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A UK BASED COST-UTILITY ANALYSIS OF RADIOFREQUENCY ABLATION OR OESOPHAGECTOMY FOR THE MANAGEMENT OF HIGH-GRADE DYSPLASIA IN BARRETT'S OESOPHAGUS

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Original article

**A UK BASED COST-UTILITY ANALYSIS OF RADIOFREQUENCY ABLATION OR
OESOPHAGECTOMY FOR THE MANAGEMENT OF HIGH-GRADE DYSPLASIA IN
BARRETT'S OESOPHAGUS**

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Abbreviations: Barrett's oesophagus – BO, Adenocarcinoma – ADC, High grade dysplasia – HGD, photodynamic therapy – PDT, National Institute of Clinical Excellence – NICE, radiofrequency ablation – RFA, quality adjusted life year – QALY, willingness to pay – WTP, intestinal metaplasia – IM, low grade dysplasia – LGD.

Keywords: Barrett oesophagus, Oesophagus, Oesophageal cancer, Health economics

SUMMARY

Background

In the UK, oesophagectomy is the current recommendation for patients with persistent high-grade dysplasia in Barrett's oesophagus. Radiofrequency ablation is an alternative new technology with promising early trial results.

Aim

To undertake a cost utility analysis comparing these two strategies.

Methods

We constructed a Markov model to simulate the natural history of a cohort of patients with high-grade dysplasia in Barrett's oesophagus undergoing one of two treatment options; (i) Oesophagectomy (ii) Radiofrequency ablation followed by endoscopic surveillance with oesophagectomy for high-grade dysplasia recurrence or persistence.

Results

In the base case analysis radiofrequency ablation dominated as it generated 0.4 extra quality of life years at a cost saving of £1902. For oesophagectomy to be the most cost effective option required a radiofrequency ablation treatment failure rate (high-grade dysplasia persistence or progression to cancer) of greater than 44%, or an annual risk of high-grade dysplasia recurrence or progression to cancer in the ablated oesophagus of greater than 15% per annum. There was an 85% probability that radiofrequency ablation remained cost effective at the NICE willingness to pay threshold range of £20000-30000.

Conclusion

Radiofrequency ablation is likely to be a cost effective option for high-grade dysplasia in Barrett's oesophagus in the UK.

INTRODUCTION

Barrett's oesophagus (BO) is estimated to be prevalent in 0.5-2% of adults in the western world, rising to approximately 15% in those with chronic gastro-oesophageal reflux disease.¹⁻³ The main complication is the development of oesophageal adenocarcinoma (ADC), the incidence of which is highest in the UK and rising faster than any other solid tumour in western countries.^{4,5} Once invasive cancer develops the outlook is poor, with a 5-year survival of only 10-13%.^{6,7} In an attempt to prevent this, it is currently recommended that patients with BO undergo surveillance endoscopy every 2-3 years. Detection of pre-malignant or dysplastic change on biopsy, signals an increased risk of malignant development, especially high-grade dysplasia (HGD) where the risk of progression to invasive cancer is 30-35% within 5-years.⁸

Current UK guidance recommends that for patients with persistent HGD despite intensive acid suppression, oesophagectomy be performed in a specialist centre in those fit for surgery.⁹ However, surgical oesophagectomy is a high risk procedure, even in tertiary centres, with a 30-day mortality rate of 3.2%, significant post operative complications in up to 40%, and long term morbidity.^{10,11}

Oesophagectomy is expensive, with an average cost to the NHS of approximately £7500 per person.

A number of alternative less invasive ablative therapies exist that aim to remove the dysplastic Barrett's epithelium and facilitate the restoration of normal squamous epithelium. Photodynamic therapy (PDT), approved by the National Institute for Clinical Excellence (NICE) for treatment of HGD in BO, involves intravenous administration of a photosensitising agent, followed by endoscopic light laser exposure to the Barrett's segment.¹² PDT is effective at eliminating HGD in BO.¹³ However, widespread acceptance of the technique has been held back by treatment related adverse events in up to 94% and a high incidence of oesophageal strictures in up to 36%.¹⁴

Radiofrequency ablation (RFA) using the HALO device is an alternative new management strategy for patients with HGD in BO. Recent results from a randomised sham controlled study have shown that it is effective at eliminating HGD in BO in up to 90% of patients with complete reversion to squamous oesophageal lining in 80% at 12 months follow up, and minimum treatment related side effects.¹⁵ The cost per patient to the NHS is not currently known and there has been no randomised controlled trial comparing RFA and oesophagectomy.

The aim of this study was to model whether RFA followed by oesophagectomy for persistence or recurrence of HGD is a cost effective option for the treatment of BO with HGD when compared to the

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2
3 current UK recommendation of oesophagectomy, and to identify critical parameters to guide further
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5 research.
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METHOD

Patients

Our model consisted of a hypothetical cohort of 100 male patients aged 64 years, the mean age of patients undergoing oesophagectomy for HGD in published trials over the last 10 years.¹⁶⁻²⁶ We assumed the following pre-treatment assessment for both strategies; endoscopy had been undertaken on two occasions revealing BO with HGD, and any visible nodules, masses or surface irregularities had been removed by endoscopic mucosal resection. Patients found to have invasive cancer after endoscopic mucosal resection were excluded from the analysis. It is assumed that patients were fit for both treatment modalities. The model included patients with either uni- or multifocal HGD.

The Model

A Markov model was constructed in Microsoft Excel to simulate the two treatment strategies; RFA with surveillance and oesophagectomy for HGD or ADC recurrence/persistence, or immediate oesophagectomy. Figures 1 and 2 summarise the structure of the treatment strategies. The model was constructed to include major procedural and post-procedural complications and mortality reported in the literature. At the end of each cycle, which corresponded to 6 months, patients would progress to a health state depending on the derived transition probabilities. UK life table mortality rates were incorporated into the model to account for age-specific mortality from other causes.²⁷ A utility and cost was attributed to each state, which patients would accumulate as they progressed through the model. The analysis followed the cohort for 25 years or to death. We estimated costs from an NHS perspective and outcomes from the viewpoint of the patient. All costs and benefits were discounted at 3.5% as recommended by the NICE.²⁸

Treatment strategies and model assumptions

Oesophagectomy

In this strategy, patients with confirmed HGD in BO underwent immediate oesophagectomy. If a patient developed ADC post operatively, it was assumed that they entered a 6-month terminal cancer phase, representing the median survival time with inoperable oesophageal cancer, and allowing the modelling of costs and measures of quality of life experienced by this group of patients, such as palliation of dysphagia with oesophageal stenting.²⁹ If a patient did not progress to terminal cancer during the first 5-years post oesophagectomy, they were considered cured. All patients were followed up in outpatient clinics post-oesophagectomy for 5-years as follows; 3-monthly for year 1, 6-monthly for the years 2 and 3, and then annually for years 4 and 5.

Radiofrequency ablation

In this strategy, patients with confirmed HGD in BO underwent a treatment course of RFA with the HALO device (Barrx Medical, Sunnyvale, California, USA). This is delivered endoscopically under conscious sedation as a day case procedure. The HALO 360 is a balloon based device able to deliver a circumferential radiofrequency burn to the mucosal lining of the oesophagus, whereas the HALO 90 allows targeting of mucosa over an approximate 90° radius. Published experience to date suggests an average of two HALO 360 and two HALO 90 sessions are needed per patient to achieve complete removal of the Barrett's segment and replace it with a neo-squamous lining.³⁰

There is no fixed surveillance strategy for patients with neo-squamous and BO post RFA. For the base case analysis we assumed the following strategy. If neo-squamous oesophagus is found after RFA, then yearly endoscopy was performed for 5-years, and if free of BO or worse pathology after that time, no further endoscopic follow-up was undertaken. If the patient had BO after RFA treatment then yearly endoscopy was performed for the first 5-years, and if free of HGD or worse at that time, endoscopic surveillance continued on a 2-yearly basis as per current UK practice. In the scenario analysis this screening protocol was altered to analyse what effect it would have on the outcome of our cohort.

If HGD or ADC is picked up during the above surveillance strategies, then the patient undergoes an oesophagectomy. This part of the RFA model has the same structure as the oesophagectomy strategy. We assumed that the risk of developing cancer in the neo-squamous oesophagus is most

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3 probable during the first 5-years post treatment, and thus after this period (as with the post
4 oesophagectomy group), the patient was considered cured.

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7 The risk of developing HGD or ADC in patients with neo-squamous oesophagus was estimated using
8 published data of having residual non-visible islands of Barrett's, termed subsquamous intestinal
9 metaplasia.¹⁵ The low value assumed no risk of residual subsquamous intestinal metaplasia and the
10 high value assumed a higher risk of having non-visible islands of Barrett's found with previous
11 ablative therapies, and assuming the residual Barrett's contained HGD.³¹

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17 There are no data on the outcome of those with treatment failure post RFA. For this we have drawn
18 parallels with data from other ablative therapies (PDT) where longer term follow up available. This
19 demonstrates that treatment failures were still operable at time of progression, and revealed disease
20 not extending beyond the submucosa (T1) on post operative staging.²² On this basis, in our model
21 those with post RFA treatment failure had operable disease but with a reduction in 5-year survival
22 consistent with the predicted more advanced disease.

23 24 25 26 27 28 29 **Search Strategy for parameters**

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31 Parameter values for transition probabilities and utilities were obtained from peer reviewed literature.
32 We searched the Medline database May 1999 to May 2009, as well as abstracts from Digestive
33 Diseases week and British Society of Gastroenterology Annual Meeting. Bibliographic lists of relevant
34 articles were searched, and in addition we obtained a list of relevant papers from the manufacturers of
35 the HALO device. We chose the most suitable study(s) to provide the parameters for the base case,
36 by using data from randomised controlled trials if available. If not available we chose data from well
37 constructed observational (cohort) studies, with inclusion criteria similar to those in our hypothetical
38 cohort. We assessed inclusion criteria, baseline assessment, size, duration of follow-up, loss to
39 follow-up and assessment of outcome. In addition to the base case values we selected a plausible
40 range (high/low values) for use in the sensitivity analysis. This range was derived from variations in
41 the published literature, or by author consensus when information was not available or there was
42 considerable uncertainty in the literature. Annual risks and 5-year survival data were converted to 6-
43 monthly probabilities using validated formulae³², with the assumption that 6-monthly progression
44 rates were constant. Derived transition probabilities are shown in table 1.

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Table 1: Transition probabilities

Description	Base case estimate	Range	Distribution	Source
RFA complications				
No complications	0.94	0.90-1	Jointly determined Dirichlet	15, 33, 34; assumption
Perforation	0.0005	0-0.005		
Stricture requiring dilatation	0.06	0-0.09		
Outcomes after RFA				
Neo- squamous lined oesophagus	0.82	0.45-0.91	Jointly determined Dirichlet	15, 33, 34; assumption
Barrett's oesophagus without HGD	0.11	0.09-0.25		
HGD or adenocarcinoma	0.08	0-0.30		
Progression probabilities during post RFA surveillance (per cycle – 6 months)				
Neo-squamous to HGD/ADC	0.0002	0-0.0027	Beta ($\alpha = 1, \beta = 4596$)	31, 35, 36
Barrett's to HGD/ADC	0.0068	0-0.0085		
Oesophagectomy complications				
Peri-operative complications	0.37	0.27-0.57	Beta ($\alpha = 26, \beta = 44$)	18, 22, 25
Anastamotic stricture	0.51	0.13-0.83	Beta ($\alpha = 27, \beta = 26$)	18, 22, 26
Progression to adenocarcinoma post oesophagectomy				
After oesophagectomy for HGD	0.001	0-0.007	No distribution	18, 22, 23, 25
After oesophagectomy for post RFA recurrence	0.0057	0-0.021	Beta ($\alpha = 18, \beta = 3239$)	22, 37
Mortality				
Death from iatrogenic oesophageal perforation	0.35	0-0.5	Beta ($\alpha = 2, \beta = 15$)	38
Death from oesophageal dilatation	0.005	0-0.01	Beta ($\alpha = 3, \beta = 551$)	38
Death from oesophagectomy	0.014	0-0.045	Beta ($\alpha = 1, \beta = 69$)	22, 23, 25, 26, 37

Utilities

Where available, we selected utilities derived using the standard gamble methodology, which avoids measurement biases associated with ratings scales, such as a visual analogue score.³⁹ We were unable to obtain utility values for all model states, and thus used known recorded values to provide a framework by which unknown values were estimated by a consensus of the authors. Low and high values were derived either from 95% confidence intervals if available, or estimated by the authors to allow for the uncertainty surrounding the individual parameter. Derived utilities are shown in table 2. Utility values were then used to generate quality adjusted life years (QALY) which were used as the outcome measure in the model.

Table 2: Health state utilities

Description	Base case estimate	Range	Distribution	Source
RFA without complications	0.94	0.84-1	Beta ($\alpha = 31, \beta=2$)	Assumptions based on reference ⁴⁰ and ⁴¹
RFA complicated by stricture	0.92	0.82-1	Beta ($\alpha = 31, \beta=3$)	
Post RFA with neo-squamous oesophagus	0.97	0.9-1	Beta ($\alpha = 42, \beta=1.3$)	
Post RFA with Barrett's oesophagus	0.95	0.883-1	Beta ($\alpha = 50, \beta=3$)	
Oesophagectomy without complications	0.92	0.77-1	Beta ($\alpha = 19, \beta=2$)	40
Oesophagectomy with complications	0.91	0.66-1	Beta ($\alpha = 9, \beta=1$)	
Anastamotic stricture post oesophagectomy	0.92	0.841-0.999	Beta ($\alpha = 41, \beta=4$)	41
Fully recovered post oesophagectomy	0.96	0.89-1	Beta ($\alpha = 46, \beta=2$)	40
Terminal oesophageal cancer	0.34	0.03-0.65	Beta ($\alpha = 3, \beta=5$)	

Costs

The costs used in the model are shown in table 3. The majority of costs were estimated from NHS reference costs.⁴² This derives costs from nationally collected data from NHS trusts and calculates an average total cost of delivering a treatment episode to a patient. The cost of RFA is not available on this national tariff and thus was estimated using direct and variable costs derived from information obtained from the UK distributor (Synetics Medical Limited, Middlesex, UK). All costs were for 2009/10 and are shown in UK pounds sterling. For the sensitivity analysis all cost were varied by +/- 25%.

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Table 3: Costs

Cost estimate (£)	Base case [†]	Reference
Treatment course of RFA	3,869	Costs supplied by Synetics Medical Ltd
Additional cost from developing perforation from RFA (excludes oesophagectomy)	2619	} NHS reference costs 2009/10 ⁴²
Routine endoscopy and biopsies	406	
Elective Oesophagectomy	6342	
Oesophagectomy with complications	9305	
Oesophageal dilatation	427	
Outpatient follow up per visit	72	
Palliation of untreatable adenocarcinoma	3863	³⁶ , NHS reference costs 2009/10 ⁴²

[†] For the probabilistic sensitivity analysis we used a Gamma distribution based on the assumption that +/- 25% formed a 95% confidence interval.

Sensitivity analysis

Deterministic

To enable thorough interrogation of the model and the input parameters we initially undertook one-way sensitivity analysis, in which the various parameters in the model are varied throughout the specified range to assess how this impacts upon study results.³⁹ For areas where uncertainties in the literature were identified or to interrogate areas where assumptions had been made, we undertook threshold analysis, which allows the critical value of a parameter central to the decision to be identified.³⁹ Where uncertainty in the methodology of the model existed such as in the time period of surveillance post RFA, a scenario analysis was undertaken to explore the effects of increasing surveillance.

Probabilistic

Probabilistic sensitivity analysis allows for all input parameters in a model to be specified as full probability distributions, rather than point estimates, allowing a representation of the uncertainty surrounding their values.⁴³ In the UK it is a requirement for all cost effectiveness models submitted to NICE. The distributions and parameters used for each variable in the model are shown in table's 1, 2 and 3. For probabilities of an event either occurring or not occurring we used beta distributions, which generates values between 0 and 1 and hence avoids unfeasible values. As the method of generating utilities used was based on standard gamble, negative values were not possible, and hence the beta distribution is appropriate. Where more than two events are possible, Dirichlet distributions were chosen, which ensures the total value of the probabilities of all events considered sum to 1. Gamma distributions cannot take negative values and have a skewed distribution, which is characteristic of many forms of cost data.

We repeatedly re-ran the model 5000 times using values randomly drawn from these distributions. To illustrate the uncertainty relating to our cost-effectiveness results we calculated a cost-effectiveness acceptability curve, which estimates the probability that an intervention is cost-effective at different values of a QALY.⁴⁴

RESULTS**Base Case**

The results from the base case analysis are summarised in table 4. For a 64 year old male patient, a strategy of RFA followed by oesophagectomy if there was disease recurrence, would be expected to cost £1902 less, and result in 0.4 more QALYs, when compared with immediate oesophagectomy.

The RFA strategy thus dominates immediate oesophagectomy. In addition the RFA strategy results in less morbidity (20.8% v 87.1%), procedure related mortality (0.4% v 2.6%), and cancer deaths (0.5% v 1%) than immediate oesophagectomy.

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Table 4: Base case results

Outcome per strategy	Oesophagectomy	RFA	Incremental ratio
Cost (£)	8555	6653	-1902
Unadjusted life-years	17.0	17.4	
QALY	13.8	14.2	0.4
Incremental cost effectiveness ratio (£/QALY)		Dominates	
Morbidity (%)			
<i>Procedural</i>	37.1	3.9	
<i>Strictures</i>	50.0	16.9	
Causes of death (% deaths)			
<i>Age-related</i>	96.4	99.1	
<i>Surgical</i>	1.9	0.2	
<i>Endoscopic</i>	0.7	0.2	
<i>Cancer</i>	1	0.5	

Sensitivity analysis

The one-way sensitivity analysis demonstrated that the following were important factors in determining the cost effectiveness of RFA; outcome post RFA, utility post RFA with Squamous oesophagus, and utility fully recovered post oesophagectomy.

Only at the most pessimistic outcome post RFA (i.e. 30% post RFA with HGD), was RFA more costly than oesophagectomy, although it still resulted in more QALYs, costing £661/QALY. Threshold analysis demonstrated that for oesophagectomy to dominate as the preferred strategy, required over 44% of patients to have residual HGD post RFA.

We altered utility values highlighted by the one-way sensitivity analysis. For oesophagectomy to become a more effective (but still more costly) option would require either a utility value of less than 0.93 post RFA with squamous oesophagus, or a utility fully recovered post oesophagectomy of over 0.99. Thus, it would require fully recovered post oesophagectomy to be a more preferable health state than post RFA with squamous oesophagus.

As there is uncertainty in the robustness of the neo-squamous epithelium post RFA, we undertook further threshold analysis to identify the HGD recurrence required to alter the results of the model. For this to occur would require an annual risk of HGD recurrence in the neo-squamous epithelium of 20%.

The need for or frequency of endoscopic surveillance after successful ablation with RFA is not currently known. We modelled a scenario of continuing surveillance in all patients post RFA, with 2-yearly endoscopy for both neo-squamous and BO, after initial yearly endoscopy for the first 5 years. With this strategy the cost of RFA increased considerably to £8168 with 14.2 QALYs. The cost of oesophagectomy remained at £8555 with 13.8 QALYs, and thus RFA still dominated as the preferred strategy.

As the method used to calculate the cost of RFA differed from other calculated costs, we undertook threshold analysis to determine how expensive treatment with RFA would need to be to alter the outcome of the model. For RFA to become a more expensive treatment strategy would require an increase of £1904 from the base case estimate, to £5773 per treatment course per patient. RFA retained its cost effectiveness at a willingness to pay (WTP) of £30000/QALY even if cost was increased to £17754, i.e. 450% more than the base estimate and over twice the cost of an oesophagectomy without complications.

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3 Altering all other variables through their specified range, including age (55-70yrs), and in addition
4 altering the discount rate (1-5%), and the length of time the cohort was followed for (5-30yrs), made
5 no critical difference to the model outcome.
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8 9 **Probabilistic sensitivity analysis**

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11 The cost effectiveness plane demonstrating the distribution of the results is shown in figure 3. This
12 scatter plot of the incremental costs and QALY pairs, generated from the probabilistic sensitivity
13 analysis, illustrates the uncertainty surrounding the estimates of expected costs and expected effects
14 associated with the RFA compared with the oesophagectomy strategy. The majority fall in the south-
15 east quadrant, the position where the RFA strategy is more effective and less costly than the
16 oesophagectomy strategy, and thus RFA is said to dominate.
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20 The cost effectiveness acceptability curve shows the probability that RFA is cost-effective as the
21 value placed upon a QALY is varied between £0 and £50,000 (figure 4). The probability that RFA is
22 cost-effective is approximately 84-86% throughout a WTP of £20000-30000/QALY, showing that RFA
23 appears highly likely to be cost-effective.
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Discussion

Our study demonstrates that for a 64 year old patient in the UK with HGD in BO, a treatment strategy of RFA followed by surveillance with oesophagectomy for HGD recurrence or progression to adenocarcinoma is less expensive and results in more discounted quality adjusted life years compared to immediate oesophagectomy. Our study supports recent findings which demonstrated that in a US setting, a strategy of RFA for HGD yielded more QALYs at less cost than surveillance, oesophagectomy, or other ablative strategies, with the exception of photodynamic therapy, which gave comparable QALYs but at a higher cost.⁴⁵

One of the roles of a health economic analysis such as ours is to identify areas of uncertainty which may guide future study. Our model has identified the following key areas. Firstly, concerns the success rate achievable by RFA at eliminating HGD from BO. Data thus far show that RFA is very effective at eliminating HGD with success in 90% or more of cases, and with removal of BO in between 60-91%. The modelling demonstrated that RFA remains cost effective even if eradication of HGD is achievable in only 60% of cases at a WTP of £30000/QALY, a figure well below the 90-97% in published trials,^{15, 33, 34, 46, 47} although the longest follow up available is currently limited to a median of 2-years.³⁴

Secondly, our one-way sensitivity analysis suggested that for oesophagectomy to become the preferred strategy, would require the utility of patients post RFA with neo-squamous oesophagus to be lower than utility of those post oesophagectomy. Utility values for patients undergoing RFA have not yet been derived, although there is some preliminary evidence that patients with resolution of dysplasia post RFA have an improvement in surrogate markers of quality of life, such as depression, stress, and difficulty sleeping as measured using a visual analogue scale.⁴⁸ We used deliberately conservative estimates of utility based around known values ascertained by standard gamble technique, considered a robust method for deriving utility values.³⁹ Although minimally invasive techniques for oesophagectomy are improving, resulting in lower morbidity and mortality, it is unlikely that a surgical approach would be a favoured patient preference.⁴⁹

A recent health economic evaluation by NICE looking at ablative therapies for treatment of HGD in BO has demonstrated that RFA with subsequent surveillance resulted in more QALYs but was considerably more expensive than oesophagectomy.⁵⁰ This in part contrasts our findings where we found that although the cost of RFA increased considerably with surveillance, it was still cheaper than

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3 oesophagectomy with more QALYs, and thus still dominated oesophagectomy as the preferred
4 strategy. We believe the explanation for the lack of parity was the inclusion of the cost of proton pump
5 inhibitors in their model in the post RFA, but not in the post oesophagectomy strategy. We would
6 argue that this unfairly biases the study in favour of oesophagectomy for two reasons. Firstly,
7 published quality of life data has suggested that up to 75% of patients post oesophagectomy still
8 complain of reflux symptoms, and this would likely have a major impact on cost incurred for
9 medication usage, and potentially on visits to their general practitioner or hospital consultations.¹¹
10 Secondly, in their model no allowance has been made for poor compliance, which would lead to
11 falsely high costs in the RFA strategy.
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21 The need for or frequency of endoscopic surveillance after successful ablation with RFA is not
22 currently known. The long term stability of the neo-squamous epithelium is not yet determined and
23 this is likely to lead to clinicians continuing surveillance on their patients, despite apparent histological
24 resolution. In our model, although the cost of RFA strategy increased considerably due to follow up
25 and surveillance, it still dominated the oesophagectomy strategy. In both the NICE health economic
26 model and the published US study, surveillance considerably added to the cost of ablative therapies,
27 and made RFA a more expensive strategy than oesophagectomy.^{45, 50} The frequency and duration of
28 follow up endoscopy for patients who have undergone successful ablation will thus need to be
29 considered very carefully, once the durability of the neo-squamous mucosa has been determined with
30 long term follow up data.
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41 Other management strategies for treating HGD in BO exist such as surveillance alone, PDT or other
42 ablative therapies. In the UK surveillance of those with HGD is not presently practiced. Several
43 previous cost effective analyses comparing ablative therapy to surveillance, have found surveillance
44 to be costly and inefficient at preventing progression to cancer.^{45, 51, 52} Studies from the US have
45 demonstrated PDT is an effective alternative to oesophagectomy, but at a wide variation in cost
46 between \$6000 and \$50000/QALY. Acceptance of PDT as an option in the UK has been hampered
47 by a stricture rate as high as 35%, and the ultimate progression to cancer in 15%.¹³ RFA is a realistic
48 option given its low complication rate, and it appears to be effective at preventing cancer deaths, with
49 terminal cancer the cause of death in only 0.5% of our hypothetical cohort. Currently no patient in
50 reported trials has progressed to inoperable cancer, but longer periods of follow up are needed before
51 this apparently low risk can be confirmed.
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3 We have made a number of assumptions in our model which warrant further discussion. There is an
4 established progression from Barrett's intestinal metaplasia (IM), through low grade dysplasia (LGD),
5 HGD to invasive adenocarcinoma. For the purpose of this model IM and LGD were grouped together.
6
7 We have based this assumption on recent data which has suggested that LGD did not appear to
8 confer an increase risk of developing cancer.³⁵ In fact the majority regressed to IM or went back and
9 forth between LGD and IM. In addition, the histological classification and inter-observer agreement in
10 the diagnosis of LGD is variable, with factors such as inflammation playing an important role in
11 misclassification. Another assumption is not distinguishing between uni- and multifocal HGD, in
12 accordance with the other economic analyses in this area.^{45, 50} There is evidence to suggest that
13 patients with multifocal HGD are more likely to have a high risk of progression to adenocarcinoma
14 compared with patients with unifocal HGD.⁵³ Even with this increased risk it is felt unlikely this would
15 affect the outcome of our model, given the outcome of our threshold analysis. In addition these
16 findings were not supported by another retrospective study.⁵⁴ The parameters used in our model
17 included patients with both histological subtypes, and thus one would expect allowance for the
18 potential increase risk with multifocal HGD.

19
20 We have excluded those with T1 disease. Endoscopic resection of oesophageal ADC confined to the
21 mucosa (T1a) is practiced in the UK, given the low likelihood of lymph node invasion.⁵⁵ However,
22 there is a high risk of recurrent disease, with cancer-free survival of 80% in one series (although these
23 patients were able to have retreatment endoscopically without influencing survival), compared to 97%
24 of those undergoing an immediate oesophagectomy.⁵⁶ There is preliminary data suggesting RFA of
25 the remaining Barrett's segment after endoscopic resection of the T1a lesion can be achieved with
26 favourable outcomes.³³ Follow up was limited to a median of 21 months, during which one patient (of
27 16 in the cohort with ADC) developed disease infiltrating into the submucosa (stage T1b), which may
28 be associated with lymphatic spread in 20%.⁵⁵ The quality of life, costs, and outcomes involved in
29 such a treatment strategy are complex, and the health economic argument is therefore best served by
30 a separate analysis.

31
32 Randomised controlled trials are generally considered the most robust method of determining the
33 benefit of a new treatment⁵⁷, and certainly one could conclude that a randomised control trial of
34 Oesophagectomy versus RFA would be the next logical step. However randomised control trials are
35 costly and time consuming. The results of the model support the case that RFA should be the

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3 optimum strategy and only with pessimistic parameters does this outcome change. However it may
4 be influenced by the outcome after RFA, and thus prospective long-term outcome data from a well
5 constructed clinical trial, with population matched controls, such as the ongoing AIM-dysplasia sham-
6 controlled trial in the US, should be sufficient to confirm that RFA is the most (cost-) effective
7 strategy. The critical issue then is whether clinicians would still have equipoise over the two strategies
8 despite the findings of the modelling, if so a definitive trial would still be needed.

9
10 In conclusion, our study has suggested that a strategy of RFA with oesophagectomy for HGD
11 recurrence is a cost effective strategy when compared with immediate oesophagectomy for the
12 management of BO with HGD in the UK. Sensitivity analysis demonstrates that RFA is likely to remain
13 the preferred option providing removal of HGD in BO is achievable in over 60%. Long term
14 prospective outcome data will help clarify whether RFA should become the first line treatment option
15 for HGD in BO in the UK.
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34 project, and his guidance throughout.
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Figure Legends

Figure 1: Transition state diagram of oesophagectomy treatment strategy

Figure 2: Transition state diagram of RFA treatment strategy

Figure 3: Cost effectiveness plane of results of probabilistic sensitivity analysis

Figure 4: Cost-effectiveness acceptability curve for the strategy of RFA compared to oesophagectomy

For Peer Review

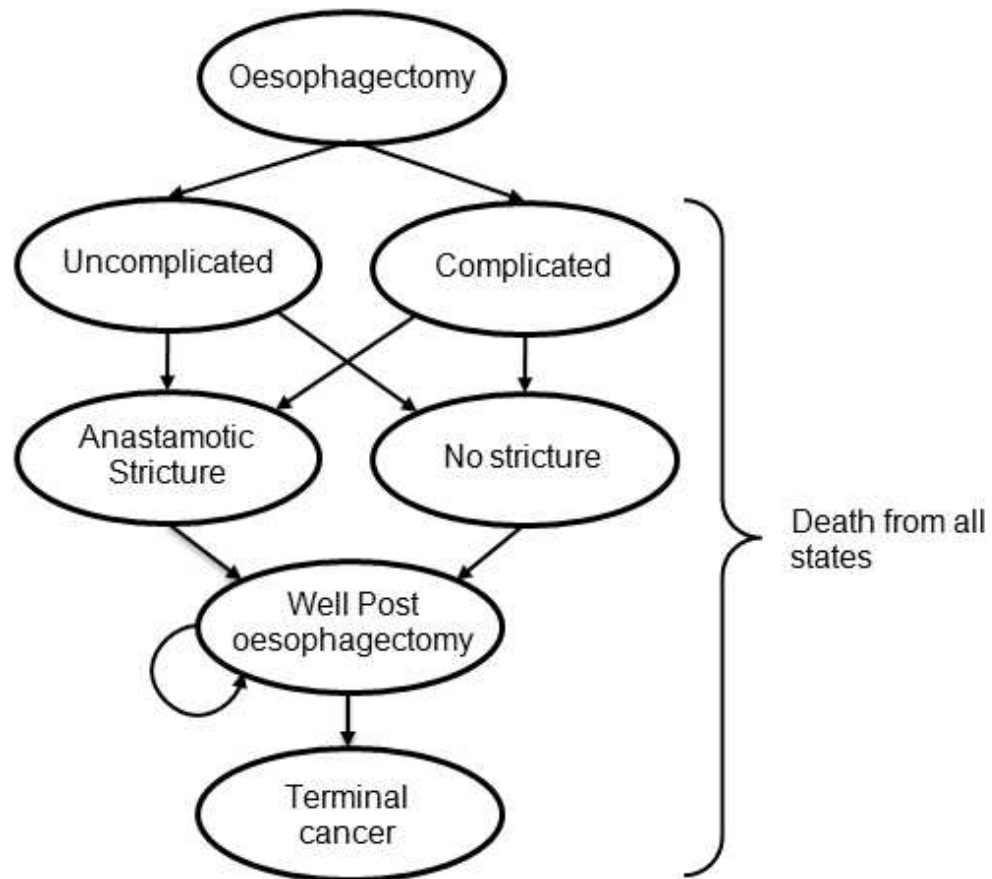


Figure 1: Transition state diagram of oesophagectomy treatment strategy
51x45mm (250 x 250 DPI)

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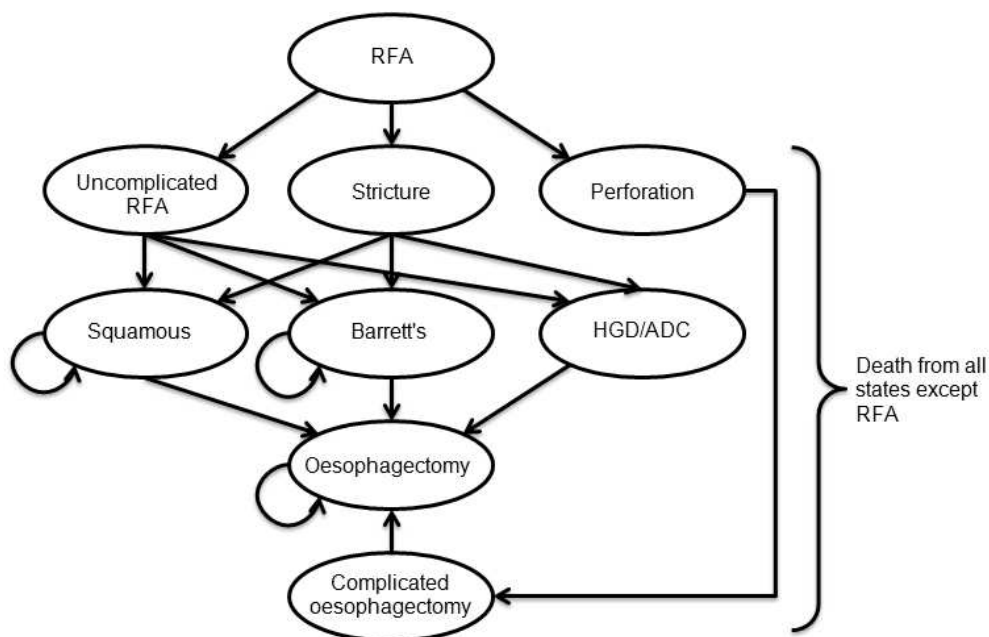


Figure 2: Transition state diagram of RFA treatment strategy
77x48mm (250 x 250 DPI)

Review

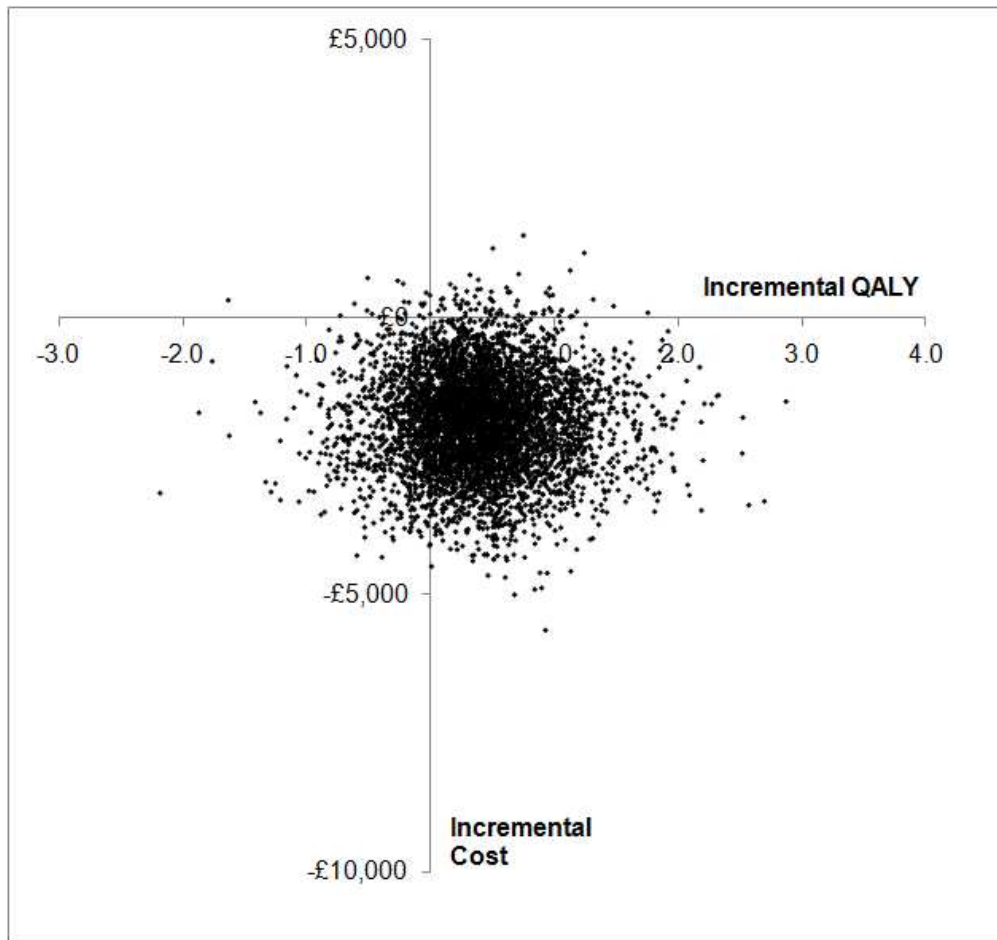


Figure 3: Cost effectiveness plane of results of probabilistic sensitivity analysis
63x60mm (250 x 250 DPI)



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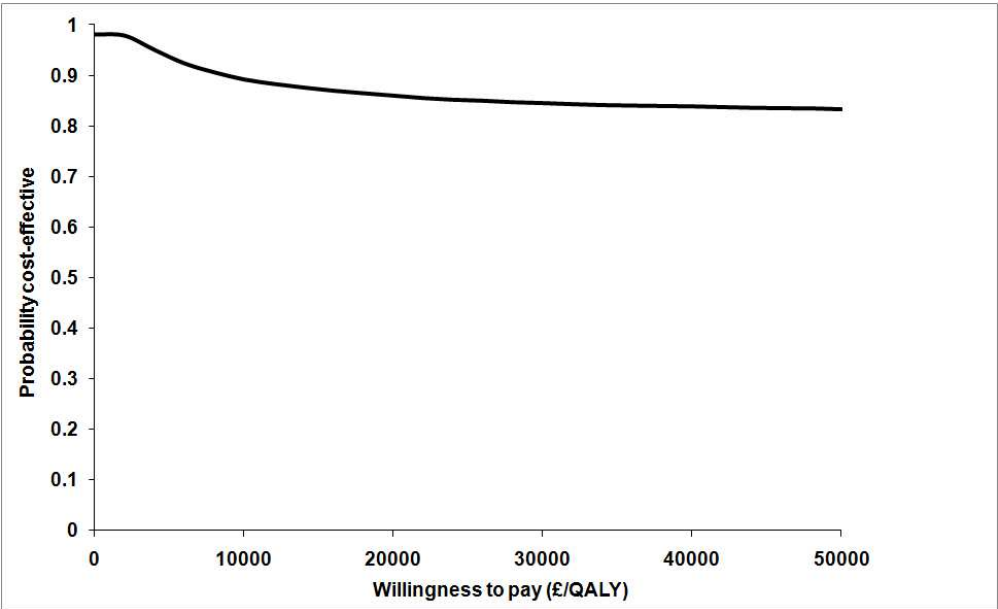


Figure 4: Cost-effectiveness acceptability curve for the strategy of RFA compared to oesophagectomy 98x60mm (250 x 250 DPI)

Review