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**ECONOMIC EVALUATION OF LAPAROSCOPIC SURGERY FOR  
COLORECTAL CANCER**

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**Short title**

**CEA OF LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER**

## **ABSTRACT**

**Objectives:** To assess the cost-effectiveness of laparoscopic surgery compared with open surgery for the treatment of colorectal cancer.

**Methods:** A Markov model was developed to model cost-effectiveness over 25 years. Data on the clinical effectiveness of laparoscopic and open surgery for colorectal cancer were obtained from a systematic review of the literature. Data on costs came from a systematic review of economic evaluations and from published sources. The outcomes of the model were presented as the incremental cost per life year gained and using cost-effectiveness acceptability curves (CEACs) to illustrate the likelihood that a treatment was cost-effective at various threshold values for society's willingness to pay for an additional life year.

**Results:** Laparoscopic surgery was on average £300 more costly and slightly less effective than open surgery and had a 30% chance of being cost-effective if society is willing to pay £30,000 for a life year. One interpretation of the available data suggests equal survival and disease-free survival. Making this assumption, laparoscopic surgery had a greater chance of being considered cost-effective. Presenting the results as incremental cost per quality adjusted life year (QALY) made no difference to the results, as utility data were poor. Evidence suggests short-term benefits following laparoscopic repair. This benefit would have to be at least 0.01 of a QALY for laparoscopic surgery to be considered cost-effective.

**Conclusions:** Laparoscopic surgery is likely to be associated with short-term quality of life benefits, similar long-term outcomes and an additional £300 per patient. A judgement is required as to whether the short-term benefits are worth this extra cost.

**Keywords:** Cost-effectiveness, Markov modelling, Colorectal cancer, Surgery,  
Systematic Review

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## **INTRODUCTION**

Colorectal cancer is one of the most common cancers in the Western world. In the United Kingdom (UK), it is the second most common cancer in women and the third most common cancer in men.

Colorectal cancer cases typically arise sporadically in individuals over the age of 50 (12), with only a small proportion of patients having a strong inherited predisposition. Further risk factors relate to diet, bodyweight, physical exercise, tobacco and alcohol consumption (4).

Surgical resection of the cancer is the main treatment and is almost always performed as an open surgical procedure. Open resection involves one long incision through the abdominal wall and is associated with high complication rates. These complications include wound infection, post-operative pain, anastomotic leakage, urinary tract infection and long-term complications such as incisional hernia. Some of the main disadvantages of open resection include incisional pain and an often lengthy hospitalisation. Laparoscopic surgery, a minimally invasive approach, might provide an alternative. Compared with open surgery it is believed to offer short-term quality of life benefits (12). Concerns over its longer-term effectiveness and cost, however, have led to a slow up-take. Furthermore, laparoscopic surgery is technically more complicated to perform and its success may be influenced by the experience of the surgical team.

Laparoscopic surgery involves several small incisions to the abdominal wall, in which ports are inserted, allowing the surgical instruments to be manipulated. A variant is

laparoscopically-assisted resection where the bowel is accessed laparoscopically but then a port site incision is enlarged which allows the excision of the disease. Anastomosis is then performed externally. In practical terms, laparoscopic and laparoscopically-assisted resections can be considered comparable as the incision sizes are relatively similar (hereafter they are collectively known as laparoscopic surgery).

This study estimated the relative cost-effectiveness of laparoscopic compared with open surgery for the treatment of colorectal cancer as well as exploring the cost-effectiveness of the different modes of surgery by stage of disease.

## **METHODS**

### **Markov Model**

A Markov model was constructed to estimate the long-term costs and benefits of a cohort of typical patients for the alternative surgical treatments (Figure 1). The model followed a cohort of patients from initial operation through convalescence (operation state) to return to usual activities ('disease-free' state). The patients may remain in this state until they die or they suffer a recurrence or metastasis and therefore have a re-operation or some other form of management. Theoretically, the patients could move between states until they all eventually die. For the purposes of the analysis, the cohort of patients have been modelled for a maximum of 25 years (the likely maximum survival for the majority of patients). The cycle length was set at six months.

The main cost components included in the model were the initial operative procedure and the costs of subsequent re-operations or management. If a recurrence occurred and a re-operation indicated, the patient is assumed to receive an open procedure. Death is the only state within the model that a patient cannot leave (it is an absorbing state).

The short-term surgical complications were principally captured through increased operating times and longer hospitalisation. The risk of an emergency re-operation within the first few weeks after surgery was explicitly modelled due to the additional operation costs incurred. Similarly, where the cost of managing other complications were not captured through increased operating time and length of stay, their probability of occurrence and cost was factored into the cost of a state.



## **Derivation of Model Parameters of Clinical Effectiveness**

The strongest source of data required for each parameter in the model were derived from a systematic review of randomised controlled trials (RCTs) of the two interventions in the treatment of colorectal cancer (12). Data on mortality, recurrence rates, re-operation rates, emergency operations and the long-term risk of hernia were all taken from this review (12). In brief, this review, an update of a previous review conducted in 2000 (20), involved a systematic literature search, restricted to the years 2000 onwards. Full details of the search strategy are available from the authors (12). All included studies needed to meet pre-specified eligibility criteria. Standard meta-analysis techniques were used to obtain overall estimates of effectiveness, where appropriate, and are reported in detail elsewhere (12). The review included a total of 46 reports describing 20 studies (19 RCTs and one individual patient data (IPD) meta-analysis). The IPD meta-analysis (2), synthesised data from a subset of patients from four of the main RCTs included within the systematic review of effectiveness; (6, 7, 9, 19).

The risk of death and recurrence were taken from the IPD meta-analysis (2) and were assigned a constant rate based on consideration of the survival curves which showed a similar rate, for both interventions (See Table 1 for parameter values used in the model). The risk of mortality following the recurrence of non-operative cancer was based on data derived from Benoist and colleagues (1). A beta distribution was used to reflect the uncertainty in this estimate. Other baseline parameters required for the model included the risk of: hernia, emergency re-operation for a post-operative complication; and re-operation for recurrent disease. The risk of hernia was identified as an important long-term complication. The severity and rates of port site hernia and

incisional hernia were included in the model. As data were sparse it was not possible to draw any distinction between the two types of hernia. The rate of hernia for open resection was derived from the rates reported in the open arms of those trials (10, 21) identified by the systematic review of effectiveness and a further focused search of non-randomised studies (5, 18). The risk of hernia per cycle was estimated for each study and the median of these was used. A triangular distribution based on the estimated 25 and 75 percentile estimates from the identified studies was used (Table 1).

It was believed that the risk of emergency surgery for most post-operative complications would be low. The one complication for which an emergency re-operation would generally be required was anastomotic leakage and, based on clinical advice, the risk of an emergency re-operation was taken to be equal to the risk of an anastomotic leakage (personal communication: Professor Z Krukowski and Ms A McKinley, 2005). The baseline risk of an anastomotic leakage was based on the rates reported in the open arms of those trials identified by the systematic review of effectiveness (12). The point estimate and distribution were defined using the same method as described above.

Should the cancer recur the individual might have a re-operation but data on this were not available from any of the included studies. Data from Grampian University Hospitals NHS Trust, however, suggested that out of over 300 resections per year, approximately 14 to 15 are re-operations (personal communication: Professor Z Krukowski and Ms A McKinley, 2005). A beta distribution was used to reflect uncertainty of the point estimate.

Data on relative effect sizes of laparoscopic versus open surgery were derived from the systematic review of effectiveness (12) and the IPD meta-analysis (2). The relative effect size of the risk of death and recurrence for laparoscopic versus open resection were based on the interpretation of the IPD meta-analysis (2) to provide an estimate of the relative difference between laparoscopic and open surgery. A normal distribution was defined using information on the confidence interval surrounding the relative difference.

A relative risk of one was assumed for the mortality rate for individuals with non-curative cancer as prognosis was taken to be the same regardless of the initial method of resection (Table 1). The relative risk of an emergency operation was based on that for anastomotic leakage, which came from the systematic review of effectiveness (12). Based on the confidence interval reported, a lognormal distribution was used to define the imprecision around this estimate. (Table 1).

The relative risk of hernia and the relative risk of a re-operation following a recurrence were also required. In both cases a relative risk of one was assumed. In the former case the evidence from the review of effectiveness was limited but there was no statistically significant difference between the rates of both types of hernia (12). In the latter case this was because the initial method of resection would not affect the method of management subsequent to a recurrence.

#### **Data on Resource Use and Cost**

Total costs included initial operation costs, hospital ward costs and any further follow-up costs. The analysis was taken from a UK NHS perspective and focussed on direct medical costs. Table 1 shows the estimated costs for laparoscopic and open resection. These costs were derived using data based on a UK RCT comparing laparoscopic with open surgery within an enhanced recovery programme (8). The follow-up costs from this RCT were only up to three months and related to a fast-track recovery programme. They do not, therefore, reflect typical length of stay estimates. These data, therefore, were combined with more typical estimates of length of stay and post-operative complications from the systematic review of effectiveness (12) to estimate the operation cost incurred in the first six months (i.e. the first cycle of the model). Added to this cost were the costs of follow-up visits, based on consultation with clinical experts to reflect the frequency of visits. Costs of two potential complications were also modelled (risk of emergency surgery and risk of incisional or port-site hernia). The cost per patient was the product of the probability of those complications occurring, combined with standard UK unit costs (16). The cost of care for those patients suffering a recurrence where re-operation would not be indicated was the cost of medications used to control symptoms. These were based on a typical drug regime of care for a patient, defined following consultation with a MacMillan Cancer Nurse (personal communication: Flora O’Dea – Hospital Specialist Palliative Care Team 2005) (3).

### **Cost-effectiveness**

The base-case analysis was based on the costs and outcomes faced by a cohort of typical patients. Results are presented as incremental cost per additional life year gained. The data are also presented as cost effectiveness acceptability curves

(CEACs), which reflect the statistical variability in the model's input parameters. These curves illustrate the likelihood that a strategy is cost-effective at various threshold values for society's willingness to pay for an additional life year. All costs and benefits were discounted, at a rate of 6% for costs and 1.5% for benefits (13). Costs were based on 2004 prices and the analysis was conducted from the perspective of the UK NHS.

### **Sensitivity analysis**

In addition to the probabilistic sensitivity analysis used to generate CEACs, sensitivity analysis focused on varying key assumptions and/or parameters in the base-case model. Sensitivity analyses surrounding the relative survival and disease-free survival estimates for laparoscopic resection were performed, as they are important drivers within the model and subject to considerable uncertainty. To further evaluate these estimates, a second analysis using alternative survival and disease-free survival estimates for both open and laparoscopic patients, based on the meta-analysis of all relevant trials was conducted (12). These estimates were manipulated to allow the mortality and recurrence rates for laparoscopic compared with open resection to be established giving point estimates of 0.97 (standard deviation of 0.03) and 0.99 (standard deviation of 0.03) respectively. Given the nature of the data, the imprecision around the relative risk was assigned a normal distribution. Further analysis also considered the use of various quality of life estimates to estimate quality adjusted life years (QALYs). Sensitivity analyses surrounding the base-line risk of hernia, mortality rates for patients with non-operative cancer and rates of re-operation following recurrence were also conducted.

## **RESULTS**

### **Base-case and equal survival**

For the base-case model, laparoscopic is dominated by open resection over the 25-year time horizon; that is laparoscopic resection is more costly and less effective in comparison to open resection (Table 2). One interpretation of the data provided by the IPD meta-analysis, however, is that there is no difference between laparoscopic and open resection in terms of survival and disease-free survival at three years (2). An analysis assuming equal survival and disease-free survival showed that laparoscopic resection was, again, more costly and no more effective (Table 2). Based on these data alone it would be unlikely that a policy maker would recommend increasing the uptake of laparoscopic surgery. The point estimates of the incremental cost-effectiveness provided do not, however, provide any indication of the uncertainty that surrounds the model parameters.

Figures 2 and 3 report the CEACs comparing laparoscopic to open surgery in terms of life years for the base-case model and for the equal survival analysis. Open surgery has a greater chance of being considered cost-effective, for the base-case analysis, at the various threshold values of society's willingness to pay for a life year. If society was willing to pay £30,000 for a life year then laparoscopic resection has approximately a 30% chance of being considered cost-effective (Figure 2). The results are driven by very small differences in survival and disease-free survival estimated to exist at three years follow-up. Therefore, an alternative interpretation of the data on survival and disease-free survival is that there are no meaningful differences and, in this situation, the likelihood that laparoscopic surgery might be considered cost-effective is greater compared with the base-case analysis (Figure 3).

### **Sensitivity analysis**

Using the two pooled estimates derived for overall survival and disease-free survival from the meta-analysis resulted in laparoscopic surgery being more costly (by approximately £350) but more effective, with an incremental cost-effectiveness ratio (ICER) of £1778 (Table 2 and Figure 4). This result is as would be expected given the pooled estimates on survival and disease-free survival used (12). This analysis serves to highlight the sensitivity of the model to these particular parameter estimates.

Utility data, though sparse, were sought in an attempt to capture the quality of life differences that might be apparent following the two forms of resection. Data were taken from one published study using the EQ-5D questionnaire to obtain utility scores (17). Based on these data it has been assumed that the recovery from both open and laparoscopic surgery was associated with a value of 0.83. It has also been assumed that, by definition, the time spent free from disease was associated with a value of 1. The value associated with the other states (except death) was also 0.83. These utility estimates were applied to the base-case model. Both the deterministic and probabilistic analyses are similar to the base-case results (See Table 2).

The estimates of QALYs do not capture any potential QALY gain that might be associated with an earlier recovery following laparoscopic surgery. Some indication of the relevance of this was assessed by looking at the QALY gain required for laparoscopic surgery to be judged worthwhile. Assuming a threshold value for society's willingness to pay for a QALY of £30,000 (14), and given the mean incremental cost of laparoscopic surgery of £289, then the implied value of the QALY

gain would need to be 0.010 QALYs (approximately three and a half days in full health).

The results from much of the other sensitivity analyses were similar to the base-case results. The model was, however, highly sensitive to changes in the relative effect sizes associated with non-operable cancer mortality and re-operation rates but there is no evidence to suggest that the management of patients would differ between the comparators. Finally consideration was given to the effect of stage of disease on the results using data presented in the IPD meta-analysis (2). Results were broadly similar to the base-case analysis, though there was considerable uncertainty surrounding parameter estimates. Further evidence on these outcomes, therefore, is warranted.

## **DISCUSSION**

It is likely that laparoscopic and open resection are similar in terms of long-term survival and disease-free survival. It is also likely that laparoscopic resection has some short-term advantages in terms of recovery in the postoperative period (12). When the cost-effectiveness measure was presented in terms of either cost per life year or QALY, laparoscopic surgery was, on average, dominated by open surgery. These results reflect the very small differences in overall survival that were apparent at three years and also the lack of available utility data in which to gauge the impact of earlier recovery following laparoscopic surgery. The results would be greatly strengthened if longer term randomised data were available. With respect to utilities, the data available to estimate QALYs were meagre and should be treated with extreme caution. Further work in this area is warranted to determine just what level



of QALY gain might be apparent following a shorter post-operative recovery and in the long-term. The importance of this can be ascertained from the fact that only a 0.01 gain in QALYs would be necessary for laparoscopic surgery to be considered cost-effective at a £30,000 threshold. It is quite plausible that a gain of this magnitude might exist when it is noted that in a comparison between laparoscopic and open groin hernia repair, the observed QALY gain was 0.006 (11).

Sensitivity analyses were performed to determine the effect of changing assumptions around the input parameters of the economic model. In doing so the probability that laparoscopic surgery might be considered cost-effective ranged from 30% to 80%. The analysis where laparoscopic surgery had an 80% chance of being considered cost-effective was when the base-case survival and disease-free survival estimates were replaced with the pooled estimates taken from the systematic review of effectiveness (12). It should be noted, however, that this pooled analysis does not take account of any potential differential timing of events.

There was little information on long-term wound related morbidities such as hernias. It is likely that the types of hernias and subsequently the costs, management and risk of hernia would also be different following both forms of resection. Because of the lack of data, however, the cost, management and associated risks were assumed to be the same for both forms of surgery. A sensitivity analysis that addressed the impact of this assumption showed little impact on results. Similarly in relation to all costs, little data were available. With respect to the main component of costs (the initial operation), these were based on data from a very small UK RCT (8). Further cost data from a larger sample would be beneficial.

One important event associated with laparoscopic surgery that was not modelled explicitly, owing to a lack of useable data, was the effect of conversion. Laparoscopic patients might be converted to open surgery for various reasons. Often these patients have worse outcomes than those not converted (12). It is unclear, however, whether patients converted to open surgery would have experienced similar complications regardless of which form of surgery had first been undertaken (i.e. they were inappropriately considered eligible for laparoscopic surgery). The effects of conversion also relate to the level of experience of the particular surgeon and their team. Less experienced surgeons and surgical teams might be expected to have a higher rate of conversion than those who are more experienced. The level of conversion (and hence cost-effectiveness) is likely, therefore, to be determined not only by appropriate patient selection but also by operator experience.

The results were sensitive to changes in the assumption that care for recurrent disease would be the same for both forms of surgery. There is, however, no evidence to suggest that the management would differ between surgeries. Should new data emerge indicating this then further work to develop this aspect of the model would be warranted.

A subgroup analysis focusing on stage of disease was also conducted. Its results were based on very meagre data and are unreliable. Other subgroups that would be relevant to investigate are age, gender and cancer site though it was not possible to incorporate these outcomes into the model owing to a lack of useable data. Further analysis and research for these sub-groups is warranted.

## **CONCLUSION**

This paper has explored the cost-effectiveness of laparoscopic surgery for colorectal cancer. This study is the first economic evaluation, using a Markov model to predict long-term outcomes, to be conducted within this area. Laparoscopic surgery is more costly and has a likelihood of being considered cost-effective of between 30% to 80% depending on the assumptions made. The implied valuation conducted found that, assuming a willingness to pay threshold of £30,000, laparoscopic surgery would need to be associated with a QALY gain of 0.01 in order to be considered cost-effective.

Further data is required relating to utility values to assess QALYs, longer term data with regards to survival and disease-free survival, evidence relating to relevant subgroups and on the risk and value of 'secondary' outcomes such as hernias.

## **POLICY IMPLICATIONS**

A judgement must be made as to whether the guidelines on open surgery should change. Currently, less than 1% of all colorectal cancer surgeries are performed laparoscopically. Given the evidence that laparoscopic surgery appears to have similar long-term outcomes compared to open surgery, as well as being associated with potential short-term benefits, there is a case to increase the current level of service provision. On the basis of evidence presented in this paper, and other evidence, the National Institute for Health and Clinical Excellence recommended that laparoscopic surgery is an acceptable method of surgery for colorectal cancer in the UK (15).

Very few surgeons or surgical teams are trained in this particular form of surgery and the implications for training of increasing the number of laparoscopic resections performed needs to be considered. Any decision that might be taken by policy makers with regards to this, however, must take into consideration the extra costs associated with laparoscopic resection and indeed whether the probable quality of life gains are worth this increased cost.

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**Table 1 All parameters used within the model**

Parameter	Value	Distribution and values used to define distributions	Source
<b>Baseline probabilities per cycle (six months)</b>			
Mortality	0.03	No distribution	Bonjer (2)
Recurrence	0.046	No distribution	Bonjer (2)
Mortality (non-operative cancer)	0.2	Beta: $\alpha=5.4, \beta=21.6$	Benoist (1)
Emergency operation rate	0.019	Tri: IQR 0.008 to 0.034	Murray (12)
Risk of hernia	0.03	Tri: IQR 0.002 to 0.012	Winslow (21), Leung (10), Patankar (18), Champult (5)
Re-operation rate (after recurrence)	0.05	Beta: $\alpha=15, b=285$	NHS Grampian
<b>Relative effect sizes</b>			
Mortality	1.016	Normal: 95% CI 0.958 to 1.054	Bonjer (2)
Recurrence	0.993	Normal: 95% CI 0.943 to 1.060	Bonjer (2)
Mortality (non-operative cancer)	1	None	Benoist (1)
Emergency operation rate	1.13	Lognormal: 0.74 to 1.73	MA from SR of Effectiveness (12)
Risk of hernia	1	None	
Re-operation rate (after recurrence)	1	None	
<b>Costs (£) 2004</b>			
Open procedure cost including follow-up to 3 months	5,852	Tri: IQR 4968 to 6272	King (8)
Relative cost of laparoscopic	1.05	Log normal: SD 0.33	King (8)
Emergency operation	1,615	Tri: IQR 1130 to 2322	NRC HRG F42 (16)
Re-operation (as open)	5,852	Tri: IQR 4968 to 6272	King (8)
Outpatient visit	99	None	King (8)
CT scan	73	Tri: IQR 56 to 91	NRC, CT (other) (16)
Colonoscopy	622	Tri: IQR 370 to 868	NRC HRG F35 (16)
Surgery for hernia	1,689	Tri: IQR 1306 to 2234	NRC HRG F72 (16)
Non-operative management following recurrence	1,216	None	Expert advice; Costs from BNF (3)
<b>Utilities (QALYs)</b>			
Initial operation	0.83	None	Norum (17)
Disease-free	1	None	
Recurrence	0.83	None	Norum (17)
Disease-free (after recurrence)	1	None	
Non-operative management	0.83	None	Norum (17)
Dead	0	None	

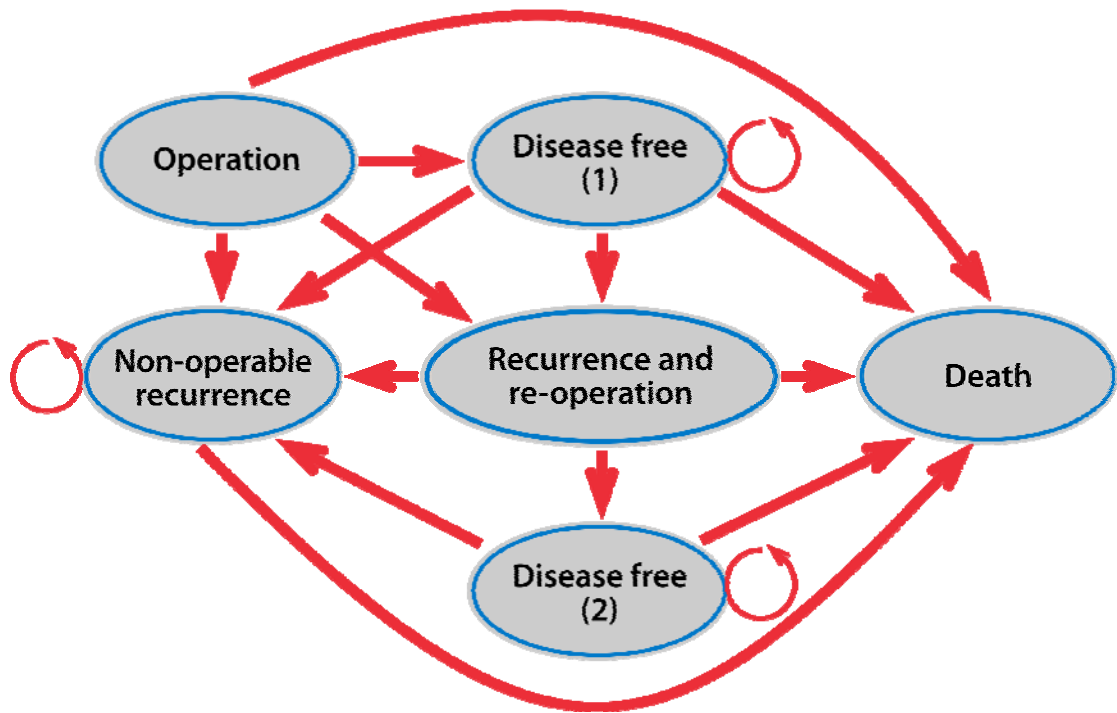
Tri = Triangular distribution; IQR = Interquartile range; MA = Meta-analysis; SR = Systematic review; CI = Confidence interval; SD = Standard deviation; NRC = National Reference Costs; HRG = Health Related Group; CT = Computed tomography; BNF = British National Formulary; QALYs = Quality Adjusted Life Years

**Table 2 Base-case and sensitivity analysis results (deterministic and probabilistic)**

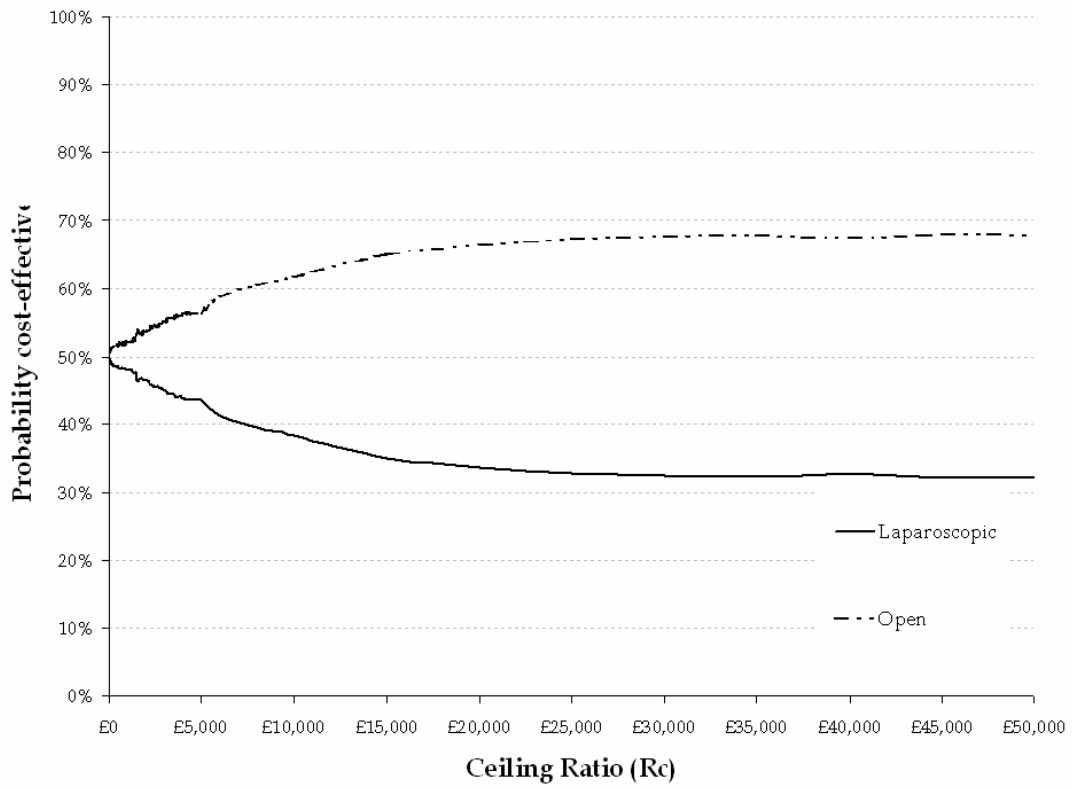
Base-case and sensitivity analysis	Procedure	Cost (£) 2004	Life years	ICER (£)	Probability of cost-effectiveness for different threshold values for society's willingness to pay for a Life Year (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	10174	15.351		61.6%	66.4%	67.6%	67.7%
	Laparoscopic	10463	15.298	Dominated	38.4%	33.6%	32.4%	32.3%
Equal Survival	Open	10174	15.351		54.7%	54.8%	54.9%	54.2%
	Laparoscopic	10490	15.351	Dominated	45.3%	45.2%	45.1%	45.8%
RR for OS and DFS from MA conducted as part of the systematic review of effectiveness (12)	Open	10174	15.351		26.7%	20.4%	18.6%	18.0%
	Laparoscopic	10511	15.541	1778	73.3%	79.6%	81.4%	82.0%
Sensitivity analysis	Procedure	Cost (£) 2004	QALYs	ICER (£)	Probability of cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Use of utility values to estimate QALYs (17)	Open	10174	14.679		61.0%	65.1%	65.7%	66.7%
	Laparoscopic	10463	14.630	Dominated	39.0%	34.9%	34.3%	33.3%

RR = Relative risk; OS = Overall survival; DFS = Disease-free survival; MA = Meta-analysis; ICER = Incremental cost effectiveness ratio; QALYs = Quality adjusted life years

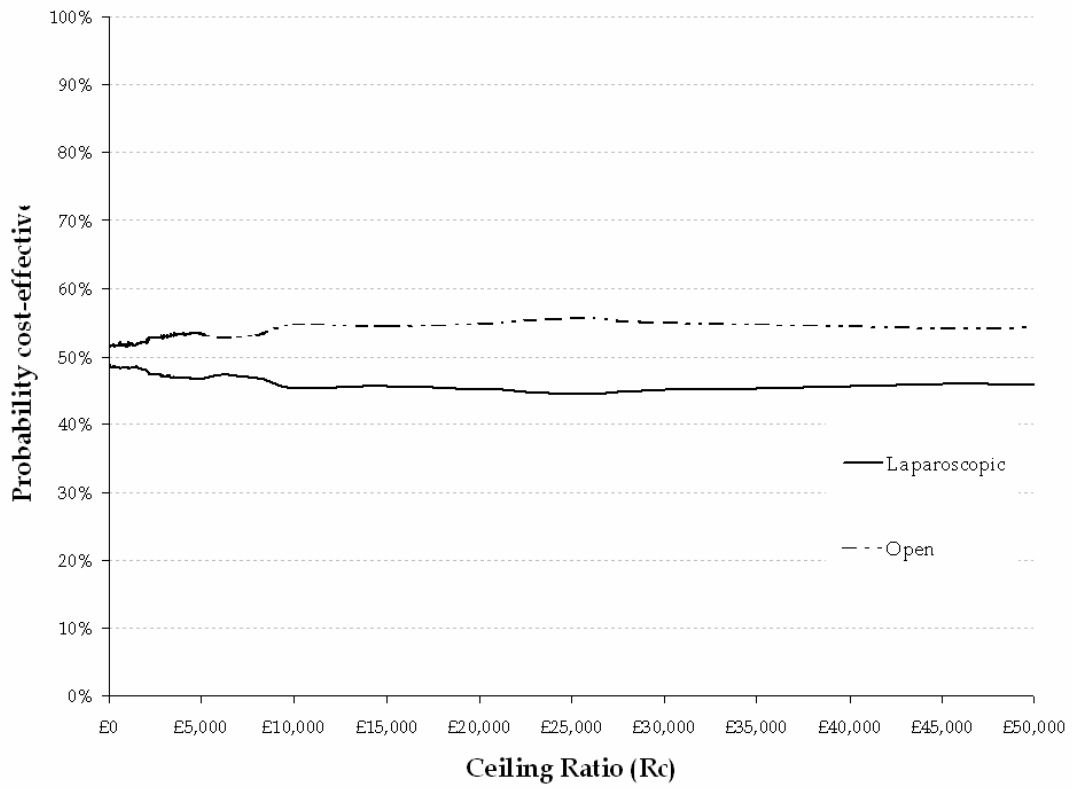
**Figure 1      Model structure**



**Figure 2**                      **Cost-effectiveness acceptability curve showing society's willingness to pay for a life year for the comparison of laparoscopic with open surgery (Base-case analysis)**



**Figure 3** Cost-effectiveness acceptability curve showing society's willingness to pay for a life year for the comparison of laparoscopic with open surgery assuming equal survival and disease-free survival





**Figure 4**                      **Cost-effectiveness acceptability curve showing society's willingness to pay for a life year for the comparison of laparoscopic with open surgery using pooled estimates of survival and disease-free survival from the systematic review of effectiveness (12)**

