EUROPEAN JOURNAL OF CANCER 44 (2008) 588–599

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Surveillance of Barrett's oesophagus: Is it worthwhile?

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ARTICLE INFO

Article history:
Received 12 July 2007
Received in revised form
21 December 2007
Accepted 7 January 2008
Available online 12 February 2008

Keywords:
Barrett's oesophagus
Surveillance
Cost-effectiveness
Markov modelling
Value of information

ABSTRACT

Objective: To assess the cost-effectiveness of surveillance of Barrett's oesophagus.
Design: Cost-utility model.
Setting: UK NHS.
Patients: One thousand 55-year-old men with Barrett's oesophagus.
Intervention: Surveillance programme: endoscopy and biopsy at 3 yearly intervals for non-dysplastic Barrett's oesophagus; low-grade dysplasia yearly; high grade-dysplasia 3 monthly.
Outcome measures: Incremental cost-effectiveness ratio, expected value of perfect information.
Results: Non-surveillance dominated surveillance (i.e. cost less and conferred more benefit), but there was substantial uncertainty around many of the model inputs. Probabilistic analyses showed that non-surveillance cost less and conferred more benefit in 75% of model runs. Surveillance was cost-effective at usual levels of willingness to pay in 11% of runs. For people with Barrett's oesophagus in England and Wales, a value of £6.5 million is placed on acquiring perfect information about surveillance of Barrett's oesophagus.
Conclusions: The PenTAG cost-utility model suggests that surveillance programmes do more harm than good.

1. Introduction and background

Barrett's oesophagus has traditionally been defined as the replacement of the normal squamous epithelium of the lower oesophagus with metaplastic columnar cells for at least 3 cm of its length. More recent definitions have stated that any segment length of intestinal metaplasia should be considered as Barrett's oesophagus.[1] Whilst the condition is usually diagnosed clinically at endoscopy, it requires histological confirmation for the presence of intestinal metaplasia. It is associated with gastro-oesophageal reflux disease (GORD): 6–14% of GORD sufferers undergoing endoscopy are reported to have Barrett's oesophagus.[2] The main interest in identifying Barrett's oesophagus is its association with oesophageal adenocarcinoma; the reported relative risk of developing adenocarcinoma varies between 30 and 125 times that of the general population.[3] Intestinal metaplasia is thought to progress through increasing degrees of dysplasia (low- and high-grade) before adenocarcinoma develops.[4] Consequently, patients with Barrett's oesophagus have been entered into endoscopic surveillance programmes on the assumption that early detection of dysplastic changes will result in earlier intervention and improved outcomes for patients. However, no clinical trials of surveillance have been undertaken. Results from

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.01.015

observational studies vary in their conclusions about the clinical effectiveness of surveillance, not least because of losses to follow-up and the exclusion of many patients as too frail to undergo the major surgery required should adenocarcinoma be detected.

Surveillance programmes are nevertheless widely undertaken in the UK, although surveillance intervals, biopsy procedures and action taken following a diagnosis of dysplasia vary considerably.[5] As costs of and pressures on endoscopy services have risen, commissioners have questioned the clinical- and cost-effectiveness of continuing to keep patients with Barrett's oesophagus under surveillance.

We conducted a systematic review of the clinical- and cost-effectiveness of endoscopic surveillance of Barrett's oesophagus and held an expert workshop to inform the development of a cost-utility model.[6] No clinical trial data were identified, so the clinical effectiveness review consisted mainly of case-series. Three previous cost-utility analyses of surveillance of Barrett's oesophagus were identified. The first two[7,8] used a Markov model to examine various treatment and surveillance strategies. The earlier study found that surveillance every 5 years compared to no surveillance was cost-effective, but the model was very sensitive to the incidence of adenocarcinoma and quality of life in the post-oesophagectomy state. The later study from the same authors reached similar conclusions, but the incremental cost-effectiveness ratio (ICER) for 5 yearly surveillance was no longer within the range usually considered cost-effective. The third study[9] also used a Markov model to examine various screening and 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. Surveillance of non-dysplastic Barrett's oesophagus was not found to be cost-effective. All three studies used a North American (USA) perspective.

We therefore developed a cost-utility model, using a UK NHS perspective, to explore uncertainties in the evidence base and identify key areas for further research.

2. Methods

2.1. Cost-utility analysis

A Markov (state transition) model was developed in Microsoft Excel. Its structure was informed by the current understanding of the progression of Barrett's oesophagus through increasing dysplasia to adenocarcinoma and by the current practise of surveillance in the UK. Its purpose was to assess the cost-effectiveness of a surveillance regimen for patients with Barrett's oesophagus compared to no surveillance. The model estimated incremental cost-utility and expected value of perfect information (EVPI).[10] The base case used costs for 2004 and took the perspective of the UK's NHS. A hypothetical cohort of 1000 55-year-old men with Barrett's oesophagus was modelled for 20 years. Cycle length was 4 weeks.

The cohort starts with the initial diagnosis of Barrett's oesophagus at endoscopy, when dysplasia may also be present (Fig. 1). The model does not include patients diagnosed with adenocarcinoma at the initial endoscopy nor those in whom Barrett's oesophagus is not initially diagnosed. The solid-lined squares represent actual categories, whereas the dotted-line squares represent diagnosed states. This allows the natural history of the disease to be modelled (movement between solid-lined squares) whilst a new surveillance regimen or treatment is only instigated when the patient is reclassified at his/her next surveillance endoscopy. Patients then move between the dotted-line diagnosed states. Lines between the boxes indicate the 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, obtained from the literature and from expert opinion.

2.2. Model inputs

As there were no RCT data, data from the systematic review of case series[6] were used to estimate transition probabilities. Incidence per patient year of follow-up was used as annual progression rates from Barrett's oesophagus through each dysplastic state to adenocarcinoma and assumed to be the same in each year (Table 1).

As no robust utility values for the health states associated with Barrett's oesophagus were identified in the literature, utility estimates for the model were obtained from the NHS Value of Health Panel, a pilot project led by PenTAG in collaboration with the Universities of Southampton and Sheffield.[11] Panel members are trained to use the standard gamble technique to express preferences in relation to short descriptions of health states.

The base case uses costs for 2004, discounted at 6%, and takes the perspective of the UK's NHS. Benefits were discounted at 1.5% in accordance with HM Treasury guidance at that time.

2.3. Model outputs

Extensive one-way sensitivity and threshold analyses were undertaken on the base case scenario, as well as probabilistic analyses using a Monte Carlo simulation of 1000 trials.

2.4. Value of information

Expected value of perfect information (EVPI) analysis is derived from the Bayesian approach to decision-analytic modelling.[10] 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 the willingness to pay threshold adopted by the decision makers and the extent to which 'perfect information' about a particular input parameter (or set of parameters) reduces the variance in the model outputs.

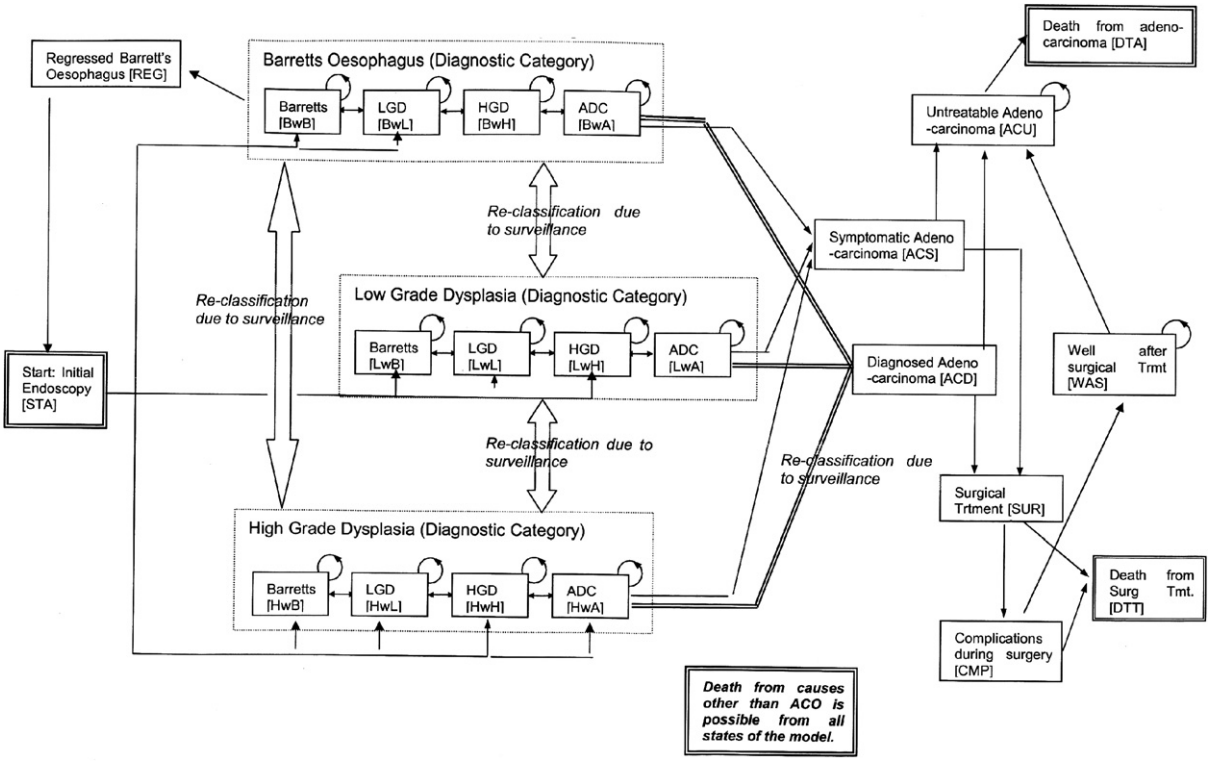

Fig. 1 – Influence diagram for patients with Barrett's oesophagus. See text for general description of model.

STA	Initial endoscopy at which all modelled patients are found to have Barrett's with or without dysplasia
REG	Barrett's initially diagnosed, now Barrett's regressed
BwB	Diagnosed state non-dysplastic Barrett's. Actual state non-dysplastic Barrett's
BwL	Diagnosed state non-dysplastic Barrett's. Actual state Barrett's with low-grade dysplasia (LGD)
BwH	Diagnosed state non-dysplastic Barrett's. Actual state Barrett's with high-grade dysplasia (HGD)
BwA	Diagnosed state non-dysplastic Barrett's. Actual state Barrett's with adenocarcinoma (ACO)
LwB	Diagnosed state Barrett's with LGD. Actual state non-dysplastic Barrett's
LwL	Diagnosed state Barrett's with LGD. Actual state Barrett's with LGD
LwH	Diagnosed state Barrett's with LGD. Actual state Barrett's with HGD
LwA	Diagnosed state Barrett's with LGD. Actual state Barrett's with ACO
HwB	Diagnosed state Barrett's with HGD. Actual state non-dysplastic Barrett's
HwL	Diagnosed state Barrett's with HGD. Actual state Barrett's with LGD
HwH	Diagnosed state Barrett's with HGD. Actual state Barrett's with HGD
HwA	Diagnosed state Barrett's with HGD. Actual state Barrett's with ACO
ACD	ACO diagnosed through endoscopic surveillance
ACS	ACO diagnosed due 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

By using probabilistic simulation in the Markov model it is possible to estimate the total value of information for differing levels of willingness to pay.

3. Results

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 high-grade dysplasia (HGD) 3 monthly, does more harm than good when compared to no surveillance (Table 2). Surveillance produces fewer quality-adjusted life years (QALYs) for higher cost than no surveillance and is therefore dominated. 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 from more surgical interventions in this arm.

3.1. *Sensitivity analyses*

Fig. 2 shows the effect on the incremental cost-effectiveness ratio (ICER) of varying individual parameter values whilst

Table 1 – Sources of inputs for the model base case and ranges

Model input	Source	Value (range)
(a) Transition probabilities		
Proportion of cohort diagnosed as non-dysplastic Barrett's oesophagus at initial endoscopy	Systematic review[6]	0.8341 (0.394–0.936)
Proportion of cohort diagnosed as LGD at initial endoscopy	Systematic review[6]	0.1205 (0.027–0.159)
Proportion of cohort diagnosed as HGD at initial endoscopy	Systematic review[6]	0.0454 (0.0–0.232)
Annual progression rate	Systematic review[6]	0.0289 (0.0185–0.05)
Barrett's oesophagus to LGD	Hurschler et al.[12] minimum reported in this systematic review Recent large study Inadomi et al.[9] previously published cost-utility analysis, based on the literature	
Annual progression rate LGD to HGD	Systematic review[6] Sontag[13] (abstract only) report on 848 LGD patients. 6% progress after an average 2.3 years – PenTAG assume a linear progression rate Inadomi et al.[9] previously published cost-utility analysis, based on the literature	0.0345 (0.013–0.05)
Annual progression rate HGD to ACO	Systematic review[6] Schnell et al.[14] reporting on 79 HGD patients, progression 9% at 5 years – assumed linear by PenTAG Weston et al.[15] 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	0.1187 (0.018–0.1362)
Annual regression from Barrett's to regressed Barrett's oesophagus	Systematic review[6] Inadomi et al.[9] previously published cost-utility analysis, based on the literature Provenzale et al.[8] – author estimate of normal mucosa diagnosed as Barrett's oesophagus	0.0243 (0.0175–0.075)
Annual regression from LGD to non dysplastic Barrett's oesophagus	Systematic review[6]. Only two studies reporting regression rates from LGD Author assumption, lower confidence level assumed to be zero. Inadomi et al.[10] previously published cost-utility analysis, based on the literature	0.1291 (0.0–0.63)
Annual regression from HGD to LGD	Systematic review[6]. Only two studies reporting regression rates from LGD Levine et al. 1996 reported in Weston et al.[15] on 16/58 patients with HGD regressed after mean of 40 months – assumed linear, and half had regressed by 40 months Weston et al.[15] report 7/15 HGD patients regressed after a median of 31.5 months – assumed linear and that half had regressed by 31.5 months	0.0476 (0.0405–0.0889)
Annual regression from ACO to HGD	Assumption	0 Not varied
Annual progression from ACO to symptomatic ACO	Ferguson and Durkin[16] Retrospective survey of 80 patients undergoing resection for ACO (12 after surveillance, 68 non-surveillance) average age at surgery 53 versus 64 years, i.e. 11 years. Annual progression calculated by PenTAG Symmetry assumed around central value. Previously published cost-effectiveness studies using values taken from Chinese study. No UK data identified	0.143 (0.0455–0.240)

(*continued on next page*)

Table 1 – (continued)

Model input	Source	Value (range)
Annual death rate from unresectable ACO	Kellokumpu-Lehtinen et al.[17]. Mortality in 106 patients with inoperable ACO in Finland Savage et al.[18] UK study of 211 patients with inoperable ACO Recent study of survival in surveillance detected versus non-surveillance detected ACO cases ($n = 23$), and same figure in earlier study of 77 ACO patients, non-surveillance and surveillance detected cases compared	0.78 (0.7–0.88)
Background rate death rate from other causes	Age specific UK data. Life table mortality for relevant age group. Adjusted as cohort ages and for rate of ACO death	Variable
Proportion of symptomatic ACOs treatable	US medical records study of 777 ACO cases (1999)[19] Symmetry around central value assumed Corley et al.[20]	0.5 (0.26–0.74)
Proportion of ACO diagnosed through surveillance treatable	US medical records study of 777 ACO cases (1999)[19] Upper limit assumed to be 1.0 Streitz et al.[21]	0.95 (0.44–1.0)
Proportion of surgical procedures with non-fatal complications	Inadomi et al.[9] and Provenzale[8] – complications not requiring surgery Post-operative complications (bleeding, small bowel infarction, sepsis, respiratory failure, chest infection and thoracic duct fistula) in study of 17 patients resected for ACO[22] Average proportion reported by van der Boogert et al.[4]	0.30 (0.0013–0.4)
Rate of ACO recurrence after surgery	De Manzoni et al.[23] recent study of 92 resected patients Symmetry around central value assumed	0.26 (0.142–0.402)
Non-surveillance arm	Danish registry study of 578 ACO cases (1999) 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 Expert opinion is that most death after surgery is due to recurrence of ACO	
Surveillance arm	Calculated as ratio from central value. Ratio of recurrence based on survival data for surveillance and non-surveillance detected cancers in Fountoulakis et al.[24]	0.0928 (0.0507–0.1435)
Mortality from surgery	Enzinger and Mayer[24]. Recent review of the literature Perioperative mortality rate in 781 oesophageal cancer patients in SW England 1996–1997[25] Average proportion reported by van der Boogert et al.[4]	0.065 (0.04–0.11)

Health state	Source	Utility value base case (standard error)
(b) Utility values		
Well after regression from Barrett's oesophagus	Population norm at age 55–64 from utility values derived from EQ5D[26] General population values in the UK used	0.8 (0.02)
Barrett's oesophagus	Value of Health Panel. Assume that equal number of patient have mild, moderate and severe GORD symptoms Median and standard error from UK general public values from systematically derived health state scenarios	0.8125 (0.025)
LGD	Value of Health Panel. Assume that equal number of patient have mild, moderate and severe GORD symptoms Median and standard error from UK general public values from systematically derived health state scenarios	0.8125 (0.025)
HGD	Value of Health Panel. Assume that equal number of patient have mild, moderate and severe GORD symptoms Median and standard error from UK general public values from systematically derived health state scenarios	0.8125 (0.025)
Diagnosed with ACO	Value of Health Panel Assume that surveillance diagnosed cases have mild ACO symptoms Median and standard error from UK general public values from systematically derived health state scenarios	0.875 (0.025)
Symptomatic ACO	Value of Health Panel Assume that ACO cases diagnosed due to symptoms have severe ACO symptoms Median and standard error from UK general public values from systematically derived health state scenarios	0.675 (0.032)

Table 1 – (*continued*)

Health state	Source	Utility value base case (standard error)
Untreatable ACO	Value of Health Panel for terminal ACO Median and standard error from UK general public values from systematically derived health state scenarios	0.400 (0.042)
Surgical treatment	Author assumption One cycle state assumed to be worse than disease symptoms but quickly resolved	0.55 (0.002)
Surgical complications	Author assumption One cycle state assumed to be worse than simple operation but quickly resolved	0.5 (0.002)
Well after surgery	Value of Health Panel Median and standard error from UK general public values from systematically derived health state scenarios	0.863 (0.016)
Death	Standard data	0

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

LGD, low-grade dysplasia; HGD, high-grade dysplasia; ACO, adenocarcinoma. 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 not likely to be important; however, the impact of changing this parameter was examined in sensitivity analysis.
BNF, British National Formulary, HRG, healthcare resource group, PPI, proton pump inhibitors.

Table 2 – Baseline results for cost-utility of surveillance of Barrett's oesophagus patients compared to non-surveillance

	Cost (£)	QALYS	Incremental costs (£)	Incremental QALYS	ICER
Endoscopic surveillance	3,869,048	11,982	–	–	–
Non-surveillance	2,951,230	12,029	–917,818	48	Dominates

other model inputs remain constant. The input parameters to which the model is most sensitive are:

- recurrence rate of adenocarcinoma after oesophagectomy in the surveillance arm (4.5% versus 9.3% in base case);
- recurrence rate of adenocarcinoma after oesophagectomy in the non-surveillance arm (7% versus 26% in base case);
- rate at which adenocarcinoma becomes symptomatic once it has developed (at least 23% versus 14.3% in base case);
- utility value of health states for Barrett's oesophagus (0.63 versus 0.81 in base case).

The figures in brackets are the values at which surveillance could be considered cost-effective at usual levels of willingness to pay (£30,000 per QALY), but they 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.

We also ran the model with the baseline variables for three other surveillance patterns: non-dysplastic Barrett's oesophagus every 5 years, 3 years or 5 years, LGD yearly, 6 monthly or 6 monthly and HGD 6 monthly, 3 monthly or 3 monthly, respectively. Non-surveillance continues to cost less and result in better quality of life whatever the surveillance pattern and costs (including none) attached to endoscopy and biopsy as the surveillance test.

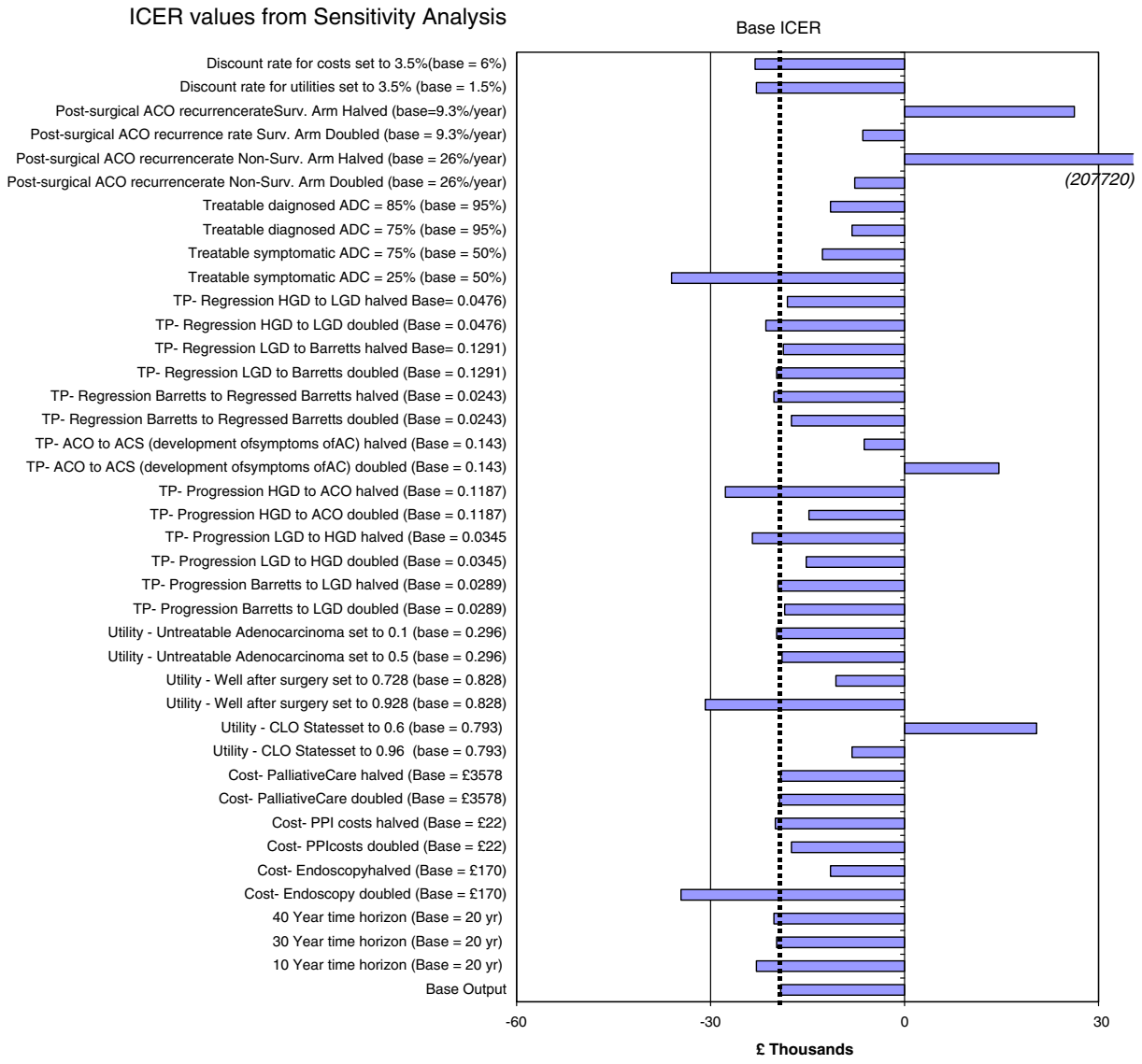

Fig. 2 – ICER values from one-way sensitivity analyses.

3.2. *Probabilistic analyses*

The probabilistic analyses showed that, in 75% of runs, non-surveillance dominates surveillance (Fig. 3a). The cost-effectiveness acceptability curve (CEAC, Fig. 3b) shows an 11% probability of surveillance being the most cost-effective option, assuming a threshold of willingness to pay of £30,000 per QALY. Surveillance is unlikely to be cost-effective even at much higher levels of willingness to pay.

3.3. *Expected value of perfect information (EVPI)*

3.3.1. *Patient-level*

Table 3 shows, for each willingness to pay threshold, the maximum value that could be gained by acquiring perfect information about all the input parameters. At a willingness to pay threshold of £30,000, 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 recorded levels of uncertainty for model parameters.

An analysis based on the maximum value per patient that could be obtained by acquiring perfect information about specific parameters of interest was also carried out (partial expected value of information, PEVPI). The output provides a probabilistic measure of model sensitivity to specific input parameters and the relative benefit of reducing this uncertainty in terms of the value of this extra information in decision-making. Table 3 shows the PEVPI values for parameters identified from the previous one-way sensitivity analysis.

3.3.2. *Population-level*

To calculate the overall value of information for the total patient population likely to be affected by a decision to implement a Barrett's oesophagus surveillance programme, it is necessary to multiply the patient-level value by the total

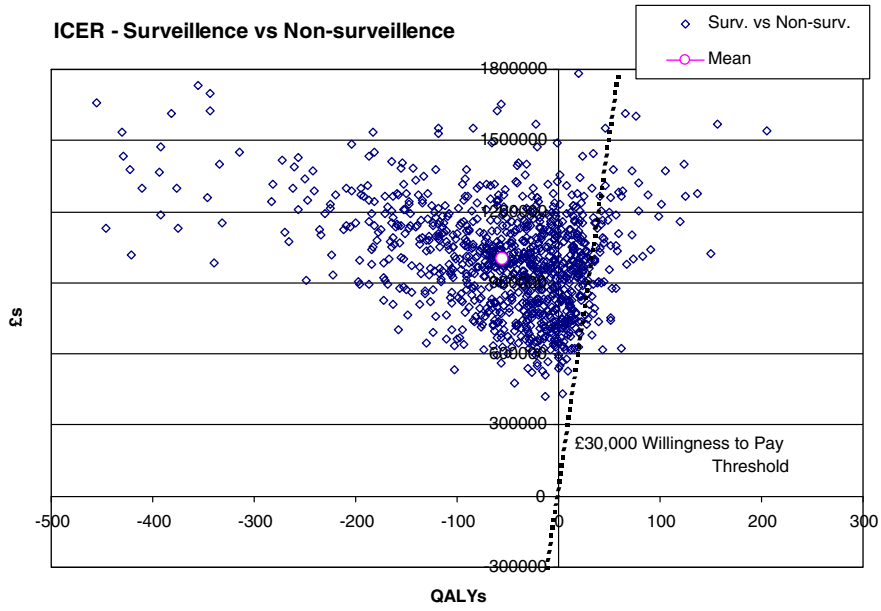

Fig. 3a – Simulation output (1000 trials) for cost-effectiveness for surveillance of Barrett's oesophagus.

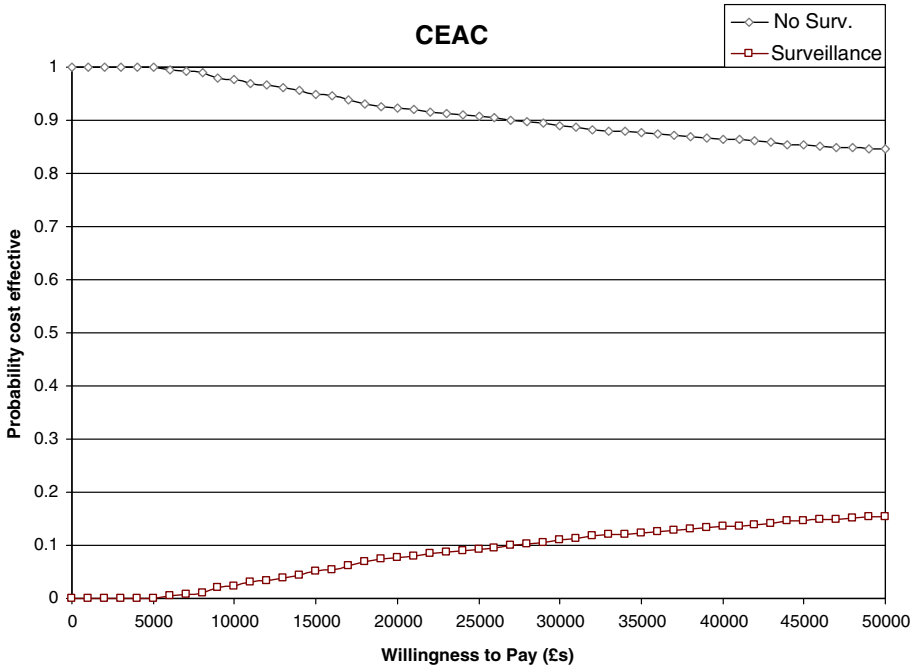

Fig. 3b – Simulation output (1000 trials) showing the probability that surveillance of Barrett's oesophagus is cost-effective at various levels of willingness to pay.

number of people affected each year over the estimated lifetime of the technology and applying the appropriate cost discount rate for future years.

The following assumptions were made for this calculation: 12.5 per 1000 of the population present annually for upper GI endoscopy,[27] of which 1.75% will be diagnosed with Barrett's oesophagus.[28,29] Using the current census population estimate for England and Wales,[30] we estimate that 11,384 people are diagnosed annually with Barrett's oesophagus, of whom 50% will be eligible for surveillance (5692). The technology is assumed to apply for 10 years, if current guidelines for surveillance remain unchanged.

Making these assumptions, 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. A similar formula has been used to calculate the total value of information for the partial EVPI analysis for the value of research aimed at

Table 3 – Expected value of perfect information

	Patient-level EVPI (£)	Population-level EVPI (£)
Total EVPI	148	6,553,619
Partial EVPIs		
Types of data		
All transition probabilities within 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

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

Table 4 – 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 have assumed that figures for progression and regression reported in clinical studies will include misdiagnosed cases due to lower specificity and sensitivity. If this under-estimates true rates, then surveillance may become less efficient
Those diagnosed with adenocarcinoma 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 treatment with proton pump inhibitors	None	
Adenocarcinoma 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 adenocarcinoma may be detected
Recurrent adenocarcinoma is terminal	None	
There is no assumed disutility (reduced quality of life) associated with being in a surveillance programme	Unknown	All are diagnosed with Barrett's – those not given surveillance may have reduced quality of life as well as those enduring regular endoscopy. No published accounts about this are available
Transitions are taken from larger studies of Barrett's oesophagus; however, this means that data about progression from those diagnosed with low- and high-grade dysplasia initially comes from a smaller sample	Unknown	
Utility value for 'well after surgery' is the same in both arms	Non-surveillance	As in general the adenocarcinomas detected outside surveillance programmes are more advanced, subsequent quality of life in the non-surveillance arm may be lower

Table 4 – (*continued*)

Assumptions and limitations	Direction of bias likely to favour	Comments
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 due to the increasing time dependency of other parameters which have not been accounted for – see text

reducing the levels of uncertainty for particular parameters within the model (Table 3).

4. Discussion

To our knowledge, the PenTAG model is the first UK-based assessment of the cost-effectiveness of surveillance of Barrett's oesophagus and the first to use probabilistic analyses, but it is limited by many gaps and uncertainties in the available data. It is important to note that the systematic review[6] undertaken to support the development of the model failed to identify any randomised trials of surveillance and failed to find proof of the clinical effectiveness of surveillance. The expert workshop also confirmed the lack of evidence for the effectiveness of surveillance and identified many uncertainties in the evidence base.[6] Consequently, the data used in the model are drawn from case-series and other non-randomised study designs.

4.1. *Model uncertainty*

We used a 20 year time frame for the model. When we ran the model for an extended time of 40 years, non-surveillance continued to dominate. 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, due to increasing frailty in the ageing cohort. We have not been 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.

A number of assumptions have been made in order to produce a functioning model (Table 4). Variables that have both a high level of uncertainty about the correct value and affect the model outputs highly are:

- Recurrence rate after surgery for those diagnosed through surveillance compared to patients presenting symptomatically.
- Time taken for adenocarcinoma to become symptomatic.
- Utility value for the health state of Barrett's oesophagus.

Transition values are uncertain for several reasons. Firstly, the estimated progression rates are based on evidence from endoscopic surveillance and are limited by the accuracy of diagnosis and the surveillance intervals. We have assumed that observed rates of progression are the same as actual natural history. The values 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 is reported in the literature relating to stage of tumour. We have assumed that cancers detected through surveillance are at an earlier stage, and therefore are associated with a lower recurrence rate, than cancers presenting symptomatically.

Currently, levels of adenocarcinoma recurrence are known after surgery, but the literature does not report on how the patients were initially identified: 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 difficult to estimate the time taken for adenocarcinoma 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, whilst others felt 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 whilst 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. We have obtained the views of a small non-representative sample of the public, using the standard gamble technique, and have assumed that the surveillance and non-surveillance arms have similar disutility associated with the requirements of surveillance and the uncertainty without surveillance. This assumption has not been validated.

The proportion of treatable cancers amongst those diagnosed through surveillance and through symptoms, and the ratio of the two proportions, was also important. Again, there is little 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, others that either the surveillance or the symptomatic figure was too high.

4.2. *Value of information*

The value of information analysis suggests 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. 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 adenocarcinoma after surgery and time taken for adenocarcinoma to become symptomatic) as the one-way sensitivity analyses.

5. Conclusion

The PenTAG cost-utility model has confirmed that it is likely that surveillance programmes of Barrett's oesophagus do more harm than good than no surveillance. These results are consistent with previous models of cost-effectiveness, the most recent of which has also shown that surveillance programmes either do more harm than good compared to no surveillance or are unlikely to be cost-effective at usual levels of willingness to pay.

However, there is much uncertainty around the inputs and the results are critically dependent on variables for which there is little reliable evidence. 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 shows that surveillance is unlikely to be cost-effective at either the usual level of willingness to pay (£30,000/QALY) or at much higher levels. The total expected value of information (EVPI) is high, with a per patient value of around £148. The population-level EVPI is driven by the number of people affected and the expected lifetime of the technology. The partial EVPIs show that the main uncertainty concerns the transition probabilities in the model, not the costs or the utilities. 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 accurately as possible in the probabilistic analysis.

Despite this lack of conclusive evidence for the effectiveness of surveillance of Barrett's oesophagus, most UK practitioners believe it to be worthwhile and some form of surveillance is usual current practise. 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 adenocarcinoma 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.

Conflicts of interest statement

None declared.

Funding

The work was undertaken as part of a grant from the Health Technology Assessment Programme (UK Department of Health), which stipulated that the work should consist of a systematic review, expert workshop and cost-utility model, but had no input to the collection, analysis or interpretation of data.

Acknowledgements

The authors wish to thank Alison Price and Naomi Gilbert for their help and the clinicians and patients who contributed to the expert workshop and commented on the model as it was developed.

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