments:
Doctors had very different views – we need more constructive meeting and research.

Again to my view the conclusions could have been more focused by more direction. If the main speakers had provided two key areas each which could have informed focused discussion this would have been more helpful.

At one level, it achieved its aims as it produced a list of key points, but I do have the feeling that issues were not thrashed out as deeply as they could have been if the layout (syndicates, plenary) had been better. I realise that the facilities were limited and that by having it in London, you probably included some people who might not have travelled to the SW.

3. How useful were the speakers in the morning?

Very	6	Quite	5	Neutral	2
Not very	0	Not at all	0		

Comments:
I was unhappy about XXXX's presentation. The others were good. Some speakers brought with them their particular biases and didn't give a balanced view of the literature, especially XXXX.

Enjoyable and polished presentations.

Very necessary – but not sure how well they understood the aims, i.e. to focus on critical areas.

Some variation in knowledge of the subject.

Some provocative talks, some less stimulating.

I exclude myself from this assessment! The medical contributors were excellent, explaining things clearly and communicating well with the audience. Even as a non-medical person, I was able to follow the key points. PowerPoint worked well and we didn't suffer death by PowerPoint.

4. In which small group did you participate?

(1 comment – not applicable)

Impact of surveillance [1] Diagnostics [5]

Treatment [3] Epidemiology, natural history, etc. [5]

5. How easy did you find it to ensure your view was heard in small group work?

Very [4] Quite [7] Neutral [0]

Not very [1] Not at all [0]

Comments:
Very useful to talk to clinicians and pathologists from other centres who face similar problems.

Having all the groups in one room was not helpful and noise from other groups interfered with my ability to hear what was being said in my group. It took time to get people involved and some people did not say very much, and yet they would have had useful contributions to make. This does not imply criticism of the group leader. It needed a better environment, possibly a smaller group.

Quite easy, well facilitated but I felt constrained from examining the relevant issues beyond surveillance.

I felt I was heard but not listened to in terms of the bigger picture re treatment.

6. Were you happy with the list of key questions produced by your group?

Very [2] Quite [8] Neutral [1]

Not very [2] Not at all [0]

Comments:
Again, it wasn't very clear before the meeting what the aims were and I wasn't sure whether treatment was aimed at pre-malignant Barrett's with high-grade dysplasia or established cancer. There are issues in all of these … the agenda wasn't clear to me. A more focused group discussion with pre-designated limits could have been more productive.

After a bit of a slow start, when I think some people seemed a bit reticent, the key points did emerge. The leader pushed well and the pressure of time helped to concentrate minds. With such key topics, ideally one needs more time to get groups to open up and thrash things out. I just had the slight feeling that people held back on debate in order to meet the time objective. However, I know that time is always a problem.

7. How useful did you find the final plenary session?

Very [2] Quite [10] Neutral [2]

Not very [0] Not at all [0]

Comments:
It could have been better focused.

More time to consider and collate the small groups' responses.

We could have debated the key questions more critically if we had had the full list in front of us. This was informative – the extent of common thinking was apparent.

At least some general conclusions were drawn but I was left feeling that we were just rubber-stamping some pre-decided conclusions!

The layout of the room did not favour good communications. Ideally, it should have been in a circular or similar formation. As it was, some contributors could not be heard. I don't think the level of participation was as high as I would have expected.

There was discussion afterwards about the question about an RCT of surveillance being from left field. I know that it would be difficult to do such a trial but will current practice ever be changed unless this type of evidence for or against surveillance is provided?

8. Please rate the venue

Excellent [2] Good [9] Neutral [0]

Poor [1] Very poor [0]

Comments:
Sorry to be negative, but the acoustics were not good.

Very easy to get to; size appropriate for the numbers.

I enjoyed the day – my form is not of much use to you as I hopped between the small groups and cannot really comment on them.

Overall a very prestigious and convenient venue, but as I have said, the room was not good for syndicate groups and the plenary session and did not encourage participation and good communications.

Additional comments

People coming from outside London probably had a very early start to attend the meeting. I may be being over-sensitive about this as I had to help with a neighbour who had a heart attack the night before the meeting, and I had to leave home at 5.00 am, so felt rather flat!

I hope the group will be successful in getting HTA to develop a clearly focused research question. The last time round it was too broad and too vague.

I enjoyed the day and found it useful.

Please invite me again. Thank you.

I will be very interested to see the document generated.

An excellent day out … and I do not mean that in any frivolous sense. Very useful discussion of the difficulties we face in this field, and a chastening reminder of how little we really know about how to deal with Barrett's oesophagus. I thought the strong support for an RCT in this area was telling. I absolutely agree that it is far from easy to know what the right trial is, and that there would be ethical problems, but the absence of RCT data in the field is remarkable.

I was delighted to be invited and found it very useful in my patient rep. role.

I was delighted to be invited along. I felt I and other patient reps had a great deal to offer. I felt some of the medical representatives were totally dismissive/discounting of any theories pertaining to Barrett's. I am concerned that the object of the exercise was merely a 'going through the motions' when the final outcome was decided before the meeting! This is about cost-cutting and restricting a surveillance programme to particular age groups. This is on the increase amongst many younger age groups and in the long term will be a false economy to limit surveillance. In my book prevention/early management is the way forward. To do this need not be costly. For example, patient history questionnaires supported by an endoscopy, placed on a database, may actually reveal a pattern of this dreadful condition evolving. It would also highlight the widening age group affected. One of the patient reps was 34! I was 35 when I was diagnosed. Treatment/surveillance was very much based at the workshop on what was already known, which I accept was partly the object of the exercise. To me though, it feels like we are shutting a door after the horse has bolted, instead of more preventative measures as I have previously addressed. Finally, I would like to say that I left feeling pretty demoralised, having attended with a lot of hope and ideas I felt may have had an impact for the future – maybe not myself, but others. I feel strongly that we need to explore possible causation factors before we can embark on a treatment programme! Thank you for inviting me and for asking my views subsequently.

Appendix 10

Quality assessment of previously published cost–utility analyses

Inadomi and colleagues (2003)[30]

Structure	
Is there a clear statement of the decision problem, the context and the perspective?	The model aims to determine the costs and consequences of: (1) screening patients with GORD compared with subsequent surveillance and (2) surveillance of Barrett's oesophagus (including those with dysplasia) in the USA. An incremental cost-effectiveness analysis is used to estimate additional costs and benefits of surveillance compared with no surveillance
Is a theory of the underlying disease detailed?	Little background information is provided about GORD, Barrett's oesophagus, ACO and current practice
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Assumes probability of further procedures over time follows a logarithmic distribution
Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	A simplified Markov model with seven disease states – Barrett's oesophagus, no Barrett's oesophagus, LGD, HGD, ACO, death, having surgery – is shown. Actual model claimed to have 7000 nodes but no details available Cohort of 50-year-old white men with GORD symptoms modelled.
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not directly but the states do appear to accord with the states involved in Barrett's oesophagus and treatment for ACO
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No evidence is given although the states do appear to map the progress of condition as currently understood
Have any important disease states been omitted from the model?	No
Options	
Is there a clear statement of the options being evaluated?	Yes, the model includes three scenarios; a natural history model, i.e. ACO diagnosed only if ACO was symptomatic, and screening all 50-years-olds followed by two surveillance strategies – one limited only to those with Barrett's oesophagus plus dysplasia (every 6 months for LGD and every 3 months for HGD), and one for all those with Barrett's oesophagus, those with dysplasia as for the first strategy, and those with Barrett's oesophagus every 2, 3, 4 or 5 years In addition, screening of white men at age 40 years was also considered.
Do these appear to cover the range of logical and feasible options?	No – advice for LGD surveillance may be every year, whilst HGD is every 3–6 months. In addition, the model assumes all 50-year-old men with GORD have endoscopic screening which is not the case in the UK. This will pick up a number of cases normally missed. The article concludes that the screening strategy is cost effective if surveillance is limited. In addition, all those entered into the screening and surveillance are assumed to accept surgery if they have ACO

continued

Time horizon	
Is the time horizon of the analysis stated?	Yes. The model is run for 30 years until the cohort is 80 years old or dead
If so, is this justified in terms of the underlying disease and the effect of interventions?	No. There are few, if any, data about Barrett's oesophagus progression over such a long period of time. Annual rates of progression are taken from much shorter term studies and no details are given about how the short-term data are adapted to the long-term model run.
Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated?	Model cycle is 1 year. Stated in the Appendix
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	No. It is not stated how adjustments are made for states shorter than this, such as patients having surgery. Also not clear how shorter surveillance intervals are incorporated
Data identification	
Are the sources of parameter values in the model clearly stated?	Most transition probabilities are from the literature. However, as stated above, the model runs for 30 years and most published literature is for much shorter periods of time. No statement is made about how these progressions were adjusted, if at all. However, it is stated that transitions were validated by running the model without surveillance or screening and comparing results to the published literature It is not clear how surveillance is incorporated into the model structure Where there was no available literature, author consensus was used. This is the case or estimates of diagnostic accuracy, utility for cancer state, death from unresectable cancer and annual development of Barrett's oesophagus Only two utility values are stated, for having ACO and post-oesophagectomy; one is from the literature based on TTO for patients who had had oesophagectomy (*n* not stated) Direct costs of care are estimated for the service deliverer and are US dollars. Taken from published 2001 Health Care Financing Administration
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No. Most data come from a variety of literature – no attempt to categorise the relevance or quality of the data is made. See above for attempts to validate transitions
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane library)?	Yes. MEDLINE and EMBASE were searched for relevant literature. No limits stated. No RCTs identified
Are ranges specified for parameters?	Yes
Is there evidence to suggest selective use of data?	No
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	Not applicable
Are the claims made about the model results tempered by the limitations of the data?	No
Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	No – there is mismatch between state length (such as surgery) and surveillance frequency (3 and 6 months for dysplasia) and the cycle length of 1 year and no account of how this is handled is given. Utility values are not given for all states, it is not clear how transition values have been calculated given a range of data from the referenced papers, it is unclear how diagnostic accuracy was incorporated and only a simplified model is reproduced

continued

Has a stochastic analysis been undertaken?	Uncertainty was examined by one-way sensitivity analyses – parameters varied are listed and the range used for each given. A Monte Carlo simulation was used to vary all parameters simultaneously
If so, do the distributions in parameter values reflect second order uncertainty?	Not applicable
Have appropriate distributions been selected for each parameter?	Unknown. These are not stated
Have interval rates been translated into transition probabilities using the appropriate formula?	Unknown – not stated
If appropriate, has a half cycle correction been applied to adjust time-related estimate in the model?	Unknown – not stated
Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	No statement is made about tests of internal consistency that were undertaken
External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No
Have any comparisons of the outputs of the model with independent external sources been reported?	No
If so, are the conclusions justified? Have discrepancies been investigated and explained?	Not applicable

Provenzale and colleagues (1994)[64]

Structure	
Is there a clear statement of the decision problem, the context and the perspective?	Stated aim to examine the benefit of surveillance and [o]esophagectomy in [Barrett's oesophagus] patients.
Is a theory of the underlying disease detailed?	Background is given about the relationship of GORD and Barrett's oesophagus to ACO, and professional societies' rationale for surveillance of Barrett's oesophagus
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Simulation begins 1 year after baseline endoscopy (not explained why) Progression through progressive dysplastic states. Patients with LGD surveyed every 6 months (based on current practice) In strategies 1 and 3–7 HGD surveyed every 3 months Assumes that the benefit of surveillance declines linearly over a 4–5 year period for ACO, as period from endoscopically detectable to symptomatic cancer is around 4–5 years.
Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	Markov model used (no diagram provided). States are: Barrett's oesophagus, LGD, HGD, ACO (both actual and diagnosed states), complete resection of dysplasia, complete resection of ACO, partial resection of ACO, ACO inoperable, death. Cohort of 10,000 55-year-old men
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not directly, but does accord with the disease process (progression through dysplastic states) and incorporates diagnostic error. Tests different possible regimens for HGD

continued

Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No evidence is given although the states do appear to map the progress of the condition as currently understood
Have any important disease states been omitted from the model?	No
Options	
Is there a clear statement of the options being evaluated?	Yes – 12 strategies were examined: 1. No surveillance, endoscopy for new or worsened dysphagia, oesophagectomy for ACO 2. No surveillance, endoscopy for new or worsened dysphagia, oesophagectomy for HGD 3–7. Endoscope every 1–5 years endoscopy oesophagectomy for ACO 8–12. Endoscope every 1–5 years endoscopy oesophagectomy for HGD
Do these appear to cover the range of logical and feasible options?	No alteration in the surveillance regimen for LGD or for HGD in options 1 and 3–7 is examined
Time horizon	
Is the time horizon of the analysis stated?	Indirectly – model run until whole cohort dies
If so, is this justified in terms of the underlying disease and the effect of interventions?	No. There are few if any data about Barrett's oesophagus progression over such a long period of time and it is not clear how data from studies with short-term follow-up are adapted to this time frame
Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated?	Cycle length is not stated
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	Not applicable
Data identification	
Are the sources of parameter values in the model clearly stated?	Data mostly taken from the literature. References are given in a table of inputs. Where no published data are available, expert opinion sought. However, it is not clear how single values used in the model are chosen from multiple references. Cumulative incidence of ACO in patients with Barrett's oesophagus is used – not clear how patients progress through dysplastic states. Utility value only given for one state – post-oesophagectomy (0.8 based on expert opinion, no recognised mechanism for estimating value used)
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No statement is made about data testing in earlier iterations of the model
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane library)?	MEDLINE and reference lists searched
Are ranges specified for parameters?	No
Is there evidence to suggest selective use of data?	No – rather it appears that not all data used are reported
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	No – only stated that opinion is sought
Are the claims made about the model results tempered by the limitations of the data?	Some limitations acknowledged – lack of RCT data, use of single-sex 55 year-old cohort, are described but no limitations of model structure or inputs beyond this. In particular, not acknowledged that the natural history of the illness is poorly understood

continued

Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	No statement is made about how transition data obtained from short-term follow-up studies are incorporated into this long-term model run. Cumulative incidence is an average from published studies Not clear how the diagnostic errors are accommodated in the model
Has a stochastic analysis been undertaken?	No One-way sensitivity analyses undertaken for some parameters (values not stated), two values found to be critical – extensive exploration of cumulative cancer incidence and utility value after oesophagectomy.
If so, do the distributions in parameter values reflect second order uncertainty?	Not applicable
Have appropriate distributions been selected for each parameter?	Not applicable
Have interval rates been translated into transition probabilities using the appropriate formula?	Unknown, not stated
If appropriate, has a half cycle correction been applied to adjust time-related estimate in the model?	Unknown, not stated
Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	No
External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No
Have any comparisons of the outputs of the model with independent external sources been reported?	No
If so, are the conclusions justified? Have discrepancies been investigated and explained?	Not applicable

Provenzale and colleagues (1999)[42]

Structure	
Is there a clear statement of the decision problem, the context and the perspective?	Builds on 1994 paper, incorporated updated estimates for cancer risk and results of QoL measures for patients having oesophagectomy Context is the lack of actual data on different surveillance strategies. Perspective of an HMO used
Is a theory of the underlying disease detailed?	Yes – briefly outlined in Introduction
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	All patients with LGD are surveyed every 6 months, all suitable patients with HGD receive oesophagectomy. The treatment for HGD is justified on the basis of the previous paper's results. Alterations in LGD surveillance interval are not explored The model takes account of diagnostic error though it is not specified how this occurs Assumptions are the same as 1994 model and not restated

continued

Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	A Markov model – modified from the 1994 version (not clear how). Disease states are: actual Barrett's oesophagus, LGD, HGD, ACO; biopsy diagnosed Barrett's oesophagus, LGD, HGD, ACO, no biopsy; complete resection of HGD, complete resection of ACO, partial resection of ACO, inoperable cancer, death Cohort of 10,000 55-year-old patients with Barrett's oesophagus modelled.
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not directly but states do appear to accord with states involved in Barrett's oesophagus and treatment. However, unlike the 1994 paper, only surgery for HGD is modelled – not for ACO (except in the non-surveillance arm), which does not accord with current UK practice
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No evidence is given, although the states do appear to map the progress of the condition as it is currently understood
Have any important disease states been omitted from the model?	No – the previous paper by these authors found that surgery for HGD was the preferred option. Surgery for ACO not HGD has not therefore been modelled here; however this may reduce the paper's relevance to the UK setting.
Options	
Is there a clear statement of the options being evaluated?	Yes – six scenarios are modelled: no surveillance, oesophagectomy for ACO, surveillance every 5, 4, 3, 2 or 1 year with oesophagectomy for HGD
Do these appear to cover the range of logical and feasible options?	No alteration in time period for LGD surveillance
Time horizon	
Is the time horizon of the analysis stated?	Not stated – assume that as before, the model is run until the whole cohort dies
If so, is this justified in terms of the underlying disease and the effect of interventions?	No – not discussed here
Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated?	Not stated
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	Not applicable
Data identification	
Are the sources of parameter values in the model clearly stated?	Transition data as before – re-listed – except for reduce estimates of annual cancer estimates from more recent literature Expert opinion for accuracy of diagnoses Utility measure for postoperative state was obtained using the TTO method with patients undergoing oesophagectomy at least 1 year previously (*n* not stated). Median value = 0.97 (interquartile range 0.83–1.0) Costs (not charges) from Duke University Medical Center and hospice fees in North Carolina, USA. Outpatient visit and doctors' fees adjusted as a proxy for costs
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No statements about validity testing or earlier iterations of the model are described
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane library)?	This is stated in the 1994 paper – MEDLINE search undertaken and expert opinion used where no published data available. Utility data as above – no information given about utilities for other states
Are ranges specified for parameters?	No

continued

Is there evidence to suggest selective use of data	Not clear
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	No details are provided
Are the claims made about the model results tempered by the limitations of the data?	Sensitivity analyses are undertaken to deal with acknowledge uncertainty in published data and expert opinion Further cautions about the conclusions are not undertaken in the conclusions
Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	Not clear how diagnostic uncertainty is incorporated Not clear what utility values are used for states other than post-operation A single annual transition rate is given for patients with Barrett's oesophagus to ACO – it is not clear how the patients regress through dysplastic states
Has a stochastic analysis been undertaken?	No
If so, do the distributions in parameter values reflect second order uncertainty?	Not applicable
Have appropriate distributions been selected for each parameter?	Not applicable
Have interval rates been translated into transition probabilities using the appropriate formula?	Unknown, not stated
If appropriate, has a half cycle correction been applied to adjust time-related estimate in the model?	Unknown, not stated
Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	No
External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No
Have any comparisons of the outputs of the model with independent external sources been reported?	No
If so, are the conclusions justified? Have discrepancies been investigated and explained?	Not applicable

Appendix 11

Scenarios used to assess health state utility values

Barrett's oesophagus on surveillance MILD

The following scenario was developed from a measure of severity in a particular disease. It used the following categories to describe the severity or frequency of different types of problem:

1. none at all
2. hardly any at all
3. a little
4. some
5. a moderate amount
6. a lot, or quite a lot of the time
7. a great deal, or all of the time.

- You get feelings such as discouragement or distress, frustration, anxiety, irritability, and worry about your health but these affect you hardly any of the time.
- Your sleep is disturbed hardly any of the time.
- You have hardly any problems with eating or drinking, but you may get pain after eating, have to eat small meals or not be unable to eat what you want.
- You may have to avoid bending over because of pain in your chest or belly, but hardly any of the time.
- You are kept from doing things with family and friends hardly any of the time.
- You may be unable to carry out daily activities, but hardly at all.
- You occasionally feel tired, generally unwell and lacking energy, but hardly at all.

Barrett's oesophagus on surveillance MODERATE

The following scenario was developed from a measure of severity in a particular disease. It used the following categories to describe the severity or frequency of different types of problem:

1. none at all
2. hardly any at all
3. a little
4. some
5. a moderate amount
6. a lot, or quite a lot of the time
7. a great deal, or all of the time

- You sometimes (three or four days per week) get feelings such as discouragement or distress, frustration, anxiety, worry about your health and irritability.
- Your sleep is moderately disturbed.
- You have some problems with eating or drinking, such as pain after eating, having to eat small meals or not being able to eat what you want.
- Some of the time you have to avoid bending over because of pain in your chest or belly.
- You are kept from doing things with family and friends a moderate amount.
- You have some problems carrying out daily activities.
- You feel moderately tired, generally unwell and lacking energy.

Barrett's oesophagus on surveillance SEVERE

The following scenario was developed from a measure of severity in a particular disease. It used the following categories to describe the severity or frequency of different types of problem:

1. none at all
2. hardly any at all
3. a little
4. some
5. a moderate amount
6. a lot, or quite a lot of the time
7. a great deal, or all of the time.

- Every day you get feelings such as discouragement or distress, frustration, anxiety, worry about your health and irritability.
- Your sleep is disturbed every night.
- You always have problems with eating or drinking, such as pain after eating, having to eat small meals or not being able to eat what you want.
- You always avoid bending over because of pain in your chest or belly.
- You are kept from doing things with family and friends every day.

- You have a great deal of problems carrying out daily activities.
- You feel very tired, generally unwell and lacking energy every day.

Symptomatic adenocarcinoma of the oesophagus MILD

- You have lost 5–10% of your body weight.
- You have difficulty swallowing. This is worse with some foods (e.g. bread) but you have no problems swallowing liquids. You do not choke on your food.
- Your appetite is sometimes not what is used to be.
- You feel tired, but not every day.
- You are able to carry out most of your normal activities.
- You feel slightly anxious and depressed on some days.
- You get mild pain behind your sternum (breastbone) and/or in the upper part of your belly two or three times per week.
- You get hiccoughs more frequently than is normal for you but not for long periods.
- You sometimes have a mild cough.
- Your sleep is occasionally disturbed.

Symptomatic adenocarcinoma of the oesophagus SEVERE

- You have weight loss, so that your weight is at least 20% lower than average for your height (e.g. if your normal weight was 10 stone, you weigh 8 stone or less).
- You have difficulty swallowing. Food feels as if it gets stuck and causes pain or discomfort.
- You are unable to eat all the foods you usually prefer, and sometimes have to have food blended in order to be able to swallow it. Sometimes you find it so difficult to swallow that you choke on your food.
- You have heartburn most days.
- You often feel nauseated. Your appetite is poor and you are unable to taste food normally.
- You get hiccoughs three or four times a week, sometimes lasting quite a long time.
- You get pain behind your sternum (breastbone) and/or in the upper part of your belly.
- Your voice is hoarse and your mouth is dry all the time.
- You have a mild cough.
- You are moderately anxious and depressed.
- Your sleep is sometimes disturbed by pain or anxiety.
- You feel tired and weak most of the time and are unable to carry out many of your usual activities.

Terminal adenocarcinoma of the oesophagus

- You are unable to wash or dress yourself without help and spend all your time in bed or in a chair.
- You are unable to carry out any activities requiring physical effort.
- It is extremely difficult to swallow. You are unable to eat solid foods. Drinking is difficult and you often choke on liquids. Sometimes it is difficult to swallow your saliva.
- Your appetite is extremely poor and you have lost a great deal of weight.
- You feel slightly short of breath most of the time.
- You have pains in your chest or the upper part of your belly every day.
- You have to take painkillers most days which make you tired and sometimes confused.
- You feel extremely weak and tired.
- You are always anxious and depressed and you find it difficult to sleep.

Post-oesophagectomy

- You feel full after eating a smaller meal than usual. Occasionally this may be severe. You have to eat small meals more often than usual.
- You find it difficult to swallow some foods.
- You sometimes feel dizzy and sweaty with palpitations and pains in the belly after eating which makes you lie down for up to an hour. After this you may have severe diarrhoea.
- You get heartburn about every other day, which may occasionally be severe.
- You feel bloated around twice a week.
- You feel a bit irritable quite often and rarely you are very irritable.
- Sometimes you feel worried, but mostly you do not.
- Sometimes you feel low on energy.
- You feel tired some of the time and occasionally very tired.
- You occasionally feel breathless.

Appendix 12

UK National Screening Committee criteria

Ideally, all of the following criteria for appraising the viability, effectiveness and appropriateness of a screening programme should be met before screening for a condition is initiated.

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an informed choice (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately estimates risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
14. There should be evidence that the complete screening programme (test diagnostic procedure, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care (i.e. value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

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