Surveillance of Barrett's oesophagus: do we yet know whether it is worthwhile?

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In 2004, the Peninsula Technology Assessment Group developed an economic model to assess the effectiveness and cost effectiveness of surveillance of Barrett's oesophagus in preventing morbidity and mortality from oesophageal adenocarcinoma. The conclusion then was that surveillance was dominated (ie, cost more and conferred less health benefit) by non-surveillance in most scenarios and that surveillance was unlikely to be cost effective at usual levels of willingness to pay. The model outputs were highly sensitive, however, to several parameters for which the data were very uncertain. While there are now better estimates of some of the model inputs, such as cancer risk and quality of life, the revised values make it less likely that surveillance could prove cost effective. There remains considerable uncertainty around other key inputs. At present, there seems little reason to change our original conclusion that surveillance of Barrett's oesophagus is unlikely to be cost effective and a definitive answer may only be possible from clinical trials now in progress. As newer endoscopic techniques for treating Barrett's oesophagus and adenocarcinoma become more widely used, however, conventional surveillance programmes may no longer be undertaken, and revised economic models will be needed to assess the cost effectiveness of the new clinical pathways.

Barrett's oesophagus is a recognised precursor condition for oesophageal adenocarcinoma.¹ It has been variously defined but remains a diagnosis made histologically following endoscopy¹ and has a variable association with the symptoms of gastro-oesophageal reflux. The cancer risk has led to patients with Barrett's oesophagus being entered into surveillance programmes in order to identify dysplasia and carcinoma at early stages amenable to treatment. While guidelines are available on surveillance protocols and intervals,¹ clinical practice is very variable.² Health benefits for patients remain unclear, particularly as many patients with Barrett's

oesophagus have not been included in surveillance programmes because they have not been considered fit for the major surgery that has been the mainstay of treatment for oesophageal adenocarcinoma.

Five years ago, the Peninsula Technology Assessment Group (PenTAG) was commissioned by the Health Technology Assessment programme to assess the effectiveness and cost effectiveness of surveillance of Barrett's oesophagus in preventing morbidity and mortality from oesophageal adenocarcinoma.³ We failed to find any trials of the clinical effectiveness of surveillance and, as a result, our systematic review consisted of two comparative studies and numerous case series and we were unable to draw any clear conclusions from this evidence base. An expert workshop held as part of the project revealed substantial gaps in the understanding of Barrett's oesophagus, its natural history and effective diagnosis and management. Significantly, the experts present were divided in their opinions on the value of surveillance programmes, including whether such programmes should be undertaken at all.

In view of the lack of rigorous studies on the clinical effectiveness of surveillance, we constructed our own economic model to assess its cost effectiveness (figure 1).^{3,4} Our baseline results indicated that surveillance was dominated by non-surveillance (ie, surveillance cost more and conferred less health benefit than non-surveillance, although the absolute difference in quality adjusted life years between the two arms was small (table 1)^{3,5} and model outputs were highly sensitive to changes to key input parameters).

The model uses a Markov state transition structure to analyse the outcomes from Barrett's oesophagus.⁴ In this model a cohort of patients enter at the initial endoscope state and then progress through the model according to the defined patient

Figure 1 Peninsula Technology Assessment Group model of surveillance for Barrett's oesophagus.

Table 1 Baseline results for cost utility of surveillance of Barrett's oesophagus patients compared with non-surveillance

	Endoscopic surveillance	Non-surveillance
Cost (£)	3869048	2951230
QALYs	11982	12029
Incremental costs (£)	—	-917818
Incremental QALYs	—	48
ICER	—	Dominates

ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years.

states, represented by boxes, and transitions, represented by arrows, in figure 1. Importantly, our model differentiates the diagnostic state of patients (dotted line boxes) and their underlying condition (solid line boxes). This enables the model to analyse the effects of differing approaches to surveillance.

As our model was constructed primarily to investigate the uncertainty of outcomes associated with different approaches to surveillance, we conducted extensive sensitivity analyses to explore these uncertainties. Table 2 lists the model variables to which outputs were particularly sensitive as well as the relative strength of evidence available to support the values used in the model (a fuller version of this table is given in the Health Technology Assessment report).³ The critically important variables, obtained from the least reliable evidence and to which the model was most sensitive, were the rate of recurrence of adenocarcinoma following surgery, the rate at which adenocarcinoma

becomes symptomatic and the utility attached to the health state of Barrett's oesophagus. One way sensitivity analyses suggested that surveillance becomes cost effective at any of the following thresholds.

- If the recurrence rate of adenocarcinoma after oesophagectomy in the surveillance arm is reduced to 4.5% from 9.3% in the base case.
- If the rate at which adenocarcinoma becomes symptomatic once it has developed is increased to at least 23% per year from 14.3% per year in the base case.
- If the utility value of health states for Barrett's oesophagus is reduced to 0.63 from 0.81 in the base case.

Other transition probabilities and health states were less important, and the model was not sensitive to the intervals at which surveillance endoscopies were carried out or the costs of running a surveillance programme or treatment. The probabilistic sensitivity analysis suggested that surveillance could be cost effective in a minority of scenarios (11%), with apparently realistic combinations of parameter values.

Five years on, are we able to reduce these uncertainties and reach a clearer, more robust conclusion about the effectiveness and cost effectiveness of surveillance?

Repeating the search strategy for our systematic review has not identified any clinical trials of surveillance but we are aware of at least one currently in progress, commissioned as a result of our report.⁶ In

Table 2 Key variables identified in modelled sensitivity analysis

Model variable	Source of variable	Level of uncertainty in data	Impact of uncertainty on model	Overall rating of importance
Levels of ADC recurrence after surgery for those diagnosed through surveillance vs those presenting symptomatically	Poor published evidence plus expert opinion	High	Very high	Very important
Time ADC 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 ADC diagnosed through surveillance that are treatable	Poor published evidence plus expert opinion	Moderate	High	Important
% of ADC 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 ADC	Poor published evidence plus expert opinion	High	Moderate	Moderately important

ADC, adenocarcinoma; HGD, high grade dysplasia; LGD, low grade dysplasia.

the absence of trial evidence, do we have any better estimates of our model parameters from other sources that would enable us to make more certain predictions about the cost effectiveness of surveillance?

Cancer risk

A recent meta-analysis⁷ has provided better estimates of cancer risk in Barrett's oesophagus: using all 47 studies included in the systematic review yielded a cancer risk of 6.1 per 1000 person years (95% CI 4.7, 7.9) but there was substantial heterogeneity in the studies. By removing early incident cancers and high grade dysplasia (HGD) at baseline, heterogeneity was mostly removed and the estimate of cancer risk reduced to 4.1 per 1000 person years, based on 12 studies. The authors also applied quality criteria to the included studies; just eight met all three criteria of large size, low likelihood of selection bias and robust definition of Barrett's oesophagus. Pooled cancer risk in these eight studies was 3.9 per 1000 person years. In our report, we only included larger studies (>300 patients, less than the criterion of >500 patients used in this systematic review) but did not apply other quality criteria. The values given here considerably reduce uncertainty but fall within the range we used in our model. Given the consistent tendency for the larger, better quality studies to report lower estimates of cancer risk, it seems very unlikely that the value needed (a doubling of the base case value) to achieve cost effectiveness of surveillance in our model is realistic. Targeting surveillance at specific high risk groups, however, may be a cost effective option: Yousef and colleagues⁷ found a cancer risk for men of 10.2 per 1000 person years.

Dysplasia progression and regression rates

Confining surveillance to those in whom dysplastic changes are present on index endoscopy may also be a

cost effective option, as those with dysplastic changes carry an increased cancer risk.⁸

Rate at which adenocarcinoma becomes symptomatic after it has developed

We have not been able to update the estimates we used originally, which were considered very uncertain, as they were based on advice from experts in the absence of published evidence. It seems unlikely that more certain estimates will ever be available as there are many factors influencing patients' decisions to consult besides the nature and severity of their symptoms.

Effect of treating Barrett's oesophagus

Originally, we included long term medical treatment costs for gastro-oesophageal reflux disease (GORD) in both the surveillance and non-surveillance arms of our model where it did not affect our estimates of cost effectiveness. The available evidence did not provide any clear indication of whether such treatment altered the long term risk of cancer. Other treatment modalities for treating Barrett's oesophagus have been available for some time in the form of various endoscopic ablative techniques¹ and there is now clearer evidence of their short term efficacy and safety but their long term impact on cancer risk is still not established. On the assumption that any effect they may have is likely to reduce cancer risk rather than increase it, these treatments make it even more unlikely that surveillance, in terms of the standard programme we modelled, can be cost effective. Since patients who have received ablative therapies are currently still kept under surveillance, there will still be the costs associated with surveillance to take into account in any treated Barrett's oesophagus arm. Better estimates of cancer risk in terms of the impact of chemoprevention⁹ can also be expected when the Aspirin Esomeprazole Chemoprevention trial reports.^{10 11}

Utilities

Five years ago we found very little evidence on which to base our estimates of utilities for health states associated with Barrett's oesophagus. As a result, we used the Value of Health Panel¹² to provide utility estimates for our model. As Barrett's oesophagus is a pathological condition with a very variable and uncertain association with symptoms, the health state descriptions used were largely based on GORD. A recent systematic review¹³ has noted that there is no specific tool to measure health related quality of life in Barrett's oesophagus and, as a result, reports results from several studies of GORD using both generic and GORD specific quality of life measures. The authors comment on the impact of a range of factors on the quality of life of patients with Barrett's oesophagus, as well as symptoms, such as the burden of endoscopic surveillance and psychological distress. In particular, they noted that patients in general overestimate their risk of developing cancer. Despite these wide ranging health impacts, the utility estimates for both dysplastic and non-dysplastic Barrett's oesophagus, where comparable, are considerably higher than those we used in our model (0.90 and above, compared with 0.8). This parameter is of critical importance in our model and higher utility values make surveillance less cost effective. It seems unlikely therefore that the threshold value of 0.63, indicated by one way sensitivity analysis as required for surveillance to be cost effective, is realistic.

Rate of recurrence of adenocarcinoma following oesophagectomy

In our model, we included oesophagectomy as the definitive treatment for oesophageal adenocarcinoma identified either through a surveillance programme or symptomatic presentation. Our estimates of the recurrence rates following treatment were therefore taken from studies of oesophagectomy although we were aware 5 years ago that other modalities for treating oesophageal adenocarcinoma and HGD were available, such as photodynamic therapy and endoscopic mucosal resection.¹ What would be the effect of modelling these therapies instead of oesophagectomy? Firstly, the estimates of recurrence of adenocarcinoma following photodynamic therapy and endoscopic mucosal resection may be higher than those following oesophagectomy although recurrences may be more amenable to further treatment, and cancer specific mortality appears similar in the limited data so far available.¹⁴ This scenario would add costs to both the surveillance and non-surveillance arms of the model but would not necessarily alter the difference in recurrence rates between the arms, which is a key parameter for the model. The main influence on this difference is likely to be the stage of the adenocarcinoma at diagnosis, with a higher proportion of those detected earlier through surveillance being considered treatable by any

modality compared with those presenting symptomatically. It is unclear whether this difference in treatability according to stage is influenced by the available treatment modalities.

What these non-surgical treatment modalities do alter substantially, however, is the proportion of the population with diagnosed Barrett's oesophagus that can be considered for treatment should adenocarcinoma develop. Historically, many patients have been excluded from surveillance programmes because they have not been considered fit for the major surgery involved in oesophagectomy, substantially reducing any population benefit from surveillance. In our study, we did not differentiate between those fit or not fit for surgery in our cohort of 55-year-old men with Barrett's oesophagus but assumed they would all be entered into a surveillance programme and treated if appropriate. The effect on the cost effectiveness of surveillance of including this larger population in a surveillance programme is uncertain. Those included are now more likely than previous surveillance populations to have other comorbidities and to be older, so are presumably more likely to die from other causes while under surveillance. They also may incur more health service costs, as they may require longer hospital stays, more follow-up and treatment, and be more subject to complications of treatment. All of these changes are likely to reduce the chance of surveillance proving to be a cost effective option. On the other hand, including a higher proportion of people with Barrett's oesophagus in a surveillance programme may reasonably be expected to pick up more cancers at a treatable stage, thus increasing the possibility that surveillance is cost effective.

Strategies for managing Barrett's oesophagus

The PenTAG model only considered two management options:

- surveillance of all patients with Barrett's oesophagus, with more frequent surveillance for those with dysplasia
- no surveillance and investigation and treatment when symptoms of adenocarcinoma developed

From this limited update of the evidence, it seems unlikely that surveillance according to this description will prove to be cost effective: updated estimates of the model parameters are either within the range we explored with sensitivity analyses (cancer risk and progression rate through dysplasia to carcinoma) or provide values that would reduce the likelihood of surveillance proving cost effective (eg, revised health state utility values).

Other studies^{15 16} that modelled these management options for a similar cohort of patients have reached similar conclusions about the probable cost effectiveness of surveillance programmes. However, other strategies for managing Barrett's oesophagus have also

been explored; targeting surveillance at those patients with the highest risk of developing cancer may be a more cost effective option—such as those who already have dysplastic changes.¹⁶

The model by Inadomi and colleagues¹⁶ has identified screening for Barrett's oesophagus and only keeping those with dysplasia under surveillance as the only cost effective option. These results conflict with those of Gerson and colleagues¹⁷ who found that screening 50-year-old men with GORD and then keeping those with non-dysplastic Barrett's oesophagus under surveillance with treatment for both HGD and adenocarcinoma as the most cost effective of a range of treatment options. This latter model uses different assumptions relative to other models for a range of key parameters relating to treatment, prevalence and the development of oesophageal adenocarcinoma. In addition, it did not incorporate quality of life estimates, so a direct comparison with cost utility models is problematic, particularly given the importance shown for the utility value assigned to patients with Barrett's oesophagus in the PenTAG model.

Given the increasing interest in, and adoption of, new modalities of treatment for Barrett's oesophagus, it is likely that cost effectiveness models need to be updated. Ablative therapies, as noted above, may be offered at an earlier stage of disease to a wider spectrum of patients than conventional surgical treatment, thus altering the rationale for subsequent surveillance: as well as regular examination for the appearance of dysplastic or carcinomatous changes, there is the monitoring for return of Barrett's oesophagus or complications of treatment. Das and colleagues¹⁸ have recently modelled the newer treatments and conclude that ablative therapy for non-dysplastic Barrett's oesophagus followed by reduced surveillance is a more cost effective option than a standard surveillance programme. It is important to note, however, that this revised programme is still not cost effective at low willingness to pay thresholds when compared with a strategy of no surveillance. A key constraint in the cost effectiveness analysis of such new techniques is the limited evidence which shows the effect of these interventions on the subsequent risk of developing oesophageal adenocarcinoma. Without such data there is always likely to be a high level of uncertainty associated with modelled outputs.

Patients treated for Barrett's oesophagus or adenocarcinoma by these newer modalities are still currently kept under surveillance although it may be possible to target or discontinue this practice when long term outcomes are clearer. The impact on quality of life is also uncertain at present.

What is still needed?

In conclusion, this brief update cannot cover every aspect of surveillance for Barrett's oesophagus in depth but there seems to be little new evidence to alter our

original conclusion from 5 years ago that surveillance is difficult to justify on cost effectiveness grounds when compared with no surveillance of Barrett's oesophagus. There may be exceptions: targeting high risk groups may be appropriate, as patients with existing dysplastic changes and certain groups, such as older men, have been shown to have a risk of developing oesophageal adenocarcinoma that may be high enough to make surveillance cost effective.

However, the general picture is now more complex with growing use of new techniques and therapies presenting different pathway options for patients.

In the light of this increasing complexity, our older models may become redundant as clinical practice continues to evolve, but without clear evidence of the effect on cancer risk and health state utilities of these new treatments, we can only speculate on their effect on the cost effectiveness of surveillance programmes. In particular, it will be important to establish whether surveillance is always necessary, and for how long, after these treatments.

This debate about cost effectiveness is unlikely to resolve until much clearer empirical data are available for our economic models. Results from current clinical trials should help substantially but will take some time to report. In the meantime, clinical practice is likely to continue to vary widely.

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