Cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's oesophagus

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Abstract

Background: Endoscopic surveillance for non-dysplastic Barrett's esophagus is contentious and its cost-effectiveness unclear.

Objective: To perform an economic analysis of endoscopic surveillance strategies.

Design: Cost-utility analysis using a simulation Markov model to synthesize evidence from large epidemiological studies and clinical data for surveillance, based on international guidelines, applied in a coordinator-managed surveillance program.

Setting: Tertiary care hospital, South Australia.

Patients: 2040 patient years of follow-up

Interventions: 1) no surveillance, 2) 2-yearly endoscopic surveillance of patients with non-dysplastic Barrett's esophagus and 6-monthly surveillance of patients with low-grade dysplasia, 3) a hypothetical strategy of biomarker-modified surveillance.

Main outcome measures: US cost per quality-adjusted life year (QALY) ratios

Results: Compared with no surveillance, surveillance produced an estimated incremental cost per QALY ratios of $60,858. This was reduced to $38,307 when surveillance practice was modified by a hypothetical biomarker-based strategy. Sensitivity analyses indicated the likelihood that surveillance alone was cost-effective compared with no surveillance was 16.0%, and 60.6% if a hypothetical biomarker-based strategy was added to surveillance, at an acceptability threshold of $100,000 per QALY gained.

Limitations: Treatment options for Barrett's esophagus which overlap with those for symptomatic gastro-esophageal reflux were omitted.

Conclusions: Using best available estimates of the malignant potential of Barrett's esophagus, endoscopic surveillance of patients with non-dysplastic Barrett's esophagus is unlikely to be cost-effective for the majority of patients and depends heavily on the progression rates between dysplasia grades. However, strategies which modify surveillance according to cancer risk might be cost-effective, provided high-risk individuals can be identified and prioritized for surveillance.

Take home message: Endoscopic surveillance of all patients with non-dysplastic Barrett's esophagus may not be cost-effective. Although the biomarker strategy remains hypothetical, health economic modeling can be used to define the

parameters (cost and efficacy) which must be met for any future biomarker strategy to be useful in the clinical context.

Key words: Barrett's esophagus; endoscopy; early detection; adenocarcinoma of the esophagus; cost-utility; endoscopic surveillance, biomarkers

Introduction

Endoscopic surveillance of Barrett's esophagus is used to identify patients at earlier curable stages, and is endorsed by several leading bodies in the UK and US[5-6] despite limited evidence that it confers a survival advantage[7-8]. As a cancer prevention strategy, endoscopic surveillance of Barrett's esophagus is controversial because the majority do not develop esophageal cancer and subsequently derive no benefit[9]. The yield of early-stage cancers for patients within a Barrett's surveillance program varies widely from 1/285 to 1/52 patient-years,[10-15] or 0.2% to 2% per year[1]. However, advocates of surveillance suggest it is the only option for early detection, and since adenocarcinoma occurs through a known sequence of metaplastic-dysplastic states, detecting pre-cancerous states within a surveillance program is critical[6].

Numerous studies were published during 1999-2009 but produced conflicting results about the value of surveillance, and are now largely outdated as they were based on poor quality evidence[16]. Clinical practice has also improved, notably with lower mortality rates reported for esophagectomy and greater use of less invasive endoscopic techniques. Some previous studies suggest surveillance is not cost-effective under any scenario tested[17-18], while others conclude that surveillance is economically acceptable under certain conditions (for example, when the surveillance interval is lengthened[19-20]). Hampering this work has been a lack of evidence for crucial inputs for modeling (e.g., quality of life, proportion of patients progressing among dysplasia grades). Moreover, analyses have not adequately scrutinized the clinical uncertainty of alternative management options for early stage cancer[16] such as endoscopic procedures [16, 21]. Mortality rates for oesophagectomy are also improving in specialist centers, and recent epidemiological studies have produced more rigorous estimates of the natural history of Barrett's esophagus[22].

Identifying risk factors and targeting surveillance to high-risk individuals might concentrate surveillance to a smaller cohort, and minimize hospital resource use in low-risk individuals. At present stratifying risk is difficult and has not entered clinical practice, although earlier studies have suggested this might be possible, and current

research is evaluating potential biomarkers for this purpose. If useful biomarkers can be identified, then they might allow the identification of high risk individuals for closer surveillance, and exclusion of patients at low risk, thereby improving cost-effectiveness. To date biomarkers which facilitate this approach are unproven, although past work has shown a combination of critical abnormalities within the tumor-suppressor genes TP53 and CDKN2A, as well as DNA content abnormalities (tetraploidy and aneuploidy), are associated with a high risk of cancer progression[23]. It is therefore reasonable to envisage that biomarker testing of BE will be practical in the near future. While the precise components of future tests are not known at this stage, the likely costs and benefits can be estimated and included in models to predict their likely overall impact [24] .

To evaluate these issues, this study assessed the cost-effectiveness of endoscopic surveillance for non-dysplastic Barrett's esophagus within a structured surveillance program. Updated epidemiological data and observational study findings were used in the modeled analysis and the model also evaluated the effect of adding a hypothetical biomarker test to identify high-risk patients. Although biomarkers are untested in clinical practice, the considerable current effort to identify predictive biomarkers for Barrett's esophagus suggests that such markers will at some stage be advocated for clinical practice. Hence, it is timely this strategy should also be evaluated for cost-effectiveness before becoming routine.

Methods

Description of Strategies

Three strategies were modeled: 1) no surveillance; 2) endoscopic surveillance alone; and 3) endoscopic surveillance modified by a hypothetical biomarker test. Endoscopic surveillance intervals were based on UK British Society of Gastroenterology guidelines; 2-yearly for non-dysplastic Barrett's esophagus with intestinal metaplasia, and 6-monthly for Barrett's esophagus with low-grade dysplasia[25]. It was assumed that appropriate scheduling of endoscopies was achieved, mucosal biopsies were collected using the Seattle protocol (i.e. 4-quadrant biopsies at 2cm intervals with histopathology checked by two pathologists if high grade dysplasia was identified)[26], diagnoses of Barrett's esophagus or dysplasia

were accurate, and all patients attended their scheduled appointments. The data used to determine the clinical outcomes was derived from a database which underpins a managed Barrett's esophagus surveillance program in Adelaide, Australia, in which there was a greater than 90% compliance with all of the above assumptions[26].

Markov Model

A health state transition Markov Model was constructed in TreeAge Pro 2011 (TreeAge Software Inc, Williamstown, MA, USA) and designed to synthesize published evidence and data from the primary patient-level dataset. A two-stage approach was taken where clinical pathways and treatments following a diagnosis of esophageal adenocarcinoma were first analyzed (the 'treatment model')[27] and then integrated within a larger surveillance model focusing on the parameters pertaining to surveillance activities (the 'surveillance model') (Figure 1) (Supplementary File). Briefly, the treatment model is a 5-year decision-analytic model and traces patients from a diagnosis of high grade dysplasia or adenocarcinoma. Treatment pathways were determined by cancer T stage, with T1 stage divided into T1a and T1b. The use of T stage rather than TNM stage was necessary because T stage can be determined for all patients undergoing endoscopic and surgical therapy, but N stage can only be identified accurately following surgical resection, and can be distorted by neoadjuvant treatment with chemotherapy or chemoradiotherapy. The main treatments included esophagectomy, endoscopic mucosal resection/radiofrequency ablation, radiotherapy, chemotherapy, or watchful waiting. Prospective data from the Australian Cancer Study cohort of 795 patients with esophageal adenocarcinoma and a cohort of 325 patients from Flinders Medical Centre (South Australia) provided the key patient-level estimates needed for survival and resource use over five years. These estimates were aggregated to populate the surveillance model.

The surveillance model tracked a hypothetical cohort through 6-monthly cycles to examine the health and cost outcomes of individuals entering a Barrett's esophagus surveillance program. To reflect real life, most members entered surveillance with a confirmed diagnosis of non-dysplastic Barrett's esophagus (95%), but with 4% having low-grade dysplasia and 1% having high-grade dysplasia[28]. The cohort

members were men and women with a starting age of 50 years and then modeled until age 80 or death (whichever came first). The model consisted of 10 health states including: Barrett's esophagus free, non-dysplastic Barrett's esophagus, low-grade dysplasia, high-grade dysplasia, esophageal adenocarcinoma (apportioned by T1, T2, T3, T4 stages and distant metastases) and all-cause death (Figure 1). Individuals could move between these mutually exclusive health states, once every six months, or remain in the same state. If a person developed esophageal adenocarcinoma, they were subject to the 5-year treatment pathways, associated cost, quality of life and survival outcomes according to T stage within the 'treatment model'. For example, surgical mortality rates from esophageal cancer ranged from 2-6% depending on T stage ([27], Supplementary File). Key outcomes of the model included incremental costs and quality-adjusted life years (QALYS).

Treatments for high-grade dysplasia or esophageal adenocarcinoma were constructed with particular attention to different clinical algorithms for T1a and T1b tumors, inclusion of post-operative mortality, inclusion of less-invasive endoscopic treatments (endoscopic mucosal resection and radiofrequency ablation) and validated structurally by clinicians[27]. Individuals who remained alive after five years following a diagnosis of high-grade dysplasia or esophageal adenocarcinoma received on-going endoscopy every six months for three years and annually thereafter. These individuals were assumed to die eventually of other causes. Individuals may die of any cause at any time during the model from any health state based on Australian age-dependent mortality tables[29], weighted by a higher proportion of men (66%) commonly observed for patients with Barrett's esophagus.

Data Inputs and Sources

Transition probabilities

Pivotal to the model are the progression rates from non-dysplastic Barrett's esophagus to adenocarcinoma, and low-grade dysplasia to adenocarcinoma, creating the model's health state transition probabilities. A literature search was undertaken to extract the most recent and relevant data estimates (Table 1). Large observational studies provided data on the progression rates reflecting the natural history of Barrett's esophagus[22, 28, 30]. For the progression from non-dysplastic

Barrett's esophagus to adenocarcinoma, the estimate of 0.33% per year was selected from a meta-analysis by Desai *et al.* 2011 on a subset of higher-quality studies. This pooled estimate excluded studies capturing prevalent cases of adenocarcinoma and high-grade dysplasia and included those with greater than five years follow-up[31]. This estimate was also very similar to those presented in recent large observational studies in Northern Ireland 0.27%[28], The Netherlands 0.39%[30], but somewhat higher than reported by Hvid-Jensen *et al.* 2011, 0.12% (95%CI: 0.09%, 0.15%), although this latter study included patients with columnar epithelium without intestinal metaplasia[22]. We tested the results using estimates 0.09% and 0.5% in a sensitivity analysis. We assessed the literature reporting corresponding progression rates for patients within a surveillance program with a focus on more recent studies (Table 2). Our estimates were taken from a prospective dataset kept by the authors at Flinders Medical Centre, Adelaide (South Australia) because this involved a relatively high number of patients and patient years of follow-up (2040), with confirmed intestinal metaplasia with any length of BE (Supplementary File). Patients also had high adherence to appointments and were followed within a well-managed surveillance program compliant with UK recommendations [26, 32] (Table 2). Under surveillance, the TreeAge model was calibrated using an implementation of the Markov model in Microsoft Excel run over a 9-year period and 2040 patient-years. The surveillance progression rates were iteratively derived from reverse-model runs, starting with estimates derived from the surveillance data. The derived rates accurately reproduced the incidences and cumulative incidences of low- and high-grade dysplasia and esophageal adenocarcinoma and gastro-esophageal junction carcinoma observed in the surveillance program. The rates and cumulative incidences were then verified in the TreeAge model. The high effectiveness in the surveillance program is attributed to active monitoring of compliance with endoscopy biopsy protocols and scheduling.

Utilities

The background utility value for the Australian population has recently been reported at 0.895[33] (with 1.0 representing best possible health) using the EQ-5D instrument and Australian quality-of-life preferences. Disutilities for the model health states were calculated as the difference between 0.895 and utilities reported in the literature relating to esophageal cancer health states [34-37], in most instances measured by

the EQ-5D (with UK preferences) (Table 1). It was assumed that patients with non-dysplastic Barrett's esophagus and low-grade dysplasia would be asymptomatic as a consequence of using proton pump inhibitor agents to control symptoms, and therefore have no disutility from the background norm.

Resource Use and Costs

The study took an Australian health system perspective and all costs (Table 1) were inflated to 2011 dollars using the Australian Consumer Price Index. Results are presented in US dollars (AUD 1 = USD 1). Itemized costs for surveillance and biomarker testing are provided in the Supplementary File. Briefly, for the surveillance program, an average cost per person was calculated as the sum of initial endoscopy at entry, subsequent endoscopies (according to the schedule for respective dysplasia grade) and histopathology testing. Administration costs for managing a surveillance program were also calculated per person and included staff, database license, letters/printing and phone calls. Biomarker testing included costs for flow cytometric cell sorting, gDNA amplification, PCRs, staff time and multiple biopsies per patient. Costs for all direct medical resources involved in diagnosis, treatment and follow-up care of esophageal cancer were derived from patient-level data collected within the Australian Cancer Study (ACS) over several years via medical chart review[27, 38] (Supplementary File). Resources included biopsies, ultrasounds, imaging, endoscopic treatments and investigations, hospitalizations, in-hospital adverse events, chemotherapy, radiotherapy, monitoring, stents and palliative care. Proton pump inhibitor medications were assumed to be taken by all individuals and were not included in the model as costs were not expected to differ across the intervention strategies. Resources were valued using national price schedules and public hospital clinical costs for inpatient surgical stays. The mean cost of an oesophagectomy included in-hospital adverse events and intensive care unit admissions for some patients. We assumed total costs for esophageal cancer, separated by T stage, occurred during the first 12 months after diagnosis.

Analyses

The mean costs and QALYs were generated using an expected (mean per person) value analysis. For each strategy, this reflects the aggregated probabilities and values assigned to alternative pathways. Costs and benefits were discounted at 5%

per year to adjust for the relative value of present costs and life years. The incremental cost-effectiveness ratios (ICER) were calculated. One-way sensitivity analyses were undertaken where each parameter was varied through a range of plausible values (Table 1) and changes to the base results were observed. We varied the surveillance frequency (3- or 5-yearly for non-dysplastic Barrett's, annual for low-grade dysplasia), the starting age (55 years, 60 years), the maximum surveillance duration (5, 10, 20 years) and the discount rate (0%, 1.5%, 3.5%). All other model parameters were tested between high and low values (Table 1) using the 95% confidence intervals where available, values reported in the literature, or ± 20%. We also considered the cost impact on the results when we increased the proportion of patients with T1a cancers receiving endoscopic treatments instead of oesophagectomy (to 90%, from a base case of 50%). Sensitivity analyses were not performed on other variables relating to the treatment of high-grade dysplasia or esophageal cancer (e.g., esophageal mortality rates, utility values for cancer stage, costs of chemoradiation); these were comprehensively undertaken in previously published analyses [27] and will have negligible effect on a surveillance population because they affect a small proportion of individuals. A probabilistic sensitivity analysis was also performed by re-sampling 5000 times at random from assigned probability distributions for each parameter to address the uncertainty of data estimates simultaneously. Gamma distributions were used for costs and beta distributions were used for probabilities and utility scores. To aid interpretation, a cost-effectiveness threshold of US$100,000 per QALY was used[39].

Modification of model using a hypothetical biomarker strategy

In addition to the standard surveillance model, we modified and re-evaluated the Barrett's esophagus surveillance program using a hypothetical biomarker test. The 'surveillance with biomarker' strategy parameters was based on the procedures, methods, and outcomes reported by Galipeau *et al.* (2007)[23]. In this study, patients with Barrett's esophagus were evaluated at baseline for TP53 and CDKN2A (p16) alterations, tetraploidy, and aneuploidy using sequencing, loss of heterozygosity, methylation-specific PCR and flow cytometry. Their patient cohort was typical for gender, age, and Barrett's esophagus segment length, compared to other specialty referral centers. The cumulative esophageal adenocarcinoma incidence and relative risk of progression to esophageal adenocarcinoma at 10 years were calculated for

patients with different numbers of the positive markers at baseline, relative to patients with no abnormalities. For our model we took used this data to estimate the risk of progression for individuals with a "positive biomarker test". A positive test was determined to be the presence of three of the abnormalities identified by Galipeau. In Galipeau's study these patients had a significantly higher cancer incidence over 10 years follow-up[23]. The diagnostic performance of the biomarker tests for predicting the progression from BE, low- or high-grade dysplasia to esophageal cancer was 40.7% sensitivity and 98.0% specificity. Under our model, patients with the "positive biomarker test" were assigned to receive more frequent (6-monthly) endoscopic surveillance. Transition rates were derived by iterating a hidden Markov model (see below) using an expectation–maximization algorithm to generate overall expected rates of progression (proportionally adjusted to be relative to our overall base rates) to cancer and dysplasia for positive or negative tests[40]. Alternative strategies were also examined where: 1) patients with a "positive biomarker test" received prompt radiofrequency ablation therapy and accrued the same outcomes as patients with high-grade dysplasia, and patients with a "negative biomarker test" received no further surveillance; and 2) patients testing negative received no surveillance for the first five years and 2-yearly surveillance thereafter.

Results

Over 30 years, the (discounted) mean cost per person for the surveillance alone strategy was $14,659, compared with $11,087 for surveillance modified by a biomarker test, and $5,226 for no surveillance. The corresponding mean QALYs were 12.192 for surveillance alone, 12.190 for the strategy of surveillance with biomarker testing and 12.037 for no surveillance. On average, the additional benefit for both surveillance strategies was equivalent to 57 additional days in good quality of life. Compared with no surveillance, the incremental cost per QALY was $60,858 for surveillance alone and $38,307 for surveillance modified by biomarker testing (Table 3). The incremental cost per QALY was improved for surveillance modified by a biomarker test due to lower costs and similar QALYs vs. surveillance alone, arising from a higher proportion of low-risk individuals with a negative test result receiving no further surveillance. In a comparison of 'no surveillance' versus patients testing

positive for biomarkers and receiving radiofrequency ablation or no surveillance for those testing negative, the results showed that ‘no surveillance’ was superior with higher QALYs and fewer total costs. However, if patients testing positive for biomarkers received 6-monthly surveillance while patients with negative tests received no surveillance in the first five years and 2-yearly surveillance thereafter, the ICER was $48,111 compared to a strategy of ‘no surveillance’.

Results showed the most sensitive estimates were the annual progression rates from non-dysplastic Barrett’s esophagus to high-grade dysplasia, and from low- to high-grade dysplasia, with high progression rates under surveillance leading to high cost-effectiveness ratios (Table 4). Low progression estimates for all non-surveillance states also increased the cost-effectiveness ratios substantially. The hypothetical increased yield of high-grade dysplasia found with positive biomarker tests and subsequent changes in management also influenced the ratios markedly (Table 4). Less frequent surveillance endoscopies improved the cost-effectiveness of surveillance substantially. When a disutility was incorporated for individuals undergoing surveillance, the ‘no surveillance’ option was superior to surveillance alone but surveillance with a biomarker remained cost-effective. Finally, the results of the two-way sensitivity analyses show surveillance with hypothetical biomarkers would be preferred at current estimates of progression from non-dysplastic Barrett’s esophagus to low- or high-grade dysplasia, under no surveillance and lower proportions of individuals with positive biomarkers (Figure 2a). The biomarker surveillance option would also be preferred under current progression estimates and higher background utility values (Figure 2b) or younger surveillance starting age (<55 years) (Figure 2c).

For the surveillance with a hypothetical biomarker test versus no surveillance, more favorable cost-effectiveness ratios were found in virtually all sensitivity analyses but relied on the base assumption of estimates of progression across dysplasia states and adenocarcinoma. In the probabilistic sensitivity analysis, using 5000 simulations, the probability that surveillance alone was cost-effective compared with no surveillance was 16.0%, while the probability was 60.6% for surveillance with a biomarker testing strategy (Figure 3), at the threshold of $100,000 per QALY gained.

Discussion

Our results indicated that the surveillance alone strategy, as presented here, is unlikely to be cost-effective, when compared with no surveillance. This result is uncertain, however, due to the volatility in the model that results from small variations in the progression rates between dysplasia grades and the subsequent development of adenocarcinoma. However, the cost-effectiveness was markedly improved under the hypothetical scenario of biomarker testing, with acceptable limits of sensitivity and specificity, which serves to differentiate surveillance program participants into low- and high-risk groups, and subsequently with more targeted treatment pathways and higher proportions of pre- or early-stage cancers detected. The cost-effectiveness of an alternative biomarker strategy remained favorable if patients testing negative for biomarkers did not receive surveillance in the first five years and received 2-yearly surveillance thereafter. In addition, if endoscopy surveillance of patients with non-dysplastic Barrett's esophagus was scheduled less frequently, either 3- or 5-yearly and/or annually for low-grade dysplasia, the cost-effectiveness of surveillance would be acceptable in most health systems. This, however, assumes that no cancers are missed or progress to advanced stage disease and there is only limited evidence to support this [43].

Several Markov modeling studies using 'no surveillance' comparators have concluded the additional gains during surveillance are not cost-effective[17-18, 35] add Roberts KJ 2011 study to ref list. Compared to our findings, the favorable cost-effectiveness ratios previously found[19-20, 44] are likely to be due to a combination of the use of very high utility values (~0.97), infrequent surveillance intervals (5 yearly) and less coverage of the costs involved. These studies also used higher rates of progression to cancer under surveillance (~0.50%). In effect, the most favorable estimates were used to produce cost-effective surveillance findings and may not represent the broader and recent evidence base. Finally, Rubenstein JH *et al.* 2005 took a different approach to us with their hypothetical cost-effectiveness study involving a biomarker testing option. Unlike our study that relied on actual 'wet lab' biomarker data, Rubenstein JH *et al.* worked backwards to try and determine how sensitive and specific a "biomarker" would need to be, and how cheap, to be

cost effective in surveillance. Compared with their Markov model, our model was more comprehensive in terms of treatment options.

In so much that cost-effectiveness was clearly improved, our study suggests that endoscopic surveillance should be limited to high-risk individuals. However, identifying these high risk individuals is currently difficult and there are no biomarker based strategies currently available for routine clinical practice. Nevertheless, if future work can identify a strategy, this might have the desired impact of lowering costs and increasing QALYs. Biomarker testing also presents an opportunity for objective assessment of risk, and could replace risk assessment based on the identification of low-grade dysplasia and the problems with variation in histopathology interpretation for this diagnosis. However, the appropriateness of biomarker testing, its efficacy within a surveillance program, its feasibility and its acceptance are yet to be determined. Further research involving patients with positive biomarkers and additional high-risk factors such as, being male, the presence of esophagitis, length of Barrett's esophagus and length of time with Barrett's esophagus[28] is warranted on economic and efficacy grounds to elicit outcomes from a more targeted high-risk surveillance population.

The extent to which these findings are transferable to other settings will depend on several factors. The costs used in our study are specific for Australia. However, their relativities to each other should be broadly similar across other Western Countries. The assumptions made were based on an established long-running program with well-managed and clearly audited follow-up procedures to ensure patient adherence to appointments and endoscopist adherence to standardized protocols [26]. Additionally, endoscopic surveillance methods are not always consistent [45-46], and a reproducible diagnosis of Barrett's esophagus, with or without dysplasia, can also be difficult in individuals with short segments and hiatus hernia [47-49]. A limitation of our analysis is that we did not test our base results against different compliance rates with surveillance scheduling. Although the 90% compliance rate may be higher than that achieved in other parts of the world, our results still showed 'surveillance alone' had a low probability of being cost-effective. Surveillance is likely to be less cost effective if a lower compliance is modeled. Finally, although the UK-based British Society of Gastroenterology guidelines do not require patients to have

confirmed IM, our sample only included patients with IM and therefore, the results are likely to be applicable to patients undergoing surveillance in the US and other countries which define BE as requiring the presence of IM.

While we have based our treatment costs on a thorough analysis of treatment patterns among a large cohort [38], we have not considered the various treatment options for Barrett's esophagus which overlap with those for treating symptomatic gastro-esophageal reflux disease, namely proton pump inhibitor medications versus anti-reflux surgery. The goal of these treatments has been to treat reflux symptoms, with a hope that this might to limit progression to cancer. However, neither anti-reflux therapy produces predictable regression, or prevents cancer development [50-51], so for this model we assumed everyone was managed with proton pump inhibitor medication. We did not model the treatment of radiofrequency ablation for low-grade dysplasia as this is still an area of controversy, and there is no consensus that these patients should undergo radiofrequency ablation. There is also a lack of outcome data for radiofrequency ablation for low-grade dysplasia to allow this approach to be modelled. If this was included, however, it is certain that the costs of the surveillance would have been higher than our base results due to the cost of radiofrequency ablation treatment added to ongoing endoscopic surveillance. Cost effectiveness for radiofrequency ablation for low-grade dysplasia can only be achieved if patients undergoing ablation can be discharged from ongoing follow-up, and there is currently no evidence to support this.

Our study enhances previous attempts to assess the cost-effectiveness of a Barrett's surveillance program for several reasons. First, we used a two-stage modeling approach, building in a detailed cancer treatment model within our surveillance model to elucidate the current drivers of cost/health outcomes of various available cancer treatments [27]. It was important to discern what features of treatment are likely to impact on costs/outcomes to ensure that when patients undergoing surveillance were identified with high-grade dysplasia or adenocarcinoma, potential cost-efficiencies of surveillance would not be jeopardized by expensive treatment options. In our model, a proportion of patients with high-grade dysplasia were promptly and actively 'treated' rather than using watchful waiting, which reflects current clinical practice. We also explored the potential for risk stratification to

influence the cost-effectiveness of surveillance. In addition, we used updated epidemiological estimates of cancer progression from large observational cohort studies (primary patient-level and published data) both involving general population Barrett's registries and long-term single-center surveillance program audit reports. Using population-based published estimates on progression rates and quality-of-life enhances the previous economic evaluations that were largely reliant on author assumptions [16].

The cost-effectiveness of appropriate management strategies for patients with Barrett's esophagus must be considered. Using current estimates of the malignant potential of Barrett's esophagus in the wider population versus those reported in surveillance program audits, surveillance of all patients with non-dysplastic Barrett's esophagus may not be cost-effective. However, further work to identify high-risk individuals, perhaps in the future using a biomarker based strategy, might enable endoscopy surveillance to be tailored to high-risk individuals and thereby improve the economic acceptability of endoscopy based surveillance of Barrett's esophagus.

Table 1: Model estimates and sources

Description	Estimate used	Sensitivity values	Source(s)
Starting age (years)	50	55, 60	Assumption
Surveillance frequency (NDBE/LGD)	2 years/6 mths	3 or 5 years or none/1 year	UK Guidelines [25]
Discount rate for costs and/or effects	5%	0%, 1.5%, 3.5%	Australian standards
Background mortality rates	Life Tables	-	[29] Weighted 66% men
Annual progression/regression rates (% per year)[1]			
Barrett's free to LGD	0.40%	-	Sharma 2009 [52]
Barrett's free to HGD	0.10%	-	Assumption
NDBE to Barrett's free (regression)	2.43%	1.75%, 0.75%	Garside 2006 [35]
LGD to NDBE (regression)	7.81%	6.65%, 8.62%	Sth Aust. data, 95%CI beta
HGD to EAC	19.38%	±20%	Sth Aust. data
No surveillance:			
NDBE to LGD	4.3%	2.8%, 6.0%	Sharma 2009 [52]
NDBE to HGD	0.16%	0.13%, 0.19%	de Jonge 2010 [30]
NDBE to EAC	0.33%	0.09%, 0.5%	Desai 2011 [31], Hvid Jensen 2011 [22], Sharma 2009 [52]
LGD to HGD	1.91%	0.86%, 0.34%	Hvid Jensen 2011 [22]
LGD to EAC	0.51%	0.19%, 1.30%	Hvid Jensen 2011 [22]
Under surveillance:			
NDBE to LGD	2.94%	±20%	Sth Aust. data
NDBE to HGD	0.39%	±20%	Sth Aust data [53-54]
NDBE to EAC	0.05%	±20%	Sth Aust data [54-55]
LGD to HGD	0.93%	±20%	Sth Aust. data
LGD to EAC	0.12%	±20%	Sth Aust. Data
Under surveillance plus biomarker:	(+ve/-ve)		
NDBE to LGD	10.94%/1.47%	±20%	[2], Galipeau 2007 [23]
NDBE to HGD	1.46%/0.20%	±20%	[2], Galipeau 2007 [23]
NDBE to EAC	0.05%/0%	±20%	Assumption
LGD to HGD	3.46%/0.46%	±20%	[2], Galipeau 2007 [23]
LGD to ACO	0.12%/0%	±20%	Assumption
Probabilities:			
EAC is T1	0.152	-	Weighted av Sth Aust/ACS
EAC is T2	0.228	-	Weighted av Sth Aust/ACS
EAC is T3	0.431	-	Weighted av Sth Aust/ACS
EAC is T4	0.052	-	Weighted av Sth Aust/ACS
EAC is DM	0.137	-	Weighted av Sth Aust/ACS
EAC is T1 under surveillance	1.000	-	Sth Aust. data, [32]
Person tests positive for 3 biomarkers	0.145	0.102, 0.189	Galipeau 2007 [23]
Utilities[3]:			
Background annual utility	0.895	0.683, 0.95	Viney 2011 [33]
Early stage EAC (T1 or T2) (disutility)	-0.168	-	Sullivan 2011 [37]
Late stage EAC (T3 or T4) (disutility)	-0.235	-	Garside 2006 Gerson 2004 [35-36]
Distant metastases (disutility)	-0.550	-	de Boer 2002 [34]
Radiofrequency ablation 1st 6mth (disutility)	-0.035	-	de Boer 2002 [34]
Costs ($AU 2011)			
Biomarker testing per person	$458	$321, $595	Sth Aust Hospital costs
Unit cost of surveillance endoscopy	$1,145	$802, $1,489	Sth Aust Hospital costs
Surveillance management per person	$163	$114, $212	Sth Aust Hospital costs
Radiofrequency ablation for positive biomarker (5 yrs)[4,5]	$18,522	$12,965, $24,079	Sth Aust Hospital costs
High grade dysplasia treatment (5 yrs)	$41,806	$29,264, $54,348	Gordon 2011 [27]
T1 cancer (5 yrs)	$66,032	$46,222, $85,842	Gordon 2011 [27]

Description	Estimate used	Sensitivity values	Source(s)
T2 cancer (5 yrs)	$83,187	$58,231, $108,143	Gordon 2011 [27]
T3 cancer (5 yrs)	$82,566	$57,796, $107,366	Gordon 2011 [27]
T4 cancer (5 yrs)	$82,938	$58,057, $107,819	Gordon 2011 [27]
Distant metastases (6 months)	$13,651	$9,556, $17,746	Gordon 2011 [27]

EAC: esophageal adenocarcinoma, ACS: Australian Cancer Study, DM: distant metastases, LGD: low-grade dysplasia, HGD: high-grade dysplasia, NDBE: non-dysplastic Barrett's esophagus

1. Rates were converted to 6-monthly probabilities using a rate to probability formula: $(1 - e^{-rate\ x\ time})$ and also adjusted for the diminishing pool of persons in the model over time
2. Rates were derived by iterating the model backwards to generate overall expected rates of progression to EAC and HGD for BM+ and BM- in our surveillance program - these rates were derived from Galipeau et al's published data for p53 LOH + aneuploidy + tetraploidy, and proportionally adjusted to be relative to our overall base rates.
3. Similar to a health-related quality of life score from 0-1 with 1=highest health status
4. Treatment costs were originally calculated over approx. 5 years with the majority occurring in the first year, therefore these were assumed to accrue during the first 12 months in the model.
5. Radiofrequency ablation costs do not include estimate of infrastructure costs, which would include the base Radiofrequency ablation machine.

Table 2: Outcomes of adenocarcinoma incidence in Barrett's esophagus in patients within a surveillance program

Source	Place	Type of Study	No. of pts	IM %	SSBE included	Mean follow-up years	Patient-years of follow-up	Adenocarcinoma		High-grade dysplasia	
								Incidence n/pt-yrs	%/yr	Incidence n/pt-yrs	%/yr
15 studies[1] 1984-2004	UK, US, Europe	Prospective and Retrospective	50 to 357	18 to 100	7 yes, 8 no	2.6 to 5.5	163 to 1293	1/52 to 1/285	ns	ns	ns
Murphy 2005 [53]	N. Ireland	Retrospective	178	100	yes	3.4	613	1/204	0.50%	1/30	0.99%
Olithselvan 2007 [54]	UK	Prospective	121	100	ns	3.5	ns	1/171	1.41%	1/161	
Switzer-Taylor 2008 [56]	NZ	Retrospective	212	88	no	3.95	895	1/100	1.00%	ns	ns
Bright 2009 [32]	Australia	Prospective	405	ns	yes	2.0	776	1/194	0.52%	1/129	0.78%
Roberts 2010 [55]	UK	Retrospective	302	ns	ns	2.2	ns	1/61	0.77%	1/302	0.15%
Adjumobi 2010 [57]	USA	Retrospective	165	ns	ns	4.2	ns	ns	0.00%	ns	0.86%
Wani 2011 [58]	USA	Prospective	210	100	yes	6.2	1364	1/160	0.44%	1/46	1.61%
Sth Aust data[2] 2012	Australia	Prospective	568	100	yes	2.0	2040	1/2040	0.05%[3]	1/255	0.39%[3]

IM: intestinalised metaplasia, ns: not stated, pt-yrs: patient-years SSBE: short-segment Barrett's esophagus

1. Table 1 in Murphy SJ *et al.* 2005 [53]
2. South Australian surveillance data - cohort overlaps with cohort in Bright 2009 [32]
3. Values selected in the economic model were EAC incidence 0.05%, HGD incidence 0.39%.

Table 3: Mean costs (US$) and health outcomes over 30 years[1]

Strategy	Costs	Life years	HGD cases /1000	Cancer cases /1000	QALYs	Δ costs	Δ QALYs	ICER
No surveillance	$5,226	26.96	73	137	12.04	ref	ref	ref
Surveillance alone vs No surveillance	$14,659	27.32	105	98	12.19	$9,433	0.16	$60,858
Surveillance with biomarker test[2] vs No surveillance:	$11,087	27.31	103	98	12.19	$5,861	0.15	$38,307
Surveillance with biomarker test[2] vs Surveillance alone	$11,087	27.31	103	98	12.19	$3,572	0.00	$1,946,085
Alternative biomarker scenarios vs No surveillance:								
1. +ve: RFA, -ve: no surveillance	$7,652	23.93	45	51	10.47	$2,426	-1.49	Dominated[3]
2. +ve: NDBE 6-monthly surveillance, -ve: no surveillance first 5 years, 2-yearly NDBE surveillance thereafter	$12,587	27.31	103	98	12.19	$7,361	0.15	$48,111

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, NDBE: non-dysplastic Barrett's esophagus, RFA: radiofrequency ablation treatment, +ve: positive biomarker test, -ve: negative biomarker test

1. Costs and QALYs presented here are discounted at 5% per year.
2. Surveillance with the biomarker test , if test is positive the patient receives 6-monthly surveillance, or for a negative test, the patient receives no surveillance.
3. 'No surveillance' produced higher costs and lower QALYs than 'no surveillance' therefore no surveillance is dominant.

Table 4. Results of one-way sensitivity analyses on incremental cost per QALY ratios (US$)

Strategy	Surveillance alone vs No surveillance	Surveillance with biomarker testing vs No surveillance
Base case	**$60,858**	**$38,307**
Start Age (base 50 years):		
55 years	$71,066	$45,475
60 years	$87,386	$57,128
Discounting (base 5% costs and effects):		
0% costs and effects	$45,653	$27,080
3.5% costs and effects	$56,000	$34,538
5% costs and 0% effects	$21,217	$13,285
3.5% costs and 1.5% effects (UK)	$36,942	$22,790
Maximum surveillance duration (base 30 years):		
5 years	$286,000	$193,000
10 years	$164,219	$106,818
20 years	$83,520	$54,600
Surveillance frequency (base NDBE 2 yrs/ LGD 6 months)		
NDBE 3 yrs/LGD 6 months	$48,187	n/a (same as base)
NDBE 5 yrs/LGD 6 months	$38,161	"
NDBE 3 yrs/LGD annual	$31,755	"
NDBE no surv/LGD annual	$10,097	
Proportion with positive biomarker test (base 14.5%)		
Low 10.2%	-	$18,431
High 18.9%	-	$126,649
Annual progression rates with no surveillance:		
NDBE to ACO low – 0.09%	Dominated[1]	Dominated[1]
NDBE to ACO high – 0.50%	"	"
NDBE to HGD low – 0.11%	$69,401	$43,970
NDBE to HGD high – 0.90%	$48,597	$30,212
NDBE to LGD low – 2.8%	$104,095	$67,925
NDBE to LGD high – 6.0%	$41,537	$25,234
LGD to ACO low – 0.19%	$116,976	$54,712
LGD to ACO high - 1.30%	$27,513	$21,765
LGD to HGD low - 0.86%	$114,824	$74,554
LGD to HGD high - 3.37%	$35,466	$21,518
Annual progression rates under surveillance:		
NDBE to ACO low – 0.04%	$60,858	$38,307
NDBE to ACO high – 0.06%	$69,654	$38,307
NDBE to HGD low – 0.31%	$39,438	$38,307
NDBE to HGD high – 0.47%	$125,623	$38,307
NDBE to LGD low – 2.35%	$50,329	$38,307
NDBE to LGD high – 3.53%	$73,876	$38,307
LGD to ACO low –0.09%	$59,703	$38,058
LGD to ACO high –0.14%	$62,497	$38,559
LGD to HGD low –0.74%	$48,932	$38,307

LGD to HGD high –1.11%	$77,943	$38,307
HGD to ACO low – 15.5%	$61,143	$38,414
HGD to ACO high – 23.3%	$60,929	$38,412
Annual progression rates under surveillance with biomarker:		
Positive		
NDBE to HGD low – 1.2%		$33,000
NDBE to HGD high – 1.8%		$46,449
NDBE to LGD low – 8.75%	n/a same as base	$34,266
NDBE to LGD high – 13.1%		$43,022
LGD to HGD low –2.76%		$31,296
LGD to HGD high –4.15%		$48,860
Negative		
NDBE to HGD low – 0.16%		$30,280
NDBE to HGD high – 0.24%	n/a same as base	$51,897
NDBE to LGD low – 1.2%		$33,117
NDBE to LGD high – 1.8%		$44,563
LGD to HGD low –0.37%		$36,528
LGD to HGD high –0.56%		$41,245
Health state quality of life (utilities) (base – annual 0.895)		
Background utility low (0.683)	$91,583	$37,813
Background utility (0.95)	$3,144,333	$35,521
Disutility for surveillance	Dominated[1]	$50,094
Costs		
Treatment costs of HGD and T1 to T4 were 30% lower	$62,748	$40,046
Treatment costs of HGD and T1 to T4 were 30% higher	$32,587	$22,889
Endoscopy cost 30% lower (base $1145): $802	$59,987	$37,503
Treatment costs when 90% patients with T1a receive endoscopic treatments (base 50%)	$59,265	$37,497

ACO: adenocarcinoma of the esophagus, HGD: high-grade dysplasia, LGD: low-grade dysplasia, NDBE: non-dysplastic Barrett's esophagus,

1. Dominated means the no surveillance strategy produced lower costs and higher QALYs than either surveillance option.
2. This also simultaneously decreases the corresponding rates of progression in the biomarker negative testing arm.

Figure Legends

Figure 1: Model schematic

Figure 2: Results of probabilistic sensitivity analysis to test parameter uncertainty. Cost-effectiveness acceptability curves are produced and provide the probability (y axis) that the strategy is cost-effective at a health system's willingness to pay for QALYs (x axis). At each threshold of willingness to pay on the x axis, the probabilities for each strategy sum to 1.

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