Systematic review of the clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer

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Contributions of authors

Alison Murray (Research Fellow) and Tania Lourenco (Research Fellow) completed the review of effectiveness. Both carried out the assessment of studies for inclusion and data extraction. Rodolfo Hernandez (Research Fellow) conducted the review of economic evaluations. Robyn de Verteuil (Training Fellow) conducted the economic evaluation with the assistance of Rodolfo Hernandez and Luke Vale (Senior Research Fellow). Cynthia Fraser (Information Officer) developed and ran the search strategies, and was responsible for obtaining papers and for reference management. Zygmunt Krukowski (Professor of Clinical Surgery; clinical expert) and Aileen McKinley (Consultant colorectal surgeon; clinical expert) provided clinical advice and critical comments. Adrian Grant (Director; methodology adviser) provided clinical and methodological advice and commented on drafts of the review.

Conflicts of interest

Professor Krukowski advised that he has no stocks or shares in any of the companies, and does not currently receive funding. He had received a travel grant from Autosuture (Tyco Healthcare) & the Royal College of Surgeons approximately 10 years ago. In the last two years he has advised Ethicon Endosurgery, Tyco Healthcare and Karl Storz Endoscopy (UK) Ltd on the development of new laparoscopic equipment. Professor Krukowski is also the chair of the data monitoring committee of the MRC CLASICC trial of conventional versus laparoscopic assisted surgery in patients with colorectal cancer.

Ms (Dr) Aileen McKinley likewise stated that she has no stocks or shares in any of the companies but was awarded a training fellowship from Ethicon Endosurgery last year. The fellowship covered travel and accommodation expenses for two trips to Hamburg. One trip was for a two day international laparoscopic colorectal meeting. The other was for a short visit (2 ½ days) to operate in the wet laboratory there; a facility not available in the UK.

The clinical department of both Professor Krukowski and Ms (Dr) Alieen McKinley use, amongst others, Ethicon Endosurgery, Tyco Healthcare, KeyMed (Medical & Industrial Equipment) Ltd and Richard Wolf UK Ltd equipment for both open and laparoscopic procedures.

Professor Grant attended a single meeting organised by Ethicon Endosurgery in 2003 to discuss possibilities for meta-analysis of trials of laparoscopic surgery for colorectal cancer.

None of the other members of the review team have any stocks or shares in any of the companies, nor do they receive any funding from these companies.

The Health Services Research Unit and the Health Economics Research Unit both received funding from NHS Grampian to provide economics and statistical support for a randomised control trial of stapled haemorrhoidplexy compared with rubber band ligation for grade II haemorrhoids. NHS Grampian is receiving funding for this trial from Ethicon Endosurgery.

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None of the authors has any financial interest in any of the companies producing products for laparoscopic surgery of colorectal cancer.

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Summary

Current guidance from the National Institute for Health and Clinical Excellence on the use of laparoscopic surgery for colorectal cancer is that open surgery is the preferred procedure and that laparoscopic surgery should only be undertaken as part of a randomised controlled trial (RCT). This guidance was based on a technology assessment review conducted in 2000. New evidence has since become available, providing additional data on both the short and long term outcomes of surgery.

Description of proposed service

In laparoscopic surgery, ports are inserted through which the laparoscopic instruments are manipulated. In practical terms a totally laparoscopic and laparoscopically-assisted procedure are considered comparable because of the size of incisions involved and hereafter jointly described as laparoscopic surgery. In hand-assisted laparoscopic surgery (HALS) the surgeon inserts a hand into the abdomen while pneumoperitoneum is maintained.

Epidemiology and background

Colorectal cancer is the second most common malignancy in England and Wales in terms both of incidence and mortality. Approximately 36,000 new cases were diagnosed in 2002 and 17,000 people died from colorectal cancer in the same year. About 80% of all patients diagnosed with colorectal cancer (including some with advanced disease) undergo surgery.

Open resection is currently the standard method for surgical removal of primary colorectal tumours. However, there is significant morbidity associated with this procedure. Laparoscopic surgery is less invasive and hence may lead to more rapid recovery from the operation. The potential impact on cure rates is not clear. The major concerns are that tumour recurrence might occur at port sites and that clearance of the tumour may be less complete than during open surgery. However, it has also been suggested that the reduced trauma to tissues may lower disruption to the immune system and hence reduce the risk of recurrence. Additionally, there are disadvantages of laparoscopic surgery relating to the longer length of the operation, the cost of materials, and the effect of surgeon experience on patient outcomes.

This review assesses the clinical effectiveness and cost-effectiveness of laparoscopic and HALS in comparison with open surgery for the treatment of colorectal cancer. This was

evaluated in terms of short-term, long-term and recurrence outcomes. The extent to which possible differential effects within pre-defined subgroups relating to the location of the cancer, the stage of the cancer, and age at diagnosis could be explored was limited by the sparsity of data.

Number and quality of studies

In total, 46 reports on 20 studies (19 RCTs and one individual patient data meta-analysis) were included in the review of clinical effectiveness. The RCTs were of generally moderate quality with the number of participants varying between 16 and 1082. Ten RCTs had less than 100 participants. The total number of trial participants who underwent laparoscopic surgery was 2429, while the total number having open resections was 2139.

Summary of benefits

Laparoscopic resection is associated with a quicker recovery (in terms of time to return to usual activities and length of hospital stay) and no evidence of a difference in mortality or disease-free survival up to three years following surgery. However, operation times are longer and a significant number of procedures initiated laparoscopically may need to be converted to open surgery. The rate of conversion may be dependent on experience both in terms of patient selection and in performing the technique.

Costs

Laparoscopic resection appears more costly to the health service than open resection with an estimated extra total cost of between £250 and £300 per patient.

Cost-effectiveness

A systematic review of four papers suggested that laparoscopic surgery is more costly than open surgery. However, the data they provided on effectiveness was poorer than the evidence from the review of effectiveness described in this report. One study compared the two forms of surgery in the context of an enhanced recovery programme. This study reported no difference in effectiveness and similar costs for both laparoscopic and open surgery. A further small study was identified comparing laparoscopic with HALS. This study also reported similar estimates of effectiveness and cost.

The economic evaluation conducted as part of this review first set out a balance sheet comparing laparoscopic with open surgery. Laparoscopic resection is associated with a

modest additional cost, short-term benefits associated with more rapid recovery, and similar long-term outcomes in terms of survival and cure rates up to three years. Assuming equivalence of long-term outcomes, a judgement is required as to whether the benefits associated with earlier recovery are worth this extra cost.

The estimates from the systematic review of clinical effectiveness were incorporated into a Markov model used to estimate cost-effectiveness for a time horizon of up to 25 years. In terms of incremental cost per life year, laparoscopic surgery is dominated (more costly and no more effective) than open surgery. With respect to incremental cost per quality adjusted life year (QALY), little data were available to differentiate between laparoscopic and open surgery. The results of the base case analysis and much of the sensitivity analysis suggest that there is approximately a 40% chance that laparoscopic surgery is the more cost-effective intervention should society's maximum willingness to pay for an additional QALY be £30,000. A second analysis assuming equal mortality and disease-free survival found that the likelihood that laparoscopic resection would be considered cost-effective at a similar threshold value was approximately 50%.

Sensitivity analyses

Broadly similar results were found in the sensitivity analyses. As few data were available on the difference in QALYs caused by the quicker recovery associated with laparoscopic surgery, a threshold analysis was performed to investigate the magnitude of QALY gain that would be required to provide an incremental cost per QALY, for which society might be willing to pay. This analysis was repeated for both the base case analysis and analysis assuming equal survival. Assuming society would be willing to pay £30,000 per QALY then the implied number of additional QALYs would be 0.009 to 0.010 compared with open surgery.

Limitations of the calculations (assumptions made)

Much information available for some outcomes was reported in a form that was unsuitable for entry into the meta-analyses. The main limitations related to the quantity and quality of the data available. For example, the best data on mortality and disease-free survival were only available for a three-year follow-up.

The nature of the data available also had an impact on the economic evaluation, which extrapolated outcomes for up to 25 years. More importantly, the data available to estimate

costs were limited while the data used to estimate QALYs should be considered highly suspect. The UK-based multicentre CLASICC trial is due to report its economic evaluation soon and a draft version [redacted] has been incorporated within the economic model. It is anticipated that this study will provide additional data on costs and will provide utility scores relevant to the UK.

Other important issues regarding implications

Should the use of laparoscopic surgery be increased from it current level of 0.1% of total resections to 25% of total resections then the extra cost to the NHS has been estimated at £2.1 million per year.

The increased adoption of laparoscopic techniques may allow patients to return to usual activities faster. This may, for some people, reduce any loss of income. However, current provision is very limited and few patients have access to laparoscopic surgery.

For the NHS, increased use of laparoscopic surgery would lead to an increased requirement for training, which may be costly. Due to the limited number of surgeons currently providing laparoscopic surgery, it may take some time before the provision of laparoscopic surgery can be increased.

Both open and laparoscopic surgery may be provided in the context of an enhanced recovery programme. Such an approach may reduce length of stay for both procedures but it is likely to lead to an increase in the total costs to the NHS.

Notes on the generalisability of the findings

The 19 trials were conducted in a wide range of setting but data relating to the subgroups are very limited. With respect to the economics data on costs, only two UK studies were identified one of which was a preliminary analysis. Such cost data, as were available, may not reflect practice within the UK. Further data, when available from the CLASICC trial, would improve the confidence with which the findings can be generalised.

Need for further research

Although useful data on long-term outcomes was available from the individual patient data meta-analysis identified as part of the review, this study only reported data for up to three

years and only included data from four RCTs. The long-term follow-up of the RCT cohorts would be very useful and ideally these data should be incorporated into a wider individual patient data meta-analysis.

Few data were available on the long-term complications of surgery such as incisional hernias. Furthermore, given the apparent similarity between the procedures in survival and disease-free survival, attention might usefully be focused on whether there are differences in secondary outcomes such as persisting pain, that may affect a patient's quality of life.

Key limitations of the economic model were the limited data on both costs and utilities. Once available, such data should be included in an updated model. At this point, further consideration should then be given as to whether additional data should be collected within ongoing trials.

Few data were available to assess the relative merits of HALS. Ideally, there should be more data from methodologically sound RCTs.

Further research is needed on whether the balance of advantages and disadvantages of laparoscopic surgery varies within subgroups based on the different stages and locations of disease.

Laparoscopic surgery for colorectal cancer is, like other laparoscopic procedures, technically challenging and performance is likely to improve with experience. This issue is important in its evaluation and further methodologically sound research related to this is warranted in the context of both trials and meta-analyses of trial data.

List of abbreviations

ACPGBI	Association of Coloproctology of Great Britain and Ireland
ALSGBI	Association of Laparoscopic Surgeons of Great Britain and Ireland
BMI	Body mass index
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CLASICC	Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer
COLOR	The COlon cancer Laparoscopic or Open Resection Study Group
COST	The Clinical Outcomes of Surgical Therapy Study Group
CT	Computer tomography
HALS	Hand-assisted laparoscopic surgery
HRG	Health care resource group
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IQR	Inter quartile range
P	Probability
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
TNM	Tumour, nodes, metastasises
WMD	Weighted mean difference

1 AIM OF THE REVIEW

Current guidance from the National Institute for Health and Clinical Excellence (NICE) on the use of laparoscopic surgery for colorectal cancer is that open rather that laparoscopic surgery is the preferred procedure and that laparoscopic surgery should only be undertaken as part of a randomised controlled trial (RCT).[1] This guidance was based on a technology assessment review conducted in 2000.[1] New data have become available since then, particularly from three large RCTs[2-4] (each with around 800 participants) and an unpublished individual patient data meta-analysis of these three trials plus a fourth moderate sized trial (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). This meta-analysis included data describing 1536 participants with follow-up for death and disease-free survival for three years after surgery.

This study takes into account these and other data in an updated review. More specifically, the aim is to determine the clinical effectiveness and cost-effectiveness of laparoscopic, laparoscopically assisted (hereafter together described as laparoscopic surgery) and hand-assisted laparoscopic surgery (HALS) in comparison with open surgery for the treatment of colorectal cancer. Where evidence allows, possible differential effects will be explored within a number of subgroups. The subgroups relate to the location of the cancer, the stage of the cancer, and age at diagnosis.

2 BACKGROUND

2.1. Description of underlying health problem

2.1.1. Introduction

The large intestine, commonly known as the large bowel, can be divided into two main sections: the colon and the rectum. The colon is about 1.5 to 1.8 m long and consists of four parts: the ascending, transverse, descending, and the sigmoid colon. The rectum is a straight, muscular tube, which commences at the end of the sigmoid colon and terminates at the anal canal.[5]

The aetiology of colorectal cancer is multifactorial including genetic and environmental factors.[5] Colorectal cancer frequently results from malignant change in an adenomatous polyp that has developed in the lining of the large intestine. Colorectal cancers are broadly divided into two groups depending on their location within the large bowel. Colonic cancer consists of all tumours occurring in the area from the large intestine proximal to the rectum. Rectal cancer is defined as a tumour within 15 cm of the anal verge.[6,7]

Colorectal cancer most commonly presents with chronic symptoms such as rectal bleeding, a change in bowel habit or iron deficiency anaemia.[6] A proportion of patients present as emergencies with bowel obstruction, perforation or bleeding. Table 2.1 provides further details of the mode of presentation.

Table 2.1 Modes of presentation of patients with colorectal cancer[8]

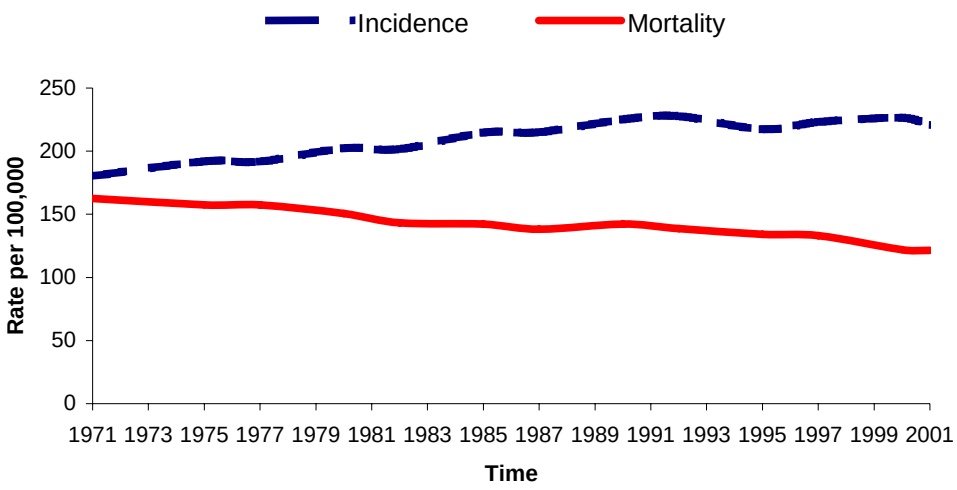
Common modes of presentation of patients with established cancer *	**Percent of all patients with colorectal cancer**
Rectal bleeding associated with a change in bowel habit	35
An abdominal or rectal mass	30
Iron deficiency anaemia below 100g/l	30
Intestinal obstruction	20
Change in bowel habit as a single symptom	10
Uncommon symptomatic presentations of patients with cancer	**Percent of all patients with colorectal cancer**
Rectal bleeding with anal symptoms and without a change in bowel habit	3
Abdominal pain as a single symptom without an abdominal mass	3

* A patient can present with more than one symptom

2.1.2. Epidemiology

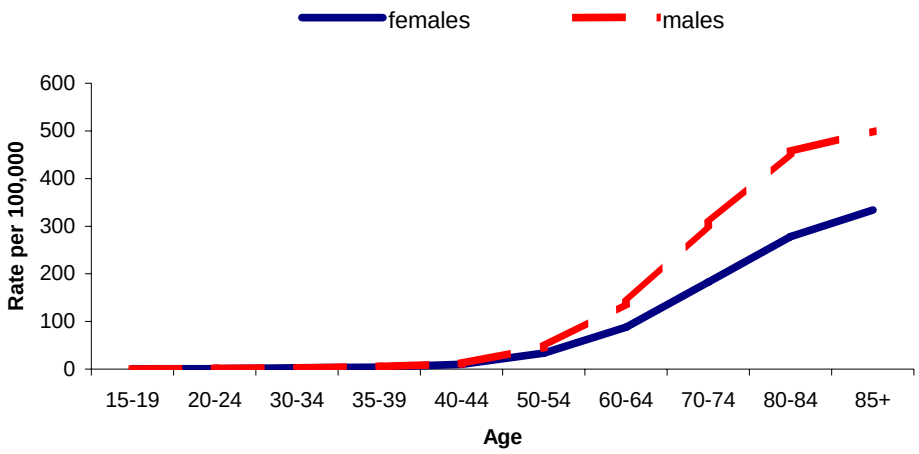
Colorectal cancer is the second most common malignancy in England and Wales in terms both of incidence and mortality.[9] Approximately 36,000 new cases were diagnosed in 2002 and 17,000 people died from colorectal cancer in the same year. Over the last three decades colorectal cancer mortality has fallen by over 25% whilst incidence has increased slowly (Figure 2.1).

Figure 2.1 Incidence and mortality rates over time in England and Wales, 1971-2001 (data specific to males only)[10]



The overall incidence of colorectal cancer is higher in men than in women (Figure 2.2). In the UK, the male to female ratio for colonic and rectal cancer is 11:10 and 7:4 respectively.[11] This holds for all age groups. There is no evidence that the pathogenesis of the disease differs by gender.[12]

Figure 2.2 **Frequency distribution of new cases by age group, England and Wales, 2001[10]**



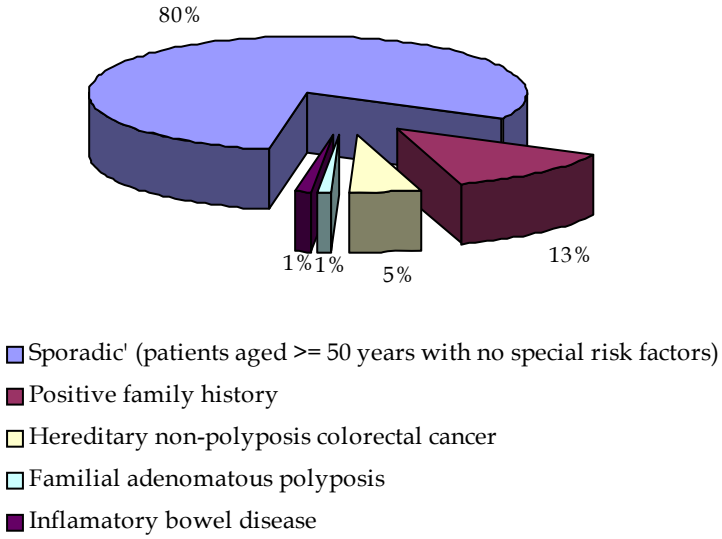
The mean age at diagnosis for colorectal cancer in the UK is 65.[13] As Figure 2.2 illustrates, the incidence of colorectal cancer rises sharply with age, with approximately 41% of patients affected being over 75 years of age, and 57% of deaths from colorectal cancer occurring in this age group.[14] Table 2.2 gives further details specific for England, Scotland, Wales and Northern Ireland.

Table 2.2 **Death rates for colorectal cancer in 2002 for England, Wales, Scotland and Northern Ireland[15]**

Death Rates per 100,000 population						
Age	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
Colon cancer						
England	1.4	5.8	20.0	56.1	119.4	200.9
Wales	2.2	7.5	21.9	65.1	114.0	191.3
Scotland	1.7	8.2	23.7	58.8	127.4	225.7
Northern Ireland	2.4	5.9	23.3	62.6	103.7	282.7
Rectal cancer						
England	0.8	4.1	12.8	27.6	57.6	98.7
Wales	0.7	5.8	11.6	30.6	50.6	101.3
Scotland	1.3	6.7	14.6	43.2	72.1	111.4
Northern Ireland	0.9	4.4	11.3	16.3	56.6	92.0

A small subgroup of colorectal cancer is caused by inherited predisposition; however, it is estimated that over 75% of cases arise 'sporadically' (Figure 2.3). Diet, including over-nutrition, high meat and fat consumption, deficiencies in vegetables, key minerals and vitamins, is a major risk factor.[11]

Figure 2.3 Risk Factors Associated with new cases of colorectal cancer. [11]



Five-year relative survival, following surgical resection, is related to the stage of the tumour and is approximately 85-95% in Dukes' A cancer (TNM* stage I) (tumour confined to mucosa and sub mucosa of the bowel), 60-80% in Dukes' B cancer (TNM stage II) (tumour penetrating through muscle layer of the bowel), 30-60% in Dukes' C cancer (TNM stage III) (metastasis to regional lymph nodes),[16] and 13% in Dukes' D cancer (TNM stage IV (distant metastasis).[17]

2.1.3. Significance in terms of ill-health

Colorectal cancer is a major cause of morbidity and mortality, particularly in the elderly. Patients with colorectal cancer may suffer pain, bleeding, frequent or irregular bowel movements, diarrhoea, and fatigue.[18,19] Studies have reported a decrease in quality of life scores during the first few months after colorectal surgery, followed by improvements three to six months after surgery.[20]

2.2. Current service provision

In the UK, open surgical resection of all malignant tissue is the recommended primary treatment for colorectal cancer.[1] Approximately 80% of all patients diagnosed with colorectal cancer (including some with advanced disease) undergo surgery.[21] Most surgical resections

* TNM: Classification of malignant tumours where T stands for tumour, N for lymphatic nodes and M for metastasis.

are performed as elective procedures. However up to 30% of primary resections present as an emergency (Table 2.3).[13]

Open surgical resection of primary colorectal tumour is the most common procedure for treating colorectal cancer. However, morbidity rates associated with this can be high. Laparoscopic surgery is less invasive. It is therefore likely to lead to more rapid recovery from the operation. It has also been suggested that the reduced trauma associated with laparoscopic procedures might minimise any disruption to the immune system caused by surgery and hence reduce the risk of recurrence.[22] However, there are concerns that tumour recurrence might occur at port sites and the potential impact on cure rates is not established. Additionally, there are disadvantages relating to the longer length of the operation, the cost of materials, and the effect of surgeon experience on patient outcomes.

Some of the disadvantages associated with open surgical resection include: incisional pain, intraoperative and postoperative metabolic stress, tissue trauma, and postoperative ileus from manual intestinal manipulation.[23] It has been postulated that laparoscopic surgery may reduce the impact of these. If so, this might justify the apparent increase in interest amongst surgeons to introduce laparoscopic techniques to treat colorectal cancer.

The open surgical procedure (laparotomy) requires a relatively long incision through the abdominal wall.[23] The surgical resection of the cancer itself involves the removal of the bowel containing the tumour, adequate disease-free longitudinal margins, any involved adjacent organs, lymph nodes and associated vessels.[12,23] For rectal cancers located in the lower two thirds of the rectum, a total mesorectal excision is performed to reduce local recurrence.[12] Upper third rectal tumours may be managed with 5cm distal longitudinal margin. Whenever possible, this is followed by anastomosis; suturing or stapling the proximal colon to the rectum/anus.

According to the 2003/2004 hospital episode statistics, 31,356 primary resections were performed in England using 473,530 bed days with patients staying in hospital for a mean of 17 days. The majority of these were colonic resections (61%). Within the six time periods surveyed, there was a relative decrease in the number of primary resections performed (Table 2.3).[13]

Table 2.3 Details of primary colorectal resections, England, 1998-2004 [13]

Year	No of resections	Emergency (%)	Male (%)	Average age (years)	Aged over 75 years (%)	Mean stay (days)*
2003/04	31,356	28.0	50.9	65.5	33	17.1
2002/03	31,705	28.6	51.4	65.5	33	17.3
2001/02	31,331	29.7	50.9	65.5	33	17.7
2000/01	31,796	27.7	50.0	66	33	17.4
1999/00	32,725	29.0	50.0	65.5	32	17.1
1998/99	32,580	24.8	50.0	66	33	17.0

* Over this time period median length of hospital stay has remained at 13 and 14 days for colon and rectal cancer respectively

2.3. Description of new intervention

2.3.1. Laparoscopic surgery

Minimally invasive approaches to treat colorectal diseases were developed to take advantage of the benefits observed in laparoscopic procedures elsewhere in the gastrointestinal tract.[24] In laparoscopic surgery, ports are inserted through which the laparoscopic surgical instruments are manipulated. In practical terms a totally laparoscopic and laparoscopically-assisted procedure are considered comparable because of the size of incisions involved. HALS is a different concept and is discussed in 2.3.3 below.

Adoption has been relatively slow since the first entirely laparoscopic colorectal resection was performed in July 1991.[24] Difficulties include working in multiple sites within the peritoneal cavity, inadequate instrumentation, evolving surgical techniques, and the necessity to remove a large specimen.[25] Taken against a background of fears about adequacy of tumour clearance these have combined to inhibit widespread adoption.

2.3.2. Laparoscopically assisted surgery

In laparoscopically assisted surgery the bowel is mobilised laparoscopically, and extracted through an enlarged laparoscopic port site with excision and/or anastomosis performed externally. As noted earlier, throughout the remainder of the document laparoscopic and laparoscopically assisted surgery have been collectively called laparoscopic surgery.

2.3.3. Hand-assisted laparoscopic surgery (HALS)

In HALS, the surgeon inserts a hand into the abdomen while pneumoperitoneum is maintained. Some surgeons find this easier than laparoscopic surgery particularly in the transitional phase between conventional and laparoscopic surgery. Advantages claimed for

placing the hand in the abdomen include tactile feedback, the ability to palpate, blunt dissection, organ retraction, control of bleeding, and rapid organ removal.[26-28]

2.3.4. Identification of subgroups of patients

Resection can be performed in patients of all ages and both genders, with any stage of cancer and location. However, stay in the intensive care unit, and postoperative hospitalisation have been reported to be significantly longer in patients older than 70 years.[29] In addition, surgical procedures for advanced colorectal cancer are most commonly used to relieve obstructing lesions and pelvic symptoms.[30] The laparoscopic treatment of rectal cancer is more difficult than for colonic cancers.[31] Currently, laparoscopic procedures are unlikely to be used in emergency situations.

2.3.5. Criteria for treatment

Laparoscopic treatment is contraindicated in patients who have significant bowel dilatation or who are intolerant of a pneumoperitoneum.[32] Furthermore, conversion from laparoscopic to open surgery may negate any advantage of an initial laparoscopic approach. Consequently, patients at high risk of conversion from laparoscopic to open surgery should be identified preoperatively and receive open surgery. Factors that may be relevant include body habitus, extensive peritoneal adhesions and local spread of the tumour.

2.3.6. Personnel involved

The number of staff employed in laparoscopic operations is usually similar to the number involved in open resections. The operating time for laparoscopic resection is believed to be longer. Laparoscopic resection is a technically more difficult procedure and there is a long learning curve,[30] in which a relatively large number of cases (30 to 50) are required for the surgeon to obtain proficiency.[29]

2.3.7. Setting

The mean length of hospital stay for patients undergoing open resections in the UK as judged from routinely collected hospital episode statistics is approximately 17 days.[13] The time from hospital admission to discharge has been suggested as being lower for patients undergoing laparoscopic surgery.[33-35]

To a large extent, length of hospital stay after surgery is dependent on local surgical policy. However, it is also influenced by prolonged pain, nausea and vomiting, persistence of ileus,

fatigue, mechanical factors (such as the presence of drains), stress induced organ dysfunction and postoperative complications[36,37] It has been claimed that an 'enhanced recovery program' specially designed to address these factors can lead to a marked decrease in length of stay[36-39] with no increased morbidity, deterioration in quality of life or increased cost.[40] An enhanced recovery program is characterised by a highly scripted preoperative and postoperative care plan regulating the introduction of analgesia, diet and ambulation.[36] It has been suggested that the length of hospital stay of patients undergoing an open resection followed by an enhanced recovery programme could match that seen after laparoscopic resection.

Irrespective of type of approach to surgery, it is widely recommended that colorectal cancer patients should be nursed in an environment that promotes independence and mobilisation with patients out of bed for two hours on the day of surgery and for six hours each day from then on.[37]

2.3.8. Equipment required

All laparoscopic techniques incur additional material costs compared with an open operation because of the requirement for an endoscopy system. This includes items such as ports, staplers, diathermy and ultrasonic instruments. These additional costs are strongly influenced by the amount of disposable equipment used.

2.3.9. Degree of diffusion

The current NICE guidance on the use of laparoscopic surgery for colorectal cancer[1] states that:

" 1. For colorectal cancer, open rather than laparoscopic resection should be the preferred surgical procedure.
2. Laparoscopic surgery should only be undertaken for colorectal cancer as part of a randomised clinical trial. "

Reflecting this, laparoscopic colorectal surgery has not been adopted widely. From 1998 to 2001 there were no changes in the percentage of colorectal cancer cases treated with laparoscopic surgery in the United Kingdom (around 0.1%).[41]

A survey[42] performed among existing members of the Association of Coloproctology of Great Britain and Ireland (ACPGBI) has identified that only 45 surgeons currently perform laparoscopic colorectal resections.

2.3.10 Anticipated costs

The current use of laparoscopic colorectal surgery is low but there is the potential for its use to increase dramatically. The anticipated cost of adopting laparoscopic surgery based on different degrees of diffusion are illustrated in Table 2.4. The total direct costs to the NHS are based on a mean cost of £6117 and £5852 for laparoscopic and open surgery respectively (the methods used to estimate these costs are described in Chapter 5). The number of resections per year is based on the data for 2003-4 reported in Table 2.3.

Table 2.4 Cost of surgery for colorectal cancer

Percentage of total resections that are laparoscopic	NHS cost (£ million)	Additional cost above the cost of current provision (£ 000)
0.1%	£183.5	£0
1.0%	£183.6	£74.8
5.0%	£183.9	£407.2
10.0%	£184.3	£822.6
15.0%	£184.7	£1,238.1
20.0%	£185.2	£1,653.6
25.0%	£185.6	£2,069.0

These projections suggest that if the use of laparoscopic resection increased to a relatively modest 1% then the total cost to the NHS in England would increase by approximately £75,000. However, these estimates are subject to considerable uncertainty. Firstly, the cost of both laparoscopic and open surgery are not known precisely. Second, the calculations have assumed a fixed operation cost and thus have not considered whether the unit cost of laparoscopic resection would change as diffusion increases. Finally, these figures do not reflect the cost of training the increased numbers of surgeons required to perform the additional operations.

3. EFFECTIVENESS

The Health Technology Assessment (HTA) report submitted to NICE in July 2000, when laparoscopic surgery for the treatment of colorectal cancer was first appraised, summarised the evidence on clinical effectiveness available at that time.[1] Not all studies included in that report met the inclusion criteria for this update and it became apparent that some randomised controlled trials (RCTs) reported before 2000 had not been included in the original review. Evidence for assessing the clinical effectiveness considered in this report therefore comprises the eligible trials from the original report as well as RCTs and individual patient data meta-analyses identified from literature searching performed for this review, plus additional pre-2000 RCTs included in systematic reviews identified from the literature search.

3.1 Methods for reviewing effectiveness

3.1.1 Search strategy

Electronic searches were undertaken to identify published and unpublished reports of RCTs and systematic reviews evaluating the effectiveness of laparoscopic and HAL surgery for colorectal cancer. Searches were restricted to the years 2000 onwards without language restriction and included abstracts from recent conference proceedings.

The main databases searched were: Medline (2000 – May Week1 2005), Embase (2000 - Week 19 2005), Biosis (2000 to May 2005), Science Citation Index (2000 – 27th May 2005), Medline Extra (11th May 2005), Cochrane Controlled Trials Register (The Cochrane Library, Issue 2 2005), Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 2, 2005), Database of Abstracts of Reviews of Effectiveness (May 2005) , HTA Database (May 2005), Health Management Information Consortium (2000 – May 2005) and Journals @ Ovid Full Text (2000- July 2005 for selected surgical journals). In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in Appendix 1.

All titles and abstracts identified in these ways were assessed to identify potentially eligible studies. Two reviewers independently assessed them for inclusion, using a study eligibility form developed for this purpose (Appendix 2). Any disagreements were resolved by consensus or arbitration. Systematic reviews were used to identify pre-2000 RCTs but were

not included in this review. Lead authors of all included RCTs were contacted directly to identify further studies and unpublished data.

3.1.2 Inclusion and exclusion criteria

Types of studies

We included individual RCTs and individual patient data meta-analyses of RCTs of laparoscopic surgery, laparoscopic-assisted surgery and HALS compared to open surgery for colorectal cancer. UK registries, providing data for a minimum of three years follow-up for any of the surgical techniques either alone or in comparison with each other, were also included. Studies were eligible irrespective of the language in which they were reported. Initially, we had intended to include cohort studies with a minimum follow-up of three years, but in the event we decided that this was not necessary as the length of follow-up available from RCTs (and particularly an individual patient data meta-analysis of RCTs) was considered sufficient to provide long-term data that were more robust than data from non-randomised cohort studies.

Types of participants

Studies of adults with colorectal cancer who have undergone surgery were included. Patients undergoing palliative treatment (non-curative surgery) were excluded. In addition, the following subgroups were considered: location of cancer; stage of cancer; and mean age at diagnosis.

Types of outcomes

The following measures of outcomes were sought:

Short-term outcomes:

Duration of operation
Anastomotic leakage
Abdominal wound breakdown
Lymph node retrieval
Number of ports used for laparoscopic resection
'Opposite' method initiated
Completeness of resection, margins of tumour clearance
Conversion
Seroma
Blood Loss
Wound Infection
Urinary tract infection
Vascular injury
Visceral injury
30-day mortality
Length of stay
Post operative pain
Time to return to usual activities

Long-term outcomes:

Overall survival	Recurrence
Disease-free survival	Incisional hernia
Health-related quality of life	Port site hernia

3.1.3 Data extraction strategy

The titles and abstracts of all papers identified by the search strategy were screened. Full text copies of all potentially relevant studies were obtained and two reviewers independently assessed them for inclusion. Reviewers were not blinded to the names of studies' authors, institutions or sources of the reports. Any disagreements were resolved by consensus or arbitration.

A data extraction form was developed to record details of trial methods, participants, interventions, patient characteristics and outcomes (Appendix 3). Two reviewers independently extracted data from the included studies. Any differences that could not be resolved through discussion were referred to an arbiter.

3.1.4 Quality assessment strategy

Two reviewers, working independently, assessed the methodological quality of the included studies. Again, any disagreements were resolved by consensus or arbitration. The methodological quality of the meta-analysis was assessed by a previously validated 9-item checklist (Appendix 4) developed by Oxman and colleagues.[43,44] Primary RCTs were assessed using the Delphi criteria list[45] (Appendix 5).

3.1.5 Data synthesis

For trials with multiple publications, only the most up to date data for each outcome were included. Dichotomous outcome data were combined using the Mantel-Haenszel relative risk (RR) method and continuous outcomes were combined using the inverse variance weighted mean difference (WMD) method. 95% confidence intervals (CI) and *p* values were calculated for the estimates of RR and WMD. The results are all reported using a fixed effects model. Chi-squared tests and I-squared statistics were used to explore statistical heterogeneity across studies and, when present, random effects methods were applied. Other possible reasons for heterogeneity were explored using sensitivity analyses. The meta-analyses were conducted using the standard Cochrane software RevMan 4.2.

Due to the lack of uniformity of the data presented by many studies, a qualitative review looking for consistency between studies was also performed. This was supplemented where appropriate by the investigation of the consistency in the direction of the results using the Sign test.[46]

Opposite method initiated was defined as a laparoscopic operation initiated when an open resection was allocated, or vice-versa. Duration of operation was defined as time from first incision to last suture or, where this was not available, time in theatre or duration of anaesthesia. Length of hospital stay was defined as time from admission to discharge. A conversion was defined as a procedure initiated as laparoscopic but converted to an open procedure.

3.2 Results

3.2.1 Quantity and quality of research available

Number of studies identified

The results of the searches are summarised in Table 3.1. The numbers retrieved from the searches in SCI, Biosis, Journals@Ovid Full Text and CENTRAL include only the additional reports found after excluding those identified from the Medline/Embase multifile search.

Table 3.1 Search results

Database	Number retrieved
Medline/Embase/Medline Extra multi file search (after deduplication in Ovid)	581
SCI	167
Biosis	14
CENTRAL	3
Journals @ Ovid Full Text	70
HMIC	35
CDSR	34
DARE	24
HTA database	30
NRR	12
CCT	1
Clinical Trials	1
Selected from conference abstracts	10
Total retrieved	**982**

A total of 982 reports were identified from the various searches of which 167 reports (157 full text papers; ten abstracts) were selected for full assessment. Table 3.2 details the numbers of these that were included and excluded.

Table 3.2 Papers selected for full assessment

Assessment	Number of papers
Included in review	33
Retained for background information	28
Excluded – did not meet inclusion criteria	77
Excluded – not relevant to review	22
Unobtainable papers	4
Systematic reviews	3
Total	**167**

Number and type of studies included

Thirty-three papers (31 full text papers and two abstracts) met the inclusion criteria for the review. In addition, 11 pre-2000 reports were included; five from the original review and six that were not included but were identified from other systematic reviews. A further two reports, both unpublished, were obtained from their authors (Bonjer, QE 11 Health Sciences Center, Halifax, 2005).[40]

Thus, in total, 46 reports describing 20 studies (19 RCTs and one individual patient data meta-analysis) were included in the review of clinical effectiveness. The sources of the most recent report of studies (primary reports), and additional reports relating to these studies

(secondary reports), are summarised in Table 3.3. The list of included studies (Bonjer, QE 11 Health Sciences Center)[2-4,22,40,47-60] and associated references[61-86] are listed in Appendix 6.

Table 3.3 Included reports

Source	Primary reports	Secondary reports
Identified from searches (2000-2005)	13	20
Pre 2000 (Original review)	3	2
Pre 2000 (Not in original review)	2	4
Unpublished	2	0
TOTAL	**20**	**26**

Number and type of studies excluded, with reasons for specific exclusions

A total of 77 reports (72 full-text papers and five abstracts) were obtained but subsequently were excluded because they failed to meet one or more of the inclusion criterion. Of these, 59 were not RCTs or individual patient data meta-analyses. Of the 18 remaining studies, three had no usable results,[87-89] two were reports of the current status of an ongoing trial,[90,91] two were comparisons of types of follow-up,[92,93] one compared medial-to-lateral versus lateral-to-medial laparoscopic dissection[94] and in ten, the authors did not report outcomes separately for participants with cancer.[95-104]

Study quality, characteristics and evidence rating

A summary of the quality assessment of the 19 full-text RCTs is presented in Table 3.4 and the detailed quality assessment score for each of the included studies is reported in Appendix 7. An adequate method of random sequence generation (computer generated or random numbers table) was performed in all but one[60] of the studies. Suboptimal approaches to concealment of randomisation (serially numbered sealed envelopes) were used in five studies.[22,48,52,58,59] The intervention groups were dissimilar at baseline in five studies in respect of the most important prognostic indicators.[50-52,57,59] Eligibility criteria were clearly specified in all 19 studies.

In the majority, it was unclear whether studies blinded the outcome assessor and patients. In addition, the 19 studies did not blind the care provider (but it is questionable if this is possible given the nature of the treatments compared). Point estimates and measures of variability were presented for the primary outcome measures in all but one study.[47] However, only seven presented an appropriate measure of variability (standard deviations, interquartile ranges or 95% confidence intervals).[3,22,40,53,56,59,60] Seven studies included an

intention to treat analysis[2-4,40,56,58,59] and it was unclear whether five other studies included an intention to treat analysis.[22,47,52,55,60]

Table 3.4 Summary of the quality assessment of the included RCTs

Criteria	Yes	No	Unclear
1. Was a method of randomisation performed?	18	0	1
2. Was the treatment allocation concealed?	6	5	8
3. Were the groups similar at baseline regarding the most important prognostic indicators?	14	5	0
4. Were the eligibility criteria specified?	19	0	0
5. Was the outcome assessor blinded?	1	2	16
6. Was the care provider blinded?	0	19	0
7. Was the patient blinded?	0	3	16
8. Were point estimates and measures of variability presented for the primary outcome measures?	18	1	0
9. Did the analysis include an intention-to-treat analysis?	7	7	5

The quality assessment scores of the individual patient data meta-analyses are tabulated in Appendix 7 (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). [redacted] (Bonjer, QE 11 Health Sciences Center, Halifax, 2005).

Characteristics of included studies

Appendix 8 provides details of the characteristics of RCTs, which are summarised in Table 3.5. Within the 19 eligible RCTs, there were 19 relevant comparisons, none of which involved a comparison with HALS. Four studies took place in the USA,[2,48,51,52] two in Germany,[55,56] two in Hong Kong,[53,50] two in the UK,[3,40] one each in Brazil,[47] China,[60] Denmark,[57] Italy,[59] Japan,[49] Spain[22] and Singapore[58] and one was a multi-centre European study.[4] Across the studies with this information recruitment dates ranged from January 1993 to March 2004. Two studies failed to provide information on recruitment dates.[50,57,104]

In the included RCTs, the number of participants randomised to laparoscopic or open resections ranged from 16[50] to 1082.[4] Three trials had more than 750 participants,[2-4] six more

than 100, and ten fewer than 100. The total number of participants allocated to laparoscopic surgery was 2429, and the total allocated open resection was 2139.

All but one study gave details of the numbers of men and women in each trial group with colorectal cancer.[59] Across studies, the percentage of males was higher than the percentage of females with the exception of two studies.[51,52] In total, there were at least 1257 men and 1162 women allocated to laparoscopic resection, and at least 1103 men and 967 women allocated to open resection. The total number of males and females does not match the total number of participants receiving laparoscopic or open resection as some trials report the gender of all eligible participants rather than the gender of the actual number of participants that received the operation.

When data allowed, the patient population was split by the anatomical site of cancer, the stage of cancer, and participant's age. Generally, studies provided only the mean or median age and range of ages, the number of participants with cancer in a specific location and its stage, for each participant group as a whole, and did not report outcomes within each participant group separately. However, ten studies provide outcome information in relation to patients who had colon resections and three studies provide information in relation to patients who underwent a rectal resection.[3,47,60]

All 19 studies gave details of participants' ages. One study, however, gave only the mean age of the participant group as a whole (patients with benign colorectal disease and colorectal cancer) and therefore the ages of participants with colorectal cancer could not be distinguished.[59] Across studies, the mean or median ages of participants allocated to laparoscopic surgery ranged from 45 years[40] to 72.3 years[60] compared with 44 years[40] to 70.4 years for patients allocated to open resection.[60]

Across the studies, the total number of participants having a colon resection was much higher than those having a rectal resection. The total number of participants who had a colon resection laparoscopically was 1800 compared with 629 rectum resections, and 1638 participants received an open colon resection compared with 499 open rectum resections.

In general, studies reported the participants' stage of cancer using either Dukes' or TNM classification (see Appendix 8 for further details). One study failed to report the stage of cancer at which participants were enrolled[55] and in one study the stage could not be clearly

reported.[3] Where specified, the majority of participants receiving either laparoscopic or conventional open interventions had either Dukes' B (TNM stage II) or Dukes' C (TNM stage III) cancer.

The individual patient data meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) included patients from four of the above trials; CLASICC, COLOR , COST and Lacy and colleagues.[2-4,22] [redacted]

Table 3.5 Summary of the baseline characteristics

Study id	Comparators	Number of participants	Age (years) *	Male/Female	Colon/Rectum
Araujo 2003[47]	Laparoscopic	13	59	9/4	0/13
	Open	15	56	10/5	0/15
CLASICC 2005[3]	Laparoscopic	526	69	296/230	273/253
	Open	268	69	145/123	140/128
COLOR 2005[4]	Laparoscopic	536	71†	326/301	536/0
	Open	546	71†	336/285	546/0
COST 2004[2]	Laparoscopic	435	70†	223/212	435/0
	Open	428	69†	208/220	428/0
Curet 2000[48]	Laparoscopic	25	66	15/10	25/0
	Open	18	69	14/4	18/0
Hasegawa 2003[49]	Laparoscopic	24	61	14/10	22/2
	Open	26	61	18/8	24/2
Hewitt 1998[50]	Laparoscopic	8	54†	4/4	8/0
	Open	8	70†	3/5	8/0
Kaiser 2004[51]	Laparoscopic	28	59	12/16	28/0
	Open	20	60	9/11	20/0
Kim 1998[52]	Laparoscopic	19	70†	8/11	19/0
	Open	19	65†	10/8	18/0
King 2005[40]	Laparoscopic	41	72	23/18	27/14
	Open	19	70	8/11	14/5
Lacy 2002[22]	Lap-assisted	111	68	56/55	111/0
	Open	108	71	50/58	108/0
Leung 2004[53]	Laparoscopic	203	67	104/99	0/203
	Open	200	66	114/86	0/200
Milsom 1998[54]	Laparoscopic	55	69†	26/29	48/7 §
	Open	54	69†	36/18	50/4 §
Neudecker 2003[55]	Laparoscopic	14	62†	7/7	14/0
	Open	16	64†	10/6	16/0
Schwenk 1998a[56]	Laparoscopic	30	64	14/16	23/7
	Open	30	65	16/14	23/7
Stage 1997[57]	Laparoscopic	15	72†	8/7	15/0
	Open	14	73†	5/9	14/0
Tang 2001[58]	Laparoscopic	118	64†	61/57	118/0
	Open	118	62†	70/48	118/0
Vignali 2004[59]	Laparoscopic	146	NR	NR	98/48
	Open	143	NR	NR	94/49
Zhou 2004[60]	Laparoscopic	82	45	46/36	0/82
	Open	89	44	43/46	0/89

Age is given as mean, unless otherwise stated
† Median
§ Some colon patients were actually upper rectum
NR: not reported

3.2.2 Description of surgery received

'Opposite' method initiated

The 'opposite' method to the one that the patient was randomised to was initiated in 46/1173 (3.9%) of those randomised to laparoscopic resections (Table 3.6). Rates varied between the trials that reported this information. [redacted]

(Bonjer, QE 11 Health Sciences Center, Halifax, 2005).

Table 3.6 'Opposite' method initiated

Study id	Laparoscopic			Open		
	N	n	%	N	n	%
CLASICC 2005[3]	526	23	4.3	268	4	1.5
COLOR 2005[4]	536	11	2.0	-	-	
Lacy 2002[22]	111	12	11	-	-	
Bonjer 2005 (unpubl) †	[redacted]					

†Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy and colleagues trials.

Number of ports

A total of seven studies provided information on the number of port-sites used for laparoscopic resection.[47-50,57,58,77] The number varied between three and five across the studies.

Conversion

In total, 12 studies reported conversions from laparoscopic to open surgery. Rates varied between trials from 0 to 46%. Overall, 417 (21%) laparoscopic procedures were converted to an open surgery amongst 1972 allocated to laparoscopic resection (Table 3.7). [redacted] (Bonjer, QE 11 Health Sciences Center, Halifax, 2005).

Table 3.7 Conversions

Study id	Number of conversions	Number allocated to laparoscopy	%
Araujo 2003[47]	0	13	0
CLASICC 2005[3]	143	526	27
COLOR 2005[4]	91	536	17
COST 2004[2]	90	435	21
Curet 2000[48]	7	25	28
Hasegawa 2003[49]	5	29	17
Kaiser 2004[51]	13	28	46
King 2005[40]	3	41	7
Leung 2004[53]	47	203	23
Stage 1997[57]	3	18	16
Tang 2001[58]	15	118	13
Bonjer 2005 (unpubl)†	[redacted]	[redacted]	[redacted]

† Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy and colleagues trials.

Surgeon prior experience

Ten of the RCTs reported that surgeons performing the procedures were experienced in laparocopic colorectal surgery.[2-4,22,48,50,51,53,57,59] However, only three trials[2-4] reported a minimum level of experience required to enter the trial. In these trials surgeons were required to have undertaken at least 20 laparoscopic colorectal operations before participating in the trial.

3.2.3 Assessment of effectiveness

Table 3.8 gives a summary of the outcomes reported in the included studies. None provided information for the following four outcomes: seroma, visceral and vascular injury, and long-term pain. The remaining outcomes are discussed in the subsequent section. The results of the meta-analyses performed for this review are given in Appendix 9.

Table 3.8 Summary of outcomes reported in the included studies

	SHORT-TERM OUTCOMES																				LONG-TERM OUTCOMES							
Study id	Duration of operation	Blood loss	Anastomotic leakage	Abdominal wound breakdown	Lymph node retrieval	Number ports used	Opposite method initiated	Completeness of resection/margins of tumour clearance	Conversion	Seroma	Infection	Vascular injury	Visceral injury	30 day mortality	Length hospital stay	Post-operative pain	Time to return to usual activities	Survival	Disease-free survival	Quality of life	Recurrence	Time to recurrence	Incisional hernia	Port site hernia	Long term pain
Araujo 2003[47]	✓			✓	✓	✓			✓						✓						✓				
CLASICC 2005[3]	✓		✓		✓		✓	✓	✓		✓			✓	✓	✓				✓					
COLOR 2005[4]	✓	✓	✓	✓	✓		✓	✓	✓		✓			✓	✓										
COST 2004[2]	✓				✓			✓	✓					✓	✓	✓		✓	✓		✓				
Winslow 2002[83]						✓					✓												✓		
Weeks 2002[82]																✓				✓					
Curet 2000[48]	✓	✓			✓	✓			✓		✓			✓	✓			✓			✓				
Hasegawa 2003[49]	✓	✓	✓		✓	✓			✓		✓				✓	✓					✓				
Hewitt 1998[50]	✓					✓									✓	✓									
Kaiser, 2004[51]	✓	✓			✓				✓		✓				✓	✓		✓	✓		✓				
Kim 1998[52]																					✓				
King 2005[40]	✓	✓	✓	✓					✓		✓			✓	✓	✓				✓					
Lacy 2002[22]	✓	✓	✓		✓		✓				✓			✓	✓	✓		✓	✓		✓	✓			
Leung 2004[53]	✓	✓	✓		✓			✓	✓		✓			✓	✓		✓	✓	✓		✓	✓	✓		
Milsom 1998[54]					✓			✓													✓				
Neudecker 2002[55]	✓																								
Schwenk 1998a[56]	✓										✓														
Schwenk 1998b[77]						✓									✓	✓									
Schwenk 1998c[78]																				✓					
Stage 1997[57]	✓	✓			✓	✓		✓	✓						✓	✓					✓				
Tang 2001[58]	✓		✓			✓			✓		✓														
Vignali 2004[59]					✓																				
Zhou 2004[60]	✓	✓	✓					✓							✓	✓		✓			✓				

Duration of operation

Of the 19 eligible studies, 16 (n = 4125) provided information on the duration of operation (Table 3.9). In all but one study[47] the duration of operation was longer in the laparoscopic group (Sign–test, p < 0.001) and this was statistically significant (p<0.05) in 12 studies. Only three studies[22,53,56] presented data in a form sufficiently similar to allow quantitative synthesis (Appendix 9, comparison 01:01). The WMD was 40 minutes (95% CI 32 to 48, p <0.001) for laparoscopic versus open surgery. This result is consistent with the data from those trials that provided data not amenable to meta-analysis (medians and ranges, e.g. the difference in medians in the UK-based CLASICC trial was 45 minutes) (Table 3.9). There was evidence of statistical heterogeneity between the three trials in the meta-analysis, but the direction of effect was consistent across the studies even though the size of effect estimates varied. Using a random effects model did not change this pattern. The cause of the heterogeneity is unclear but in Leung and colleagues[53] all participants suffered from rectal or sigmoid cancers, in Lacy and colleagues[22] all participants had colon cancer, and in Schwenk and colleagues,[56] both groups were included. Furthermore, Leung and colleagues[53] had many more participants with TNM stage IV as compared to the other two studies.

Table 3.9 Duration of operation (minutes)

Study id	Laparoscopic		Open		p value	Comments
	n		n			
Araujo 2003[47]	13	228	15	284	0.04	Mean
CLASICC 2005[3]	526	180 (135-220)	268	135 (100-180)		Median (IQR)
COLOR 2005[4]	536	145 (45-420)	546	115 (40-355)	<0.001	Median (range)
COST 2004[2]	435	150 (35-450)	428	95 (27-435)	<0.001	Median (range)
Curet 2000[48]	18	210 (128-275)	18	138 (95-240)	<0.05	Unknown
Hasegawa 2003[49]	24	275 (184-410)	26	188 (127-272)	<0.001	Mean (range)
Hewitt 1998[50]	8	165 (130-300)	8	107.5 (90-150)	0.02	Median (range)
Kaiser 2004[51]	28	125 (70-270)	20	65 (45-125)	<0.05	Mean (range)
King 2005[40]	41	187 (168-207)	19	140 (121-163)	0.001	Geometric mean (95% CI)
Lacy 2002[22]	111	142 (52)	108	118 (45)	0.001	Mean (SD)
Leung 2004[53]	203	190 (55)	200	144 (58)	<0.001	Mean (SD)
Neudecker 2003[55]	14	205 (120-260)	16	165 (100-285)	<0.05	Median (range)
Schwenk 1998a[56,104]	30	219 (64)	30	146 (41)	<0.01	Mean (SD)
Stage 1997[57]	15	150 (60-275)	14	95 (40-195)	0.05	Median (range)
Tang 2001[58]	118	88 (15-220)	118	70 (20-195)		Median (range)
Zhou 2004[60]	82	120 (110-220)	89	106 (80-230)	0.051	Mean (range)

Blood loss

Blood loss data were not reported in a form sufficiently similar to allow for a quantitative synthesis (Table 3.10). Nine studies[4,22,40,48,49,51,53,57,60] provided information on the quantity of blood lost for patients undergoing laparoscopic or open interventions. Eight studies favoured the laparoscopic group,[4,22,40,48,49,53,57,60] and six of the nine studies reported a statistically significant difference. Based on the Sign-test, there was a statistically significant difference between the two interventions (Sign-test, p = 0.039). The largest trial that provided data, reported a median difference in blood loss of 75 millilitres.[4] The other trials are broadly consistent with this.

Table 3.10 Blood loss (millilitres)

Study id	Laparoscopic		Open		p value	Comments
	n		n			
COLOR 2005[4]	536	100 (0-2700)	546	175 (0-2000)	<0.0001	Median (range)
Curet 2000[48]	18	284 (100-700)	18	407 (100-1000)	<0.05	Unknown
Hasegawa 2003[49]	24	58 (1-350)	26	137 (32-355)	0.0034	Mean (range)
Kaiser 2004[51]	28	146.4 (100-1000)	20	100 (100-800)		Mean (range)
King 2005[40]	41	11 (27%)	19	18 (95%)	<0.001	Number with blood loss >100ml
Lacy 2002[22]	111	105 (99)	108	193 (212)	0.001	Mean (SD)
Leung 2004[53]	203	169 (0-3000)	200	238 (0-5836)	0.06	Mean (range)
Stage 1997[57]	15	275 (50-2100)	14	300 (50-2150)		Median (range)
Zhou 2004[60]	82	20 (5-120)	89	92 (50-200)	0.025	Mean (range)

Anastomotic leakage

A total of 55 (3%) leakages were reported amongst 1640 allocated laparoscopic resections versus 34 (2.5%) amongst 1373 allocated open resections (Appendix 9 Comparison 01:02: RR 1.13, 95% CI 0.74 to 1.73, p = 0.58). The direction and size of effect varied across the eight studies. These results were particularly influenced by the COLOR and CLASICC trials.[3,4] The difference remained statistically non-significant when colon and rectum patients were considered separately (Appendix 9 Comparison 01:20).

Abdominal Wound breakdown

Out of the 19 included studies, three reported abdominal wound breakdown.[4,40,47] In two studies the proportion of patients that had an abdominal wound breakdown appeared to be higher in the open group;[4,40] however, the confidence intervals were wide enough for clinically important differences between laparoscopic and open resection to exist (Appendix 9 Comparison 01:03: RR 0.63, 95% CI 0.26 to 1.52, p = 0.30).

Lymph node retrieval

Twelve studies provided information on the mean or median number of lymph nodes retrieved (Table 3.11). Seven studies[3,47,49,51,53,54,57] showed more lymph nodes retrieved in the open group than in the laparoscopic, two[48,59] showed more in the laparoscopic group and in three studies there were no differences (Sign test, p = 0.289). Meta-analysis of the three trials[22,53,59] reporting data suitable for synthesis showed no statistically significant difference between groups (Appendix 9 Comparison 01:04: WMD –0.41, 95% CI –1.42 to 0.59, p = 0.42). The mean number of lymph nodes retrieved reported in the individual patient data meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax) was [redacted].

Table 3.11 Lymph node retrieval (number)

Study id	Laparoscopic		Open		p value	Comments
	n		n			
Araujo 2003[47]	13	5.5	15	11.9	0.04	mean
CLASICC 2005[3]	526	12 (8-17)	268	13.5 (8-19)		median (IQR)
COLOR 2005[4]	536	10 (0-41)	546	10 (0-42)	0.35	median (range)
COST 2004[2]	435	12	428	12		median
Curet 2000[48]	18	11 (2-23)	18	10 (1-21)		Unknown
Hasegawa 2003[49]	24	23 (7-50)	26	26 (15-56)	0.25	mean (range)
Kaiser 2004[51]	28	13.3 (1-32)	20	14 (3-27)		mean (range)
Lacy 2002[22]	111	11.1 (7.9)	108	11.1 (7.4)		mean (SD)
Leung 2004[53]	203	11.1 (7.9)	200	12.1 (7.1)	0.18	mean (SD)
Milsom 1998[54]	42	19 (5-59)	38	25 (4-74)		median (range)
Stage 1997[57]	15	7 (3-14)	14	8 (4-15)		median (range)
Vignali 2004[59]	144	15.2 (8.6)	145	15.0 (7.7)	0.9	mean (SD)
Bonjer 2005 (Unpubl)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*mean*

† Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy and colleagues trials.

Completeness of resection

Complete surgical resection of colorectal cancer is an absolute requirement, albeit no guarantee of cure. The adequacy of resection can be assessed by proximal, distal and circumferential disease-free margins during histological examination. In rectal cancer, the distal and circumferential margins are particularly important.

Table 3.12 describes the results of studies reporting completeness of resection in terms of proximal, distal and circumferential resection margins. Further data were reported in two RCTs[4,54,60] and in one meta-analysis (Bonjer, QE 11 Health Sciences Center) using other

definitions, which were not always well described (Table 3.13). Furthermore, whilst the CLASICC trial included rectal cancers most trials were limited to colonic cancer. There appears to be no statistical difference in this outcome between laparoscopic and open surgery, however meta-analysis of four studies[3,4,54,60] reporting sufficiently comparable data showed a slightly better rate for open resections but the difference was again not statistically significant (Appendix 9 Comparison 01:05: RR 1.15, 95% CI 0.74 to 1.77, p value = 0.53).

Table 3.12 Resection margins

Study id	Laparoscopic		Open		p value	Comments
	n		n			
Proximal resection margins						
COLOR 2005[4]	526	0	538	1	1.0	Number of positive resection margins
COST 2004[2]	435	13 (2-78)	428	12 (3-50)	0.38	Median (range) centimetres
Distal resection margins						
COLOR 2005[4]	526	1	538	1	1.0	Number of positive resection margins
COST 2004[2]	435	10 (2-40)	428	11 (1-42)	0.09	Median (range) centimetres
Leung 2004[53]	203	4.5 (3.0)	200	4.5 (2.7)	0.97	Mean (SD) centimetres
Circumferential resection margins						
CLASICC 2005[3]	439	46 (10.5%)	228	20 (8.8%)		Number of positive resection margins
Colon	*246*	*16 (0.4%)*	*131*	*6 (4.6%)*	*0.45*	
Rectum	*193*	*30 (0.5%)*	*97*	*14 (14.4%)*	*0.8*	
COLOR 2005[4]	526	9 (1.7%)	538	8 (1.5%)	1.0	Number of positive resection margins

Table 3.13 Other data on resection margins

Study id	Laparoscopic			Open			p value	Comments
	N	n	%	N	n	%		
Milsom 1998[54]	42	0	0	38	0	0		Positive surgical margins
Zhou 2004[60]	82	0	0	89	0	0		Cancer cell found in the cut margins
Bonjer 2005† (unpubl)			[redacted]			[redacted]	[redacted]	[redacted]

† Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy and colleagues trials

Wound infection

Meta-analysis of data from the nine trials[3,4,22,40,48,49,53,58,83] that reported wound infections showed no statistically significant difference between the laparoscopic group and open group although the confidence interval was wide (Appendix 9 Comparison 01:06: 96/1620 versus 86/1348: RR 0.86, 95% CI 0.64 to 1.14, p = 0.29).

Urinary tract infection

A total of six studies reported urinary tract infections. There was no statistically significant difference in the proportion of patients having a urinary tract infection in the laparoscopic group when compared with the open group, but again the confidence interval was wide and did not rule out clinically important differences (Appendix 9 Comparison 01:07: 25/1050 versus 21/1029: RR 1.15, 95% CI 0.66 to 1.98, p = 0.62). The direction of effect favoured laparoscopic surgery in two studies[4,58] but the difference was not statistically significant.

30-day mortality

Seven RCTs[2-4,22,40,48,53] and one meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax) provided information on operative and 30-day mortality. [redacted] Data were also available from the seven individual RCTs. Three studies reported operative mortality,[22,48,53] two reported 30-day mortality,[2,40] one reported the number of people that died in hospital,[3] and another reported 28-day mortality[4] (the latter was treated as 30-day mortality for meta-analysis purposes). In terms of operative mortality, the overall direction of effect favours laparoscopic surgery, however the difference was not statistically significant and the confidence interval is wide (6/339 versus 7/326, RR 0.84, 95% CI 0.29 to 2.47, p = 0.75). Also, 30-day mortality was non-significantly less in the laparoscopic group than in the open group (8/1011 versus 15/992, RR 0.57, 95% CI 0.25 to 1.29, p = 0.18).

Length of hospital stay

All 14 studies that provided information on length of hospital stay reported lower mean or median stay in the laparoscopic group and this was statistically significant in 11 studies (Table 3.14). The direction of apparent effect towards laparoscopic surgery is supported by the Sign-test (p < 0.001). Four RCTs reported data suitable for quantitative synthesis.[4,22,60,77] Across them, the average length of stay was significantly shorter in the laparoscopic group than in the open group (Appendix 9 Comparison 01:09: WMD –2.58, 95% CI –3.12 to –2.03, p < 0.001)). This result was consistent with the data from those trials that reported data not amenable to meta-analysis (Table 3.14). Nonetheless, there was a marked heterogeneity observed in the meta-analysis of this outcome, but there was consistency in the direction of effect, reflecting variation in the size of estimated effect across studies. Using the random effects method, the WMD was –2.63 days (95% CI –4.82 to –0.44, p = 0.02). The main source of heterogeneity appeared to be from the study by Zhou and colleagues, where the average

age of participants was lower than the rest of the studies included in this review. Additionally, all participants in the Zhou study had rectal cancer. When data from Zhou and colleagues were excluded from the analysis, the trend towards laparoscopic surgery was maintained but the weighted mean difference was decreased (WMD –1.40, 95% CI –2.10 to –0.70, $p < 0.0001$). It should be noted that Schwenk and colleagues[77] kept their patients in hospital for at least seven days regardless of the type of surgery.

Table 3.14 Length of hospital stay (days)

Study id	Laparoscopic		Open		p value	Comments
	n		n			
Araujo 2003[47]	13	10.5	15	NR*	0.42	mean
CLASICC 2005[3]	526	9 (7-14)	268	11 (8-15)		median (IQR)
- colon	*273*	*9 (7-12)*	*140*	*9 (8-13)*		*median (IQR)*
– rectum	*253*	*11 (9-15)*	*128*	*13 (9-18)*		*median (IQR)*
COLOR 2005[4]	536	8.2 (6.6)	546	9.3 (7.3)	<0.0001	mean (SD)
COST 2004[2]	435	5 (4-6)	428	6 (5-7)	<0.001	median (IQR)
Curet 2000[48]	18	5.2	18	7.3	<0.05	Unknown
Hasegawa 2003[49]	24	7.1 (4-15)	26	12.7 (6-57)	0.0164	mean (range)
Hewitt 1998[50]	8	6 (5-7)	8	7 (4-9)		median (range)
Kaiser 2004[51]	28	5.9 (3-13)	20	6 (5-9)	<0.05	mean (range)
King 2005[40]	40	5.2 (4.2-6.5)	18	7.4 (6.0-9.2)	0.018	geometric mean (95% CI)
Lacy 2002[22]	111	5.2 (2.1)	108	7.9 (9.3)	0.005	mean (SD)
Leung 2004[53]	203	8.2 (2-99)	200	8.7 (3-39)	<0.001	mean (range)
Schwenk 1998b[77] (Schwenk 1998a)	30	10.1 (3.0)	30	11.6 (2.0)	<0.05	mean (SD)
Stage 1997[57]	15	5 (3-12)	14	8 (5-30)	0.01	median (range)
Zhou 2004[60] - *rectum*	82	8.1 (3.1)	89	13.3 (3.4)	0.001	mean (SD)

NR* not reported except as longer than laparoscopic group

Postoperative pain

Five studies included a measure of postoperative pain(Table 3.15).[3,53,57,77,82] Between the first day and two weeks post-operation, four studies favoured the laparoscopic group[3,53,57,77] and one did not show any differences between the two interventions[82] (Sign-test $p = 0.125$). Three studies measured pain at one to three months postoperatively but this did not differ significantly between the two interventions.[3,57,82] Data were not presented in a form sufficiently similar to allow quantitative synthesis. Results in terms of analgesic requirements, consistently favoured the laparoscopic group (Table 3.16). In four studies, patients in the laparoscopic group required fewer days of postoperative analgesia than in the open group,[2,49,51,60] and this was statistically significant in three. A further study recorded that the number of participants in the laparoscopic group requiring opioid

supplements was less than that required in the open group (9/41 (22%) versus 14/19 (74%)).[40] In another study, patients in the laparoscopic group required 35 mg less morphine in the first 48 hours as compared with the open group[50] (Sign-test p = 0.031).

Table 3.15 Postoperative pain – Pain scores

Study id	Measure	Laparoscopic		Open		p value	Comments
		n		n			
CLASICC 2005[3]	EORTC QLQ-C30 (pain) at 2 weeks post-op	526	40	268	35	ns	Estimated from graph
	EORTC QLQ-C30 (pain) at 3 months post-op	526	21	268	19	ns	Estimated from graph (back to baseline)
Leung 2004[53]	VAS at 1 day post-op	203	4.6 (2.4)	200	5.4 (2.3)	0.003	Mean (SD)
Schwenk 1998b[77] (Schwenk 1998a)	VAS at rest at 1 day post-op	30	17.5 (0-50)	30	26 (0-50)	0.2	Median (range)
	Cumulative VAS score during rest for first week post-op	30	161 (17-729)	30	252 (123-441)	0.07	Median (range)
Stage 1997[57]	VAS at rest at 1 day post-op	15	15	14	16	ns	Estimated from graph
	VAS at rest at 5 days post-op	15	0	14	5	ns	Estimated from graph
	VAS at rest 30 days post-op	15	0	14	0	ns	Estimated from graph
Weeks 2002[82] (COST 2004)	Pain distress at 2 days post-op	203	2 (1-3)	198	2 (1-3)	ns	Median (IQR)
	Pain distress at 2 weeks post-op	201	1 (1-2)	194	1 (1-2)	ns	Median (IQR)
	Pain distress at 2 months post-op	199	1 (1-1)	180	1 (1-2)	ns	Median (IQR)

EORTC QLQ-C30: European Organisation for research and treatment of cancer (100: better); VAS: visual analogue score (0: better)

Table 3.16 Postoperative pain – Analgesic requirement

Study id	Measure	Laparoscopic n		Open n		p value	Comments
COST 2004[2]	Duration of parenteral narcotics (days)	435	3 (2-4)	428	4 (3-5)	<0.001	Median (IQR)
	Duration of oral analgesics (days)	435	1 (1-2)	428	2 (1-3)	0.02	
Hasegawa 2003[49]	Analgesic requirement (post-op days)	24	1.7 (0-4)	26	3.4 (0-17)	0.0022	Mean (range)
Hewitt 1998[50]	Analgesic requirement (mg of morphine in first 48 hours)	8	27 (0-60)	8	62 (28-88)	0.04	Median (range)
Kaiser 2004[51]	Use of analgesics (days)	15	2 (0-3)	20	4 (2-7)	<0.05	Mean (range)
King 2005[40]	Epidural insufficiency requiring opioid supplements	41	9 (22%)	19	14 (74%)	<0.001	
Zhou 2004[60]	Parenteral analgesics (days)	82	3.9 (0.9)	89	4.1 (1.1)	0.225	Mean (SD)

Time to return to usual activities

Only one study reported data on time to return to usual activities.[53] This study was based in Hong Kong and compared laparoscopic (n=203) with open surgery (n=200) in patients with rectosigmoid cancer. The authors report that the average time to resume household activities in the laparoscopic group (mean 32 days, range 4 to 365) was lower than that in the open group (mean 44 days, range 7 to 198, p = 0.002).

Health related quality of life

Four studies, using a variety of instruments, reported the quality of life of people undergoing laparoscopic or open resections (Table 3.17).[3,40,56,82] In three studies the quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC-QLQ-C30).[3,40,78] In one study, quality of life was measured using two distinct instruments: Quality of Life Index and the Global Rating Scale.[82]

Three studies reported higher quality of life following laparoscopic surgery and in one quality of life score were similar in both laparoscopic and open groups,[40] however this was a randomised study embedded within an enhanced recovery program (Sign-test p = 0.125).

One study reports that patients assigned to laparoscopic surgery who were converted to open, showed poorer quality of life at baseline and at every follow-up assessment than patients who underwent laparoscopic resection.[82]

Table 3.17 Quality of Life

Study id	Measure	Laparoscopic	Open	Comments
CLASICC 2005[3]	EORTC-QLQ-C30	55	52	Estimated from graph at 2 weeks
King 2005[40]	EORTC-QLQ-C30	NR	NR	Scores were similar at 2 weeks
Schwenk 1998c[78] (Schwenk 1998a)	EORTC-QLQ-C30	NR	NR	Scores favours lap at 1 and 4 weeks (p=0.05)
Weeks 2002[82] (COST 2004)	QLI	1 (0-2)	1 (0-2)	Median (IQR) at 2 weeks
	Global QoL	80 (70-90)	75 (60-90)	

EORTC QLQ-C30: European Organisation for research and treatment of cancer (100: better)
QLI: quality of life index (0: normal functioning, 1: moderately impaired functioning, 2: severely impaired functioning);
Global QoL: Global quality of life (0: death; 100: excellent health)

Overall survival

A total of seven RCTs[2,3,22,48,51,53,60] (personal communication: Prof P.J. Guillou, University of Leeds, 2005) and one individual patient data meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) provided information on overall survival for patients undergoing laparoscopic or open resection. Length of follow-up of the RCTs ranged from one to 108 months. Bonjer and colleagues (2005) reported a 'time to event' meta-analysis based on individual patient data of four big trials: COST, CLASICC, COLOR and the study conducted by Lacy and colleagues. Figure 2, of this study is reproduced below (Figure 3.1). [redacted] As Bonjer and colleagues did not include all relevant studies, the data from six of the individual RCTs were included in a meta-analysis to determine whether the results of these studies were consistent with these from Bonjer and colleagues. The results of this analysis showed no difference between groups (Appendix 9, Comparison 01:10, RR 1.03 95% CI 0.98 to 1.09, p= 0.28). The direction of effect was not consistent across the studies. One study slightly favoured laparoscopic resection,[51] and another four slightly favoured open resection.[2,22,48,53] The results of this meta-analysis should be treated with caution as the length of follow-up of the RCTs varied and only the proportion of deaths not time to death was utilised. The remaining RCT was a three-year follow-up of the CLASICC trial. [redacted]

[redacted] (personal communication: Prof P.J. Guillou, University of Leeds, 2005).

Figure 3.1 Reproduction of Bonjer Figure 2 - Disease free survival (DFS) and overall survival (OS) according to randomised open or laparoscopically-assisted surgery. The numbers of patients at risk with respect to DFS for the two groups are shown at the bottom (top row: laparoscopic-assisted)

[redacted]

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Disease-free survival

Five RCTs[2,22,51,53] (personal communication: Prof P.J. Guillou, University of Leeds, 2005) and one meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) provided information on disease-free survival. [redacted] A meta-analysis of the data provided by the remaining four RCTs showed no difference in disease free survival (Appendix 9, Comparison 01:11 RR 1.01 95% CI 0.95 to 1.07, p = 0.83).

Recurrence

Seven RCTs[2,22,47,48,51,53,57] and one meta-analysis (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) provided information on recurrence. Considering 1528 patients over the six trials, cancer recurrences appeared less frequently in the laparoscopic group than in the open resection group. Two studies favoured the open group[51,53] and another three favoured the laparoscopic group,[2,22,48] but none of the differences were statistically significant (Appendix 9 Comparison 01:12: 135/789 versus 144/765, RR 0.92, 95% CI 0.74 to 1.14, p =

0.44). The results of this meta-analysis should be treated with caution as the follow-ups of the RCTs ranged from three to 108 months. [redacted]

In terms of wound recurrence alone, there were only three reported cases of wound recurrences across the four studies[2,51-53] that reported this outcome: two cases of wound recurrence in the laparoscopic group and one in the open group[2] (Table 3.18). Eight studies provided information on port-site recurrence.[22,49,51-54,57,60] Out of 483 patients, three were found to have a port-site recurrence (Table 3.19).[22,60]

Table 3.18 Wound recurrence

Study id	Follow-up (months)	Laparoscopic	Open	p value
COST 2004[2]	median 4.4 years	2/435 (0.5%)	1/428 (0.2%)	0.50
Kaiser 2004[51]	median 35 (range 3-69)	0/28	0/20	
Kim 1998[52]	(range 1-12)	0/19	0/19	
Leung 2004[53]	lap: median 52.7 (IQR 38.9); open median 49.2 (IQR 35.4)	0/167	0/170	

Table 3.19 Port site recurrence

Study id	Follow-up (months)	Laparoscopic
Hasegawa 2003[49]	Median 20 (range 6-34)	0/24
Kaiser 2004[51]	Median 35 (range 3-69)	0/28
Kim 1998[52]	Range 1-12	0/19
Lacy 2002[22]	Median 43 (range 27-85)	1/106
Leung 2004[53]	Lap: median 52.7 (IQR 38.9); Open median 49.2 (IQR 35.4)	0/167
Milsom 1998[54]	Lap: median 18 (range 1.5-46); Open: median 20.4 (range 3-48)	0/42
Stage 1997[57]	Median 14 (range 7-19)	0/15
Zhou 2004[60]	Range 1-16	2/82

Incidence of incisional hernia

Only two studies provided information on this outcome.[53,83] The average follow-up in one was 2.5 years[83] and in the other 4.2 years.[53] Incisional hernias were reported in 17 out of 249 (7%) in the laparoscopic group and 13 out of 243 (5%) in the open group, wherein one of which was a port-site hernia, but this difference was not statistically significant (Appendix 9, Comparison 01:14)

3.2.4 Important subgroup differences for laparoscopic versus open techniques

Patients undergoing conversions

Three studies reported separate outcome data for patients undergoing conversions.[3,48,51] Appendix 10 gives a summary of outcomes reported for converted patients. The pattern observed in conversion patients for duration of operation, urinary tract and wound infection, and overall survival was similar to that observed for both laparoscopic and open resection groups. Converted patients however, displayed higher blood loss and longer length of hospital stay. In addition, although lymph node retrieval was higher, tumour recurrence appeared to be greater than that observed for the other two groups successfully managed according to their allocation. Data for converted patients were limited and therefore these results should be interpreted with caution.

Effect of surgeon experience

Three trials reported the effect of surgeon experience on outcomes.[2-4] The COST trial found no experience-based trends for conversion, length of stay or quality of life measures[2,82]. However, the CLASICC trial reported a decline in number of conversions by year of recruitment from 38% in the first year to 16% in the sixth year.[3] The COLOR trial also found that the duration of surgery for laparoscopic procedures reduced with increasing numbers of patients per centre (p=0.03), although number of lymph-nodes harvested and length of hospital stay did not differ significantly.[4]

Location of cancer

Subgroup analysis showed no evidence that the treatment effect size for anastomotic leakages was different for colon compared with rectal cancer. However, the evidence is limited as only two RCTs reported anastomotic leakages in rectal patients[3,60] (Appendix 9 Colon: Comparison 01:15:01 RR 1.27, 95% CI 0.70 to 2.31, p = 0.44; Rectum: Comparison 01:15:02 RR 1.25, 95% CI 0.63 to 2.46, p = 0.52).

Stage of cancer

Two RCTs provided subgroup analysis by stage of cancer for overall survival.[2,53] In both of these trials there was no significant difference in overall survival of patients undergoing laparoscopic resection compared to open resection for cancer stages I, II or III (p>0.05). The meta-analysis of individual patient data compared overall and disease-free survival for patients undergoing laparoscopic with open resection by stage of cancer (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). [redacted]

[redacted] Figure 4 of this study is reproduced below (Figure 3.2). [redacted]

Figure 3.2 Disease free survival (top panel) and overall survival (bottom panel) according to randomised procedure and stage

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Figure removed – Academic in Confidence

Age

No separate data were provided in the included studies to compare older and younger patients.

3.3 Summary and conclusions of the evidence for and against the intervention

This update considered data from over 4500 randomised participants across 18 RCTs of generally good quality. The data indicate that after laparoscopic resection, length of hospital stay is shorter, blood loss and post-operative pain are less, and return to usual activities is likely to be faster than after open resection. The duration of operation for laparoscopic resection is longer. Lymph node retrieval, completeness of resection and quality of life do not appear to differ between the two approaches, although clinically important differences could not be ruled out. The occurrence of complications such as anastomotic leakage, abdominal wound breakdown, incisional hernia, wound and urinary tract infections are similar, again with wide confidence intervals. Operative and 30-day mortality, were also statistically similar in both groups. [redacted] (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) [redacted] There was also no evidence of a difference in the number of recurrences (including wound recurrences). Furthermore, after laparoscopic resection port-site recurrences were found in less than 1% of patients.

In this review, the results for duration of operati on and length of stay displayed significant heterogeneity. Consistency on the direction of effect was, however, observed in the two outcomes. Much of the variation might be due to differences in the characteristics of participants, particularly differences on patients' age, and location and stage of cancer. In part this may have been due to the differences in the specific aims and objectives of the trials, which led to important differences in inclusion criteria. Other likely sources of heterogeneity include differences in the way in which those outcomes were defined, in the operator experience, and in the length of follow-up.

A low conversion rate is a key issue in laparoscopic resection as it is associated with better short-term outcomes. In this review, we identified that converted patients have higher blood loss and longer length of hospital stay. Furthermore, there is evidence from the CLASICC trial that conversion rates fall with experience. There is good evidence that laparoscopic resection is associated with short-term benefits in terms of a more rapid recovery.

Clinical effect size

A summary of the clinical effect sizes for all outcomes derived from the meta-analyses where data were available is given in Table 3.20. A summary of clinical effect for other outcomes is given in Table 3.21.

Table 3.20 Summary of the clinical effect size from meta-analysis

Outcome	Number of trials	Effect size	95% CI	p value
Duration of operation	3	39.65†	31.64 to 47.67	<0.001
Lymph node retrieval	3	-0.41†	-1.42 to 0.59	0.42
Length of hospital stay	4	-2.58†	-3.12 to –2.03	<0.001
Completeness of resection	4	1.15	0.74 to 1.77	0.53
Anastomotic leakage	8	1.13§	0.74 to 1.73	0.58
Abdominal wound breakdown	3	0.63§	0.26 to 1.52	0.30
Positive resection margins	4	1.15§	0.74 to 1.77	0.53
Wound infection	9	0.86§	0.64 to 1.14	0.29
Urinary tract infection	7	1.15§	0.66 to 1.98	0.62
30-day mortality	3	0.57§	0.25 to 1.29	0.18
Operative mortality	4	0.84§	0.29 to 2.47	0.75
Overall survival	7	1.03§	0.98 to 1.09	0.28
Disease-free survival	5	1.01§	0.95 to 1.07	0.83
Recurrence*	7	0.92§	0.74 to 1.14	0.44
Recurrence – Wound	4	1.97§	0.18 to 21.62	0.58
Hernia	2	1.49§	0.76 to 2.9	0.29

§ Relative risk
† Weighted Mean Difference
* Total number of recurrences when reported as it is by the author

Table 3.21 Summary of clinical effect size for other outcomes

Outcome	Number of trials	Effect
Duration of operation	15	15 (12)* studies report shorter duration of operation in the open group; range of differences: 14 to 87 minutes
Blood loss	9	8 (7)* studies report less blood loss in the laparoscopic group; range of differences: 25 to 123 millilitres
		1 favours open; difference: 46.4 millilitres
Lymph node retrieval	11	No significant differences reported
Positive resection margins	6	No significant differences reported
Length of hospital stay	13	13 (11)* studies report shorter length of hospital stay in the laparoscopic group; range of differences: 0.1 to 5.6 days
Postoperative pain		
Pain scores	5	4 (1)* studies report less pain in the laparoscopic group
Analgesic requirement	6	6 (5)* studies report less analgesic requirement in the laparoscopic group
Time to return to usual activities	1	1 (1)* study reports less time away from usual activities in the laparoscopic group
Health related quality of life	4	3 favour laparoscopic group

(n)* Studies that reported statistically significant results at the 0.05 level

4 SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS

4.1 Methods

4.1.1 Search Strategies

Studies that reported both costs and outcomes of laparoscopic and/or HALS techniques compared to open surgery for the treatment of colorectal cancer were sought from the systematic review of the literature. No language restrictions were imposed but as this review is an update of an earlier review conducted in 2000, the searching was limited to studies published between 2000-2005.

Databases searched were Medline (2000 – May Week 2 2005), Embase (2000 - Week 21 2005), Medline Extra (23rd May 2005), Science Citation Index (2000 – 27th May 2005), NHS EED (May 2005), HTA Database (May 2005), Health Management Information Consortium (2000 – May 2005) and Journals @ Ovid Full Text (2000 – July 2005 for selected surgical journals). In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Other sources of information consulted included: references in relevant articles; selected experts in the field; references of consultees' submissions. Full details of the search strategies used are documented in Appendix 1.

4.1.2 Inclusion and exclusion criteria

To be included, studies had to compare, in terms of both costs and outcomes, strategies involving laparoscopic and/or HALS compared to open surgery for treatment of colorectal cancer. Studies were included even if they made no formal attempt to relate cost to outcome data in a cost-effectiveness or cost-utility analysis. One reviewer assessed all abstracts for relevance and full papers were obtained for those that appeared potentially relevant.

4.1.3 Data extraction strategy

The following data were extracted for each included primary study using the framework provided for abstracts prepared for the NHS Economic Evaluation Database.[105]

1. *Study identification information*
    - Author and year
    - The interventions studied

- The type of economic evaluation
- The country of origin and currency reported

2. *The intervention, study design and main outcomes*
   - Fuller description of treatment
   - Numbers receiving or randomised to each intervention
   - Outcomes studied

3. *Sources of data*
   - Effectiveness data
   - Mortality and comorbidity (if measured)
   - Cost data
   - Quality of life (if measured)

4. *Methods and study perspective*

5. *Results*
   - Costs
   - Benefits
   - Incremental cost-effectiveness/utility ratio (ICER)
   - Sensitivity analyses

6. *Additional comments relating to the design and reporting of the economic evaluation*

For reviews of economic evaluations, data were extracted on the nature of the review methodology used, the inclusion criteria for studies, the number of studies identified, the method of quality assessment for individual economic evaluations and the conclusions drawn on the relative efficiency of the alternative methods.

4.1.4 Quality assessment strategy

One economist assessed included studies using the NHS-EED guidelines for reviewers.[105] The systematic review provided by the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) was assessed using the following criteria adapted from Oxman and colleagues[44,106] and Mulrow and Cook,[53,107] used in a recent study of the quality of systematic reviews of economic evaluations.[108]

The following questions were addressed for the quality assessment of reviews:

A. Is it unlikely that important relevant studies were missed?
B. Were the inclusion criteria used to select articles appropriate?
C. Was the assessment of studies reproducible?
D. Were the design and/or methods and/or topic of included studies broadly comparable?
E. How reproducible are the overall results?
F. Will the results help resource allocation in healthcare?

Each stem (A to F) was answered by one of the following: 'Impossible to judge', 'No', 'Partly', 'Yes'.

4.1.5 Data synthesis

No attempt was made to synthesise quantitatively the primary studies that were identified. Data from all included studies were instead summarised and appraised in order to identify common results, variations and weaknesses between studies. If a study did not report incremental cost effectiveness ratios (ICERs) but provided sufficient data, then, where possible, the data were reanalysed to provide estimates of ICERs. The data were then interpreted alongside the results of the systematic review of effectiveness so that conclusions could be drawn on the relative efficiency of the different surgical strategies.

The results of the systematic review of economic evaluations reported in this chapter were compared to those drawn from the consultee submissions and similarities and differences highlighted.

4.2 Results

4.2.1 Number of studies identified

The results of the literature searches are presented in Table 4.1. The number of reports retrieved from the searches in SCI and Journals @ Ovid Full Text are the totals after deduplication against the results of the Medline/Embase multifile search.

Table 4.1 Results of searching for studies on cost-effectiveness

Database	Hits screened	Selected for full assessment
Medline/Embase/Medline Extra multi file search (after deduplication in Ovid)	256	28
SCI	63	5
NHS NEED	5	0
HTA Database	30	3
HMIC	35	2
Selected from conference abstracts	3	3
Total	**392**	**41**

Of the studies selected for assessment, three studies[53,66,109] met the inclusion criteria. Two additional unpublished papers were obtained from experts in the field (Franks, Thames Valley University, 2005).[40] A further study that compared laparoscopic against HALS and, as a consequence did not meet the inclusion criteria, was also identified. However, a summary of this study is provided as part of the Section 4.4.[104]

4.2.2 Study identification and key elements

Two studies compared laparoscopic colon resection with open colon resection in the treatment of colon cancer,[66,109] but one of them focused on right hemicolectomy;[109] a further study compared laparoscopic-assisted with conventional open resection for rectosigmoid carcinoma,[53] and two compared laparoscopic versus open resection for colorectal cancer (Franks, Thames Valley University, 2005).[40] One of these was in the context of an enhanced recovery program.[40]

Four studies were classified as cost-consequence analyses. That is, costs were compared with various different measures of effectiveness. Two were based on single centre RCTs[40,53] and one was based on data from ten Swedish centres.[66] The fourth study was based on a single centre cohort-matched study conducted in China (Table 4.2).[109] Two studies considered costs from a societal perspective[40,66] while the others adopted a hospital perspective (Table 4.2).[53,109] The fifth study was described as a [redacted] (Franks, Thames Valley University, 2005).

Table 4.2 Characteristics of the included studies

Study id	Design	Sample	Follow-up	Perspective
Franks 2005 unpublished (UK)	Multicentre RCT (CLASICC)	[redacted]	[redacted]	[redacted]
Janson 2004 [66](Sweden)	Single centre from a multicentre RCT	Laparoscopic: 98 Open: 112	36 months	Societal
King 2005[40] (UK)	Single centre RCT	Laparoscopic: 43 Open: 19	3 months	Societal
Leung 2004[53] (Hong Kong)	Single centre RCT	Laparoscopic: 203 Open: 200	52.7 months (mean) 49.2 months (mean)	Hospital
Zheng 2005[109] (China)	Single centre cohort matched	Laparoscopic: 30 Open: 34	27 months (mean) 26 months (mean)	Hospital

The study by Franks and colleagues represented a preliminary analysis conducted on a subset of patients from the CLASICC trial who had agreed to be included in the economic evaluation. The dates for data collection were not reported. The Swedish study collected data from January 1999 to May 2002;[66] the study by King and colleagues from January 2002 to March 2004,[40] the study by Leung and colleagues, conducted in Hong Kong, collected data from September 1993 to October 2002,[53] and the Chinese study from September 2002 to February 2003.[109] In all five studies costs were estimated prospectively from the same sample as that used for collecting the effectiveness data (Franks, Thames Valley University, 2005).[40,53,66,109]

4.2.3 Patient group, study sample and study design

The sample sizes in four of the five studies were modest (Table 4.2). In the cohort matched study, patients with colon cancer underwent laparoscopic right hemicolectomy surgery and were matched with patients who received open right hemicolectomy surgery.[109] Patients for the open surgery group in this study were matched for gender, age, Dukes' staging, tumour site, previous abdominal operation and extent of resection, and randomly selected from 87 patients who underwent open surgery during the same period.

The analysis in all studies was conducted on an intention to treat basis, however, the follow-up period varied considerably between studies (Table 4.2). The outcome measures also varied between studies (Table 4.3).

Table 4.3 Outcome measures used in the included studies

Study id	Endpoints
Franks 2005 (UK)	– [redacted]
Janson 2004 [66](Sweden)	– Complication rate (e.g. anastomotic leak, bowel perforation, wound rupture, ileus, post-operative bleeding, incarcerated abdominal hernia, endoscopic dilation, closure loop ileostomy) – Re-operations – Mortality – 3-year survival
King 2005[40] (UK)	– Requirement of opioid analgesia – Anti-emetic administration – Major morbidity (e.g. haemorrhage, anastomatic leak, wound dehiscence and sepsis requiring at least high dependency support) – Hospital stay – Length of stay for readmissions – Mortality
Leung 2004[53] (Hong Kong)	– Duration of operation – Blood loss – Anastomotic leakage – Lymph node retrieval – Completeness of resection/ margins of tumour clearance – Conversion – Wound infection – Urinary tract infection – 30 day mortality – Post-operative pain – Survival – Disease-free survival – Recurrence
Zheng 2005[109] (China)	– Operation time – Blood loss – Specimen length – Lymph node yield – Pathological staging (Dukes' staging) – Analgesic requirements – Time to flatus passage – Time to resume normal diet – Duration of hospitalisation – Morbidity – Local recurrence rate – Metachronous metastasis rate – Mortality – Cumulative survival probability

4.2.4 Methods of economic analysis

The four trial based papers (Franks, Thames Valley University, 2005)[40,53,66] presented details on which items were included in the cost calculations, while no details were reported in the Chinese study.[109] Relatively good details of unit costs were presented in the Swedish and UK

studies[40,66](Franks, Thames Valley University, 2005) while no unit costs were reported in the other two studies.[53,109] Discounting was performed only in the Swedish study while it was actually relevant in all studies with a follow-up greater than 12 months. [redacted] (Franks, Thames Valley University, 2005).[40,66] Three papers did not use any summary measure of health benefits[40,53,109] and left the results disaggregated [redacted] (Franks, Thames Valley University, 2005). In the Janson and colleagues study, the mean cost for re-operated patient for each arm of the trial was presented (although it is not reported in this chapter).[66]

One-way sensitivity analyses was performed in three studies. Changes in perioperative, equipment, recovery, ICU and hospital costs were considered in the study by Franks and colleagues. They also considered a subgroup analysis by location of cancer (colon or rectum) (Franks, Thames Valley University, 2005). Cost per minute for the operating room, anaesthesia and recovery room time were explored in the Swedish study[66] while duration of in-patient stay and the consumption of community resources after discharge were explored in the Study by King and colleagues.[40]

4.2.5 Results

The results of the included studies are summarised in Table 4.4. [redacted] (Franks, Thames Valley University, 2005).

In Janson and colleagues total cost, including productivity loss, were not significantly different between the laparoscopic and open groups. However, total costs, excluding productivity losses (that is cost to the healthcare system), were significantly higher for the laparoscopic group compared to the open group (€9474 vs. €7235; P=0.018), as were the costs related to the first admission, and the costs of primary surgery.[66]

In King and colleagues the results reflected the increased duration of laparoscopic procedures and also the increased use of disposable equipment in theatre. However, in their analysis, King and colleagues found that these costs were more than offset by lower post-operative costs such as re-operations, and productivity cost savings resulting from the earlier return to usual activities.[40]

Similarly the health service costs from Leung and colleagues were also higher for laparoscopic than for open surgery and this difference, as with the other two RCT-based analyses, was statistically significant ($P<0.001$).[53] However, no significant difference was observed in the total cost of operation and drugs between the two groups in the Chinese study (CNY1000 circa £67 - www.bloomberg.com 24/08/2005).[109]

Overall, the magnitude of the mean additional cost of laparoscopic compared with open surgery varied considerably between studies. For example the relative cost of laparoscopic surgery compared with open surgery varied between 95%[40] and 130%.[53]

Table 4.4 Cost data reported in the included studies

Study id		Laparoscopic	Open	Difference (%)	P value
Franks 2005 unpublished (UK)	[redacted]				
[redacted]					
[redacted]					
Janson 2004[66] (Sweden)	Total cost*	€11,660	€9814	€1,846 (18.8)	P=0.104
Perspective: Societal	Total costs, excl. productivity losses*	€9474	€7235	€2,239 (30.9)	P=0.018
	First admission*	€6931	€5375	€1,556 (28.9)	P=0.015
	Primary surgery*	€3493	€2322	€1,171 (50.4)	P=0.001
King 2005[40] (UK)	Total Cost	£6433	£6790	-£357 (-5.3)	95%CI: -2167 to 2992
Perspective: Societal	Total Costs – indirect costs	£5,985	£6,068	-83 (-1.4%)	NA
	Theatre Costs	£2885	£1964	£921 (46.9)	95%CI: 1251 to 586
Leung 2004[53] (Hong Kong)	Direct costs**	US$9297	US$7148	US$2,149 (30.1)	P<0.001
Perspective: Hospital					
Zheng 2005[109] (China)	Total cost operation and drugs***	Y11,499 (sd: 2619)	Y10,228 (sd: 2373)	Y1,271 (12.4)	P=0.131
Perspective: Hospital					

* €1 circa £0.67
** US$1 circa £0.55
*** Y=Chinese Yuan (Renminbi); Y1 circa £0.067

The data on the relative effectiveness of laparoscopic compared with open surgery for the RCTs are reported in detail in Chapter 3. For details on the Zheng and colleagues[109] study see Appendix 11. Only one measure of effectiveness was common across all four studies: complications. Table 4.5 reports the number of complications (see Table 4.3 for types of complications) in each study. Only two studies reported P-values for the difference between the number of complications in the laparoscopic and open groups[40,109] and in these the difference was not statistically significant.

Table 4.5 Number of complications reported in the included studies

Study id		Laparoscopic	Open	Difference (%)	P value
Franks 2005 unpublished (UK)	Total complications	[redacted]	[redacted]	[redacted]	[redacted]
Franks 2005 Unpublished (UK)	Major complications	[redacted]	[redacted]	[redacted]	[redacted]
Janson 2004[66] (Sweden)	Total complications	33 (33%)	26 (23.2%)	7 (9.8)	NA
	First admission	21 (21%)	18 (16.1%)	3 (4.9)	NA
	After discharge	12 (12%)	8 (7.1%)	4 (4.9)	NA
King 2005[40] (UK)	Major morbidity	6 (15%)	5 (26%)	1 (-11)	Odd ratio: 0.40 (0.10 to 1.66) P=0.208
Leung 2004[53] (Hong Kong)	Complications of surgery	40 (7%)	45 (2%)	-5 (-2.8)	NA
Zheng 2005[109] (China)	Major complications	5 (16.7%)	10 (29.4%)	-5 (-12.7)	P=0.23

NR = not reported, NA = not available

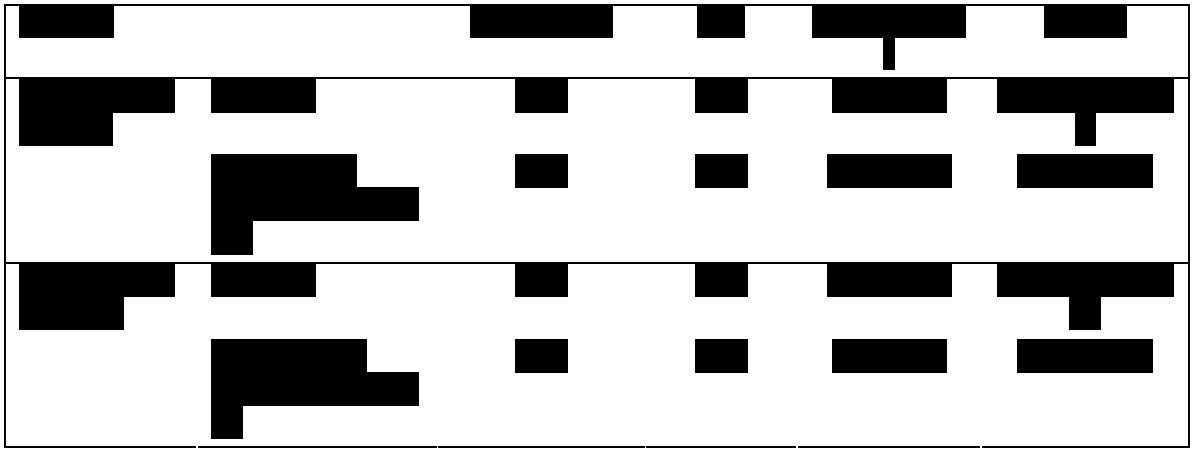
Using the data presented in Tables 4.4 and 4.5 the incremental cost per complication avoided can be calculated (Table 4.6).

Table 4.6 Incremental cost per complication avoided

Study id	Incremental cost	Difference in complications (%)	ICER
Franks 2005 unpublished(UK) [redacted]	[redacted]	[redacted]	[redacted]
Franks 2005 unpublished(UK) [redacted]	[redacted]	[redacted]	[redacted]
Janson 2004[66] (Sweden) Societal perspective	€1,846	-10%	Open dominates
Janson 2004[66] (Sweden) Health Service perspective	€2,239	-10%	Open dominates
King 2005[40] (UK) Societal perspective	-£357	11%	Laparoscopic dominates
King 2005[40] (UK) NHS perspective	-£83	11%	Laparoscopic dominates
Leung 2004[53] (Hong Kong)	US$ 2,149	3%	US$ 76,872
Zheng 2005[109] (China)	CNY 1,271	13%	CNY 10,008

Based on mean data for costs and complications open surgery is dominant (i.e. less costly and more effective) in one study[66] while in another, resulted in laparoscopic surgery being dominant.[40] For the two studies laparoscopic surgery could avoid a complication at a cost of [redacted] (Franks, Thames Valley University, 2005), USD 76,872[53] and CNY10,008,[109] (approximately £42,000 and £780, respectively).

[redacted]



4.3 Comment on the submission by the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI)

The cost-effectiveness review submitted by the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) included three RCT-based analyses[53,62,66] and four non RCT-based analyses.[35,109-111] Two of the former[53,66] and one of the non RCT-based[109] were included in this review. All studies included in the ALSGBI review compared laparoscopic with open surgery for colorectal diseases and were broadly comparable. The principle difference was that the ALSGBI review included studies which involved outcomes not presented in a disaggregate form for colorectal cancer and non-colorectal cancer patients. Furthermore, the ALSGBI review did not report the search strategies used. However, it seems unlikely that any important relevant studies had been missed.

The ALSGBI review concluded: "the operative costs for laparoscopic resection of colorectal cancer are higher because of longer operating time and the use of more expensive devices. However, these costs are offset by shorter hospital stay, less use of analgesia, less use of blood products and less complications in short and long term". The first part of this statement agrees with the findings of the review reported in this chapter, however, the data available from the review presented in this chapter do not suggest that the additional operative costs are offset by cost savings resulting from fewer complications and shorter length of stay.

4.4 Summary of results and discussion

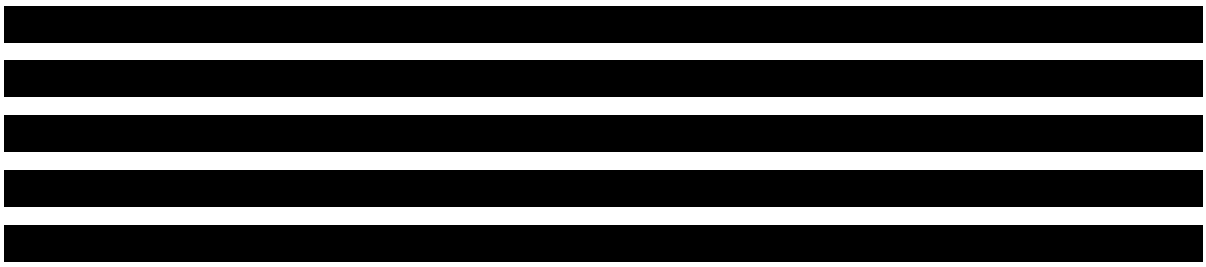
In the previous review conducted for NICE on this subject, eight studies were identified.[21] This review reported that: "No consistent patterns were found, with most studies showing no significant difference in cost between the two procedures. It is clear that length of stay is consistently (although not always significantly) shorter in the case of laparoscopic surgery, and so the differences in cost are mainly a question of relative cost of hospital days and hours in theatre used in the papers".

The four RCT-based analyses identified by this updated review appear to have statistically significant longer operating times for laparoscopic surgery. This is consistent with the data in the review of effectiveness reported in Chapter 3. However, the study by Zheng and colleagues reported no statistically significant difference.[109] With respect to length of

hospital stay this appeared to be longer in the open groups: again, a result consistent with the review of effectiveness reported in Chapter 3. Overall in terms of these findings the results of the review presented in this chapter are consistent with the findings of Vardulaki and colleagues.[17]

The five articles included in this review concluded that operation cost for laparoscopic procedure was statistically significantly higher than open surgery. The mean total cost of laparoscopic appeared to be greater than open surgery in all studies except in King and colleagues.[40] However, there was no evidence of a statistically significant total cost difference between laparoscopic and open surgery.

The submission by Ethicon Endosurgery was a brief presentation of some of the key issues in the consideration of laparoscopic surgery (Submission to National Institute for Health & Clinical Excellence by Ethicon Endo-surgery, July 2005). It did not contain a systematic review nor an economic model. The submission concluded that the long term clinical outcomes are equivalent. The evidence reported in Chapter 3 suggests that this conclusion may be warranted for a three year follow-up for survival and disease free survival. The results presented in this chapter and Chapter 3 also tend to support Ethicon Endo-surgery's conclusion of shorter recovery following laparoscopic resection and that enhanced recovery programme may help to lower total costs. The submission also contended that the conversion rate is potentially a key driver of total cost of laparoscopic surgery. The evidence supporting this claim is indirect. It is likely that the total cost of laparoscopic surgery is increased as conversions increase although as, reported in Chapter 3, the evidence for comparing converted, non-converted laparoscopic and open patients is limited. It is less clear how reducing the risk of conversion would effect the difference in cost when laparoscopic and open surgery are compared for similar patients. Although Ethicon Endo-surgery contend that the costs of laparoscopic surgery may be lower when there are lower rates of conversion.



[redacted] (Franks, Thames Valley University, 2005).

The incremental cost per complication avoided, shown in the previous section, should be interpreted extremely cautiously. For example, all the studies had relatively small sample sizes and differences in number of complications (used as effectiveness measure in these calculations) between laparoscopic and open groups were not statistically significant. With respect to the estimates of complications the estimates of the individual studies are likely to be less reliable than estimates derived from the review of effectiveness. Data from the review of effectiveness provides no evidence of a difference in complication rates. [redacted] (Franks, Thames Valley University, 2005). In addition, the data from Zheng and colleagues was a relatively small non-randomised study which might be subjected to selection bias.[109]

The measure of total cost used differed substantially between studies. For example, Franks and colleagues (Franks, Thames Valley University, 2005), Janson and colleagues[66] and King and colleagues[40] considered indirect costs while the other two studies considered only direct costs from surgery and hospital stay.[53,109] The costing methodology was also poorly described in these latter two studies. For example Zheng and colleagues reported only final cost figures and no details on the way calculations were obtained.[109]

It is unclear the extent to which the costs from the three non-UK studies would be applicable to the UK. One UK study had a very small sample size, and it was based on a single centre.[40]

[redacted] (Franks, Thames Valley University, 2005). The study by Janson and colleagues[66] was larger and the relative difference in cost between the two interventions (see Table 4.4) may help inform decision-makers in the UK. However, the relatively short follow-up in both studies indicates that a modelling exercise with a longer time horizon might add valuable information for decision-making.

In addition to the studies comparing laparoscopic to open surgery a further study was identified comparing conventional laparoscopic surgery with HALS.[104] This study was a prospective RCT conducted in Barcelona, Spain. A total of 54 patients were enrolled in the study, 27 to laparoscopic and 27 to HALS. The groups were well matched in terms of age, sex, body mass index (BMI), location of disease, percentage of malignant diagnoses, and type of surgical procedure. Twenty-two individuals in each group were cancer patients.

Table 4.7 Summary of results from Taragona and colleagues

Intervention	Operation time Mean (range)	Conversions*	Operation cost*
Laparoscopic (n=27)	135 (109-240)	6	€1959 +-593
HALS (n=27)	129 (70-300)	2	€2035 +-512

* no statistically significant differences

The study found no evidence of a statistically significant difference in terms of operation time or conversion rates (Table 4.7). The authors also did not find any statistically significant differences in terms of bowel sounds, refeeding, overall morbidity rates, re-operation and hospital length of stay. Total costs, calculated by adding the cost of using the operating room (no disposable materials plus salaries) to the cost of disposable instruments, were also not statistically different. The authors concluded, "Although it is a more aggressive procedure, HALS preserves the feature of minimally invasive approach, maintains all the oncological features of conventional laparoscopic surgery, and does not increase the cost".

4.5 Conclusions

This chapter presents the overall evidence available on cost effectiveness analyses of laparoscopic surgery for colorectal cancer compared to open procedure, based on a systematic review of the literature and on the revision of the review submitted by the Association of Laparoscopic Surgeons of Great Britain and Ireland. Laparoscopic surgery was generally more costly than open surgery as the former seems to involve longer operation times and higher equipment costs, although the evidence is mixed. With respect to effectiveness, the data used by the individual studies is likely to be imprecise and unreliable when compared to the data available from a systematic review of effectiveness

(Chapter 3). Thus, the evidence provided by the included economic evaluations using longer-term outcomes such as survival is likely to be imprecise and unreliable.

There is a suggestion that the short-term benefits of laparoscopic surgery in terms of a shorter recovery may make laparoscopic surgery appear less costly. However, the measurement and inclusion of such costs (indirect costs) in an economic evaluation is contentious.

No data were identified comparing HALS with open surgery. Evidence comparing laparoscopic to hand assisted laparoscopic surgery is very limited and provides no evidence of a difference in either costs or effects.

5 ECONOMIC EVALUATION

5.1 Introduction

In this chapter the data available on the costs and effects will be used to provide information on the relative cost-effectiveness of laparoscopic compared with open resection for colorectal cancer. This has been facilitated using two approaches. The first compares laparoscopic with open resection using a balance sheet approach and the second more formally synthesises the available data in an economic model. With the balance sheet the differences between interventions, in terms of costs and natural and clinical measures of effectiveness are presented. Such an approach served to highlight the choices and trade-offs between the two forms of resection.

Nonetheless, any decision based on the balance sheet approach is made using an implicit (rather than an explicit) synthesis of the available data. In the economic model the disparate effects of surgery for colorectal cancer are considered. However, the results of this model are tentative because, as described below, the model is constrained by the paucity of data available for some model parameters.

5.2 The balance sheet approach

A balance sheet is a method of presenting a cost consequence analysis that can be used to identify who bears the costs and who reaps the benefits from any change in the way surgery is performed. Costs and benefits are measured in units that seem appropriate for each patients parameter.

5.2.1 Methods

Estimates of the relative effects of laparoscopic compared with open resection are taken directly from Chapter 3. These data have been used to describe differences in both the short term and the long-term health effects of the different forms of resection. Data on the costs of resection was derived using data reported in a paper by King and colleagues[40] (this paper is summarised and critiqued in Chapter 4) and data from the systematic review of effectiveness (reported in Chapter 3).

The study by King and colleagues[40] defined the cost of resection in terms of five components relevant to the perspective of the NHS (theatre costs; hospitalisation costs; post-operative costs, chemotherapy and radiotherapy and follow-up costs at three months). For each component, and

also for the total cost, an estimate was provided of the mean value for both laparoscopic and open resection. In addition, an estimate of the mean difference between the two forms of resection and the statistical imprecision surrounding these mean differences was also provided. Using the methods described below, the data from King and colleagues was used in the re-estimation of costs for laparoscopic and open resection.

Theatre costs

The length of time in surgery for both laparoscopic and open resection reported by King and colleagues was broadly consistent with the findings of the systematic review of effectiveness. Therefore, the data reported for theatre costs by King and colleagues was used. This makes the assumption that the use of disposable equipment for laparoscopic resection observed by King and colleagues is typical of practice within the UK. King and colleagues did not report information on the statistical precision surrounding estimates of theatre cost for each intervention. However, they did report an estimate of the variability of the mean difference in theatre costs. It was assumed that the theatre costs of both procedures were subject to this imprecision. Consequently, it was apportioned on a pro rata basis to each intervention and assumed to be evenly distributed around the mean value using a triangular distribution. The values used to estimate this distribution are reported in Table 5.1.

Hospitalisation costs

The study by King and colleagues[40] involved a comparison of the two forms of resection in the context of an accelerated discharge scheme. It is likely that the lengths of stay observed in this study may not be representative of practice within the UK. Therefore, the length of stay for open resection was based on the mean length of stay for Health Care Resource Group (HRG) 07 (15.2 days) from the Hospital Episode Statistics[112] for 2004, the most frequently recorded HRG for colorectal cancer resection (the other HRGs have a similar length of stay). A distribution for this parameter was constructed using the median length of stay, the only other available evidence, and the mean length of stay for this HRG. Using these two pieces of data the use of alternative distributions was investigated. A Weibull distribution was chosen as it provided a plausible lower estimate of length of stay and also allowed the possibility of substantially greater length of stay. The length of stay for laparoscopic resection was derived by adding the estimate for the weighted mean difference in length of stay from the length of stay for open resection. The length of stay data for both operations were then combined with information on the cost per day for a surgical high

dependency unit (assumed one day stay for both procedures) and a surgical ward (the remainder of the stay). Both ward costs were taken from King and colleagues.[40]

Post-operative costs

The post-operative costs estimated by King and colleagues[40] included the use of medications as well as surgery for complications. The estimate for laparoscopic resection was very much less than that for open resection. This appeared to be due to the higher rates of complications seen in the open arm of the study. The evidence from the review of effectiveness presented in Chapter 3 showed no statistically significant difference in post-operative complications. Therefore, it has been assumed that the cost of open resection for this element is the same as laparoscopic resection.

Chemotherapy and follow-up costs

The final two elements of total cost estimated by King and colleagues[40] were the costs of chemotherapy and radiotherapy and follow-up costs up to three months from the initial operation. Follow-up costs were collected via patient completed questionnaires administered at two weeks and three months follow-up. These questionnaires requested information on the number of: inpatient days, outpatient visits, GP visits, use of district (community) and stoma nursing services. It is unclear whether the statistically non-significant differences observed for this or any of the other cost components are real or are a consequence of the imprecision caused by the small sample size. The distributions around these chemotherapy and follow-up costs were estimated using the same methods as described earlier for theatre costs. The data used to derive these distributions are also described in Table 5.1.

Table 5.1 Data used to estimate cost estimates for each element of total cost

Parameter	Value	Distribution	Data used to define the distribution
Estimation of theatre costs			
Laparoscopic resection	£2885	Triangular	Derived using data below
Open resection	£1964	Triangular	Derived using data below
Ratio laparoscopic to combined cost of open and laparoscopic	0.595	NA	NA
Range of CI around mean difference in cost	£664.6	NA	NA
Estimation of hospital costs			
Length of stay (open)	15.2 days	Weibull	Median stay 11 days
WMD laparoscopic vs. open	-2.6 days	Normal	95% CI –3.1 to –2 days
Cost per day (HDU)	£530	Not applicable	Not applicable
Cost per day (surgical ward)	£162	Not applicable	Not applicable
Chemotherapy and radiotherapy cost			
Laparoscopic resection	£175.5	Triangular	Derived using data below
Open resection	£176.5	Triangular	Derived using data below
Ratio laparoscopic to combined cost of open and laparoscopic	0.499	NA	NA
Range of CI around mean difference in cost	£265	NA	NA
Follow-up cost			
Laparoscopic resection	£359.6	Triangular	Derived using data below
Open resection	£593.6	Triangular	Derived using data below
Ratio laparoscopic to combined cost of open and laparoscopic	0.377	NA	NA
Range of CI around mean difference in cost	£234	NA	NA

NA - Not applicable.

Estimation of total costs

Table 5.2 summarises the estimates of cost of laparoscopic and open resection obtained using the methods described above. Monte Carlo simulation employing 10,000 iterations was then performed

to generate a distribution for the incremental cost of laparoscopic compared with open resection. This was conducted using the Microsoft EXCEL add-on, Crystal Ball.

It should be noted that these estimated costs do not reflect any interactions between components of total cost. For example, the follow-up costs and the hospital costs estimated by King and colleagues[40] may be correlated. This is because hospital costs are influenced by the number and type of complications. These complications would also be expected to influence follow-up costs.

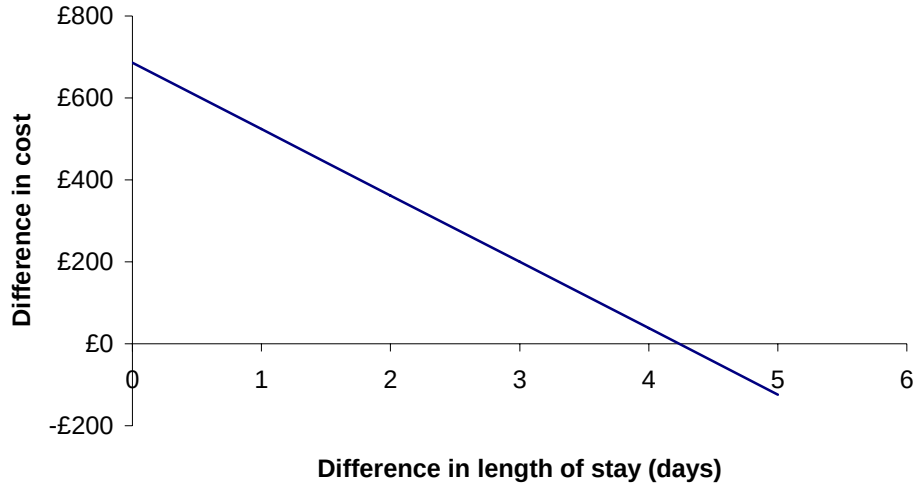
Table 5.2 Estimates of cost of laparoscopic and open resection.

Components of cost	Type of resection		Difference
	Laparoscopic	Open	
Theatre cost	£2885	£1964	£921
Hospital cost	£2409	£2830	-£421
Post-operative cost	£287	£287	0
Chemotherapy and radiotherapy	£176	£177	-£1
Follow-up costs at three months	£360	£594	-£234
Total cost	**£6117**	**£5852**	**£265**
			95% CI –3829 to 4405*

* 95% CI is based on the 2.5 and 97.5 percentile points from the range of values produced by the Monte Carlo simulation

One of the key determinants of the difference in cost between laparoscopic and open surgery was the difference in length of stay. To consider the importance of this a threshold analysis was conducted to consider what difference in length of stay would lead to an equal cost (Figure 5.1).

Figure 5.1 Threshold analysis on effect of differences in length of stay on cost



The threshold analysis suggests that should laparoscopic resection be associated with a length of stay that is on average just over four days less than open surgery then the costs of the two surgeries would be equivalent. A difference of this magnitude was not observed in any of the studies included in the review of effectiveness presented in Chapter 3. The analysis also indicates that should the difference in length of stay reduce, as may occur in an enhanced recovery programme, the incremental cost of laparoscopic compared with open surgery increases (to over £500 when the difference in length of stay was one day).

5.2.2 Results

Table 5.3 presents the balance sheet for the comparison of laparoscopic with open surgery for colorectal cancer.

Table 5.3 Balance sheet comparing laparoscopic with open resection

Favours laparoscopic resection	Favours open resection	Trials contributing data
	Proportion of laparoscopic procedures converted (21%)	12
	Shorter operation time (40 mins less, 95% CI 32 to 48)	16 (3 in MA)
Shorter hospital stay (WMD 2.6 less, 95% CI 3.1 to 2.0)		14
Less blood loss (about 75ml per operation)		9 (4 in MA)
Less time away from usual activities (32 vs. 44 days)		1
Less post-operative pain and analgesia (1 day less on average)		5 & 6
No statistically significant difference in:		
Cost (mean difference £265, 95% CI –3829 to 4405)*		
Anastomotic leakage (RR 1.13 95% CI 0.74 to 1.73)		8
Abdominal wound breakdown (RR 0.63, 95% 0.26 to 1.52)		3
Wound infection (RR 0.89, 95% 0.67 to 1.10)		9
Urinary tract infection (RR 1.15, 0.66 to 1.98)		6
30-day mortality (RR 0.57, 0.25 to 1.29)		7
Incisional hernia RR 1.49 95% CI to 0.76 to 2.9)		2
Disease-free survival (RR 1.01, 0.95 to 1.07)		5 plus 1 MA
Overall survival (RR 1.03 95% CI 0.98 to 1.09)		7 plus 1 MA
Health related quality of life (sign test p = 0.125)		4

* Laparoscopic surgery is probably more costly but results are imprecise. Ranges are the 2.5 and 97.5 percentile points from the range of values produced by the Monte Carlo simulation, RR = relative risk, MA = patients patient data meta-analysis by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005)

As Table 5.3 illustrates after laparoscopic resection, length of hospital stay is shorter, blood loss and persistent pain are less and return to usual activities is likely to be faster than after open resection (although data came from one RCT conducted in Hong Kong[53] and may not be generalisable to the UK). The duration of operation for laparoscopic resection is longer and a significant number of patients are converted from laparoscopic to open resection. Findings relating to overall and disease-free survival suggest similar rates of these outcomes when comparing laparoscopic with open resection for a three year follow-up. With respect to cost, although differences are non-significant, it is likely that laparoscopic resection is associated with a modest incremental cost

compared with open surgery. For other outcomes, even though there are trends favouring one method of resection over another, the confidence intervals are sufficiently wide enough that clinically and economically important differences cannot be ruled out.

Overall it would seem likely that laparoscopic resection is associated with a modest additional cost (approximately £260), short-term benefits associated with more rapid recovery; and similar long-term outcomes in terms of survival and cure rates up to three years. A judgement is required as to whether the findings with respect to survival and disease-free survival will persist in to the longer term. If survival and disease-free survival do remain similar, then a further judgement is required as to whether the benefits associated with earlier recovery are worth this extra cost.

5.3 Economic Model

The economic evaluation was conducted using a Markov Model (constructed in TreeAge Pro 2005). The model estimates the long-term costs and benefits of a cohort of typical patients for the different surgical procedures. The model follows a cohort of patients from their initial operation through their convalescence (operation state) to their return to usual activities (defined in the model as a '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 patient management. Conceptually the patients could move between states within the model until they all eventually die. For the purposes of the analysis, however, the cohort of patients has been modelled for a maximum of 25 years (which represents the maximum survival for the majority of the patients) following the initial operation.

Following their initial surgery, patients could move into one of the following states:

- Disease-free;
- Recurrence of the disease where it may be possible to have a second operation or some form of non-operative management;
- Disease-free (after a recurrence); where a patient following a successful second operation remains until they have a second recurrence/metastasis or die;
- Non-operable recurrence resulting in non-curative management of the disease; and
- Death

A cost per patient for each health state in the Markov model has been calculated using the methods outlined below. The main cost components in the model are the initial operative procedure and the costs of any subsequent re-operation or management. It has been assumed that if a recurrence occurred and a re-operation was indicated, the patient would be operated on using an open procedure regardless of the surgical procedure they originally received. Death is the only state within the model that a patient cannot leave (i.e. it is an absorbing state). As all general surgical procedures carry some risk of complications, the costs of post-operative complications has been included but will not be explicitly modelled as their effect would principally have been captured through increased operating times and longer hospitalisation. However, the risk of an emergency re-operation within the first few weeks after surgery has been explicitly modelled, due to the additional operation costs incurred. Similarly, where the cost of managing other complications would not be captured through increased operating time and length of stay, estimates of the management cost and probability of occurrence have been factored into the cost of a state.

The cycle length (the minimum period between transitions) of the model has been set at six months as this would be the first instance that a recurrence or metastasis might be detected. Thus, the model will run for a maximum of 50 cycles. An outline of the model is described in Appendix 12.

5.3.1 Estimation of model parameters

Baseline parameters

Where quantitative synthesis was possible, the outputs of the systematic review of effectiveness (Chapter 3), were presented as relative risks for dichotomous variables and weighted mean differences for continuous variables. For these data to be incorporated into the model they needed to be combined with estimates of baseline rates for one of the interventions. Furthermore, while it might be argued that such relative effect sizes are transferable between settings,[113] it is important to ensure that they are applied to baseline rates that are applicable to the UK, so that the resultant absolute differences between interventions are more likely to be applicable to the UK.

Estimation of the risk of death was based on the survival curve for open resection provided by Bonjer and colleagues, reproduced as Figure 3.1 (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). These data provided estimates of survival up to three years post surgery. Overall survival for open resection for each six month time period up to 36 months was estimated from these curves. From these data a mortality rate for each six-month cycle length was calculated. As interpreting

rates from these curves is an imprecise method, and the mortality rates for each six-month period were similar, a constant mortality rate was assumed (Table 5.4).

The risk of recurrence of local or of metastatic disease was based on data on disease-free survival also provided by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). These data were estimated using the same methods as described for the risk of death described above. As with the risk of death a constant risk of recurrence was assumed (Table 5.4).

The risk of death following the recurrence of non-operative cancer was based on data derived from Benoist and colleagues.[114] This study is a case-matched study set in France, which had the aim of determining the best treatment strategy for patients with asymptomatic colorectal cancer and irresectable synchronous liver metastases. Patients were recruited between 1997 and 2002 with 27 patients being treated with chemotherapy, without an initial primary resection, compared with 32 patients who were initially treated by resection of the primary tumour. The 27 chemotherapy patients (intervention group) were matched by age, sex, performance status, primary tumour location, number of liver metastases, nature of disease and the type of chemotherapy to the 32 patients who underwent resection of the primary tumour (control group). The mean age of the chemotherapy and resection groups was 61 and 60 respectively. Whilst this study is currently the best available data for this particular subset of patients, it should be noted that the very small sample size may result in imprecise estimates. The study setting might also impact upon the generalisability of results for the UK as this study, set in France, may have treatment regimes that differ from standard treatment in the UK.

For the purposes of the model, the risk of death for patients with inoperable cancer was based on the interpretation of the survival curve for the "chemotherapy group" from the aforementioned study.[114] This population was deemed to have similar characteristics to the patients undergoing non-operative management of recurrent disease within the model. The actuarial survival for the total time period of 24 months, divided into six month time periods, was estimated from this curve. A mortality rate for each six month cycle length was calculated and from this, a constant mortality rate obtained. Based on these data, a mortality rate for inoperable cancer with the value of 0.2 was calculated and is shown in Table 5.4. In order to reflect the statistical imprecision surrounding the occurrence of an event a Beta distribution was used. This distribution was used as it has been argued that it provides realistic representations of proportions.[115] For TreeAge, the α parameter

required for this distribution is the number of patients who experienced the event of interest and the β parameter is the number of patients who did not experience the event.

Other baseline parameters required for the model related to the risk of hernia, the risk of an emergency re-operation for a post-operative complication and the risk of a re-operation for recurrent disease. The risk of hernia was identified as a potentially important long-term complication of both forms of resection. The severity and rates of the different type of hernia (port site or main incision) were identified as review outcomes as it was believed that they may have differed between laparoscopic and open resection. However, the data available were sparse and no distinction has been drawn between the two types of hernia. The rate of hernia for open resection was derived from the rates of hernia reported in the open arms of those trials identified by the systematic review of effectiveness. These data were supplemented by rates of hernia reported in the non-randomised studies included in the submission by the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI submission to NICE, 2005). From these data the risk of hernia per cycle was estimated for each of the studies that provided data (Appendix 12). The median estimate of the risk of hernia per cycle was selected for use in the model with a triangular distribution based on the estimated 25 and 75 percentile from the identified studies (Table 5.4).

The risk that a patient might require an emergency operation for a complication of surgery for colorectal cancer was allowed for within the model. Although a variety of different complications might result in the need for a re-operation, it was believed, based on clinical opinion, that the risk of re-operation for most of these would be low. The risk of complications requiring non-operative management was not explicitly included in the model as the effect of these would principally be captured through longer operating times and length of stay.

The one complication for which it was believed that a greater proportion would require an emergency operation was anastomotic leakage. In the model it has been assumed that the risk of an emergency re-operation is equal to the risk of an anastomotic leakage. The base line 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 (Appendix 12). From these data the median observed risk of anastomotic leakage was selected for use in the model with a triangular distribution based on the interquartile range of rates from the identified studies (Table 5.4).

Should the cancer recur the patients might have a re-operation. Data on this risk were not available from any of the included studies. However, data from NHS Grampian suggest that out of over 300 procedures per year approximately 14 to 15 are for recurrence or residual disease. Based on these data, a Beta distribution was used to allow for greater uncertainty of the point estimate. This distribution was calculated as outlined above for the mortality rate for inoperable cancer.

It should be noted that the baseline effects do not change over time.

Table 5.4 Baseline parameter values used in the model

Baseline parameters	Value	Distribution	Values for Distribution
Transition Probabilities			
Mortality	0.030	No distribution	
Recurrence	0.046	No distribution	
Mortality (non-curative cancer)	0.2	Beta	A=5.4, β=21.6
Other Probabilities			
Emergency operation rate	0.019	Triangular	IQR 0.008 to 0.034
Risk of hernia	0.003	Triangular	IQR 0.002 to 0.012
Re-operation rate (after recurrence)	0.05	Beta	A=15, β=285

Derivation of relative effect sizes

Data on the relative effect sizes were derived from the systematic review of effectiveness and the meta-analysis by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). The relative effect size of death for laparoscopic compared with open resection was derived from the estimate of three-year survival reported by Bonjer and colleagues. [redacted]. These estimates of an absolute difference were converted into a relative effect size for laparoscopic surgery (Table 5.5). The confidence intervals around the point estimate reported by Bonjer and colleagues assumed a normal distribution. These data were used to estimate a similar distribution around the relative effect size.

The relative effect size for recurrence was also based on data taken from Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). [redacted]. The same methods used to estimate the relative difference in mortality were used to estimate the relative difference in recurrence and an associated distribution (Table 5.5).

It was assumed that the relative risk of mortality faced by a patient with non-curative cancer was one (Table 5.5). This assumption was made, as it was believed that once a recurrence occurred, the prognosis would be the same regardless of the initial method of resection.

Other relative effect sizes were also required for the model. The first of these relates to the relative risk of an emergency operation. For the same reason as described above, the relative risk for this parameter was based on that for anastomotic leakage. These data were derived from the systematic review of effectiveness reported in Chapter 3 (Table 5.5). The statistical imprecision surrounding the point estimate was characterised by lognormal distributions for relative risks due to the methods used to derive these relative effects.

Two other relative effect sizes required for the model are the relative risk of hernia and the relative risk of a re-operation after a recurrence. In both cases a relative risk of one has been assumed. In the former case, the evidence from the review of effectiveness is limited but there is no statistically significant difference between the rates of both types of hernia. In the latter case, a relative risk of one has been assumed as it is believed that the initial method of resection would not affect the method of management subsequent to a recurrence (Table 5.5).

Table 5.5 details the point estimates of the relative effect sizes used in the model. Also included in the table are the 95% confidence intervals surrounding the point estimates and distributions used. It should be noted that a further assumption has been made that the relative effects do not change over time.

Table 5.5 Relative effect sizes used in the model

Parameter	Point estimate	Limits of 95% CI		Distribution
		Low	High	
Transition Probabilities				
Mortality	1.016	0.958	1.054	Normal
Recurrence	0.993	0.943	1.06	Normal
Mortality (non-curative cancer)	1	1	1	
Other Probabilities				
Emergency operation rate	1.13	0.74	1.73	Lognormal
Risk of hernia	1	1	1	
Re-operation rate (after recurrence)	1	1	1	

Absolute parameter values for each intervention were derived by applying the relative effect sizes to estimates of the absolute rate for open resection (Table 5.4) with the relative rates reported in Table 5.5.

Resource use and costs

The main cost component included in the model are the costs associated with the initial operation. The method used to derive the cost for open resection is described in Section 5.2.1. A triangular distribution for the cost of open resection was used to help evaluate the uncertainty around this cost estimate. The cost of laparoscopic resection was estimated by multiplying the cost of open resection with an estimate of the relative cost of laparoscopic resection (i.e. the cost of open resection plus the difference in cost between laparoscopic and open resection. The product of this was then divided by the cost open surgery). A Monte Carlo simulation using 10,000 iterations was conducted using the Excel add on Crystal ball to create a log normal distribution around the relative difference between laparoscopic and open resection. The choice of a lognormal distribution was made empirically as this distribution appeared to best fit the data from the Monte Carlo simulation.

The cost of surgical resection would be incurred in the first cycle of the model. Other costs would also be incurred in this cycle relating to the cost of emergency surgery and the cost of an outpatient visit and computed tomography (CT) scan at six months (other outpatient visits might be made in the first cycle but these have been subsumed into the cost of surgical resection). The cost of emergency surgery was taken from the national reference costs for HRG F42 (a general abdominal, very major or major procedure).[116] A triangular distribution was defined for this cost based on the interquartile range of costs reported for this HRG (Table 5.6). The cost of an outpatient visit made at six months was based on the unit cost reported by King and colleagues.[40] The cost of a CT scan

was taken from the national reference cost and a distribution for this cost was defined using the same method used for emergency surgery.

For patients who are disease-free, regular review is performed. Based on clinical guidelines[117] it was assumed that patients would receive a CT scan and outpatient visit at 12 months and 24 months postoperatively. Patients would also be reviewed and undergo colonoscopy after three years and then subsequent colonoscopy every five years until approximately age 70. The cost of a colonoscopy was taken from the national reference cost and based on HRG F35 (an endoscopic or intermediate procedures for the large intestine). The distribution for this cost was defined using the same method used for emergency surgery. As costs in this state are likely to be incurred several times over the course of a patient's life, a table was constructed in TreeAge to allow these costs to be taken account of at the given time point in which they were incurred. The limitation of using a table to define these costs, however, is that the uncertainty surrounding these cost estimates cannot be explored as distributions could not be incorporated into the costs in the table.

The cost of a hernia repair was likewise based on the national reference cost. The cost used related to HRG F72 (abdominal hernia procedures less than age 70) and a distribution for this cost was defined using the same method used for emergency surgery (Table 5.6).

The cost of care for patients who suffered some degree of recurrent cancer would, of course, be dependent upon the nature of the disease. Should further surgery be indicated it has been assumed that it will cost the same as the initial open surgical resection as, based on expert opinion, it was deemed unlikely that any re-operation would be performed laparoscopically. In addition, to the cost of a re-operation, patients might receive medications for the control of symptoms if surgery is not indicated. The cost for a typical regime of care for a patient was defined following consultation with a MacMillan Cancer Nurse (personal communication: Flora O'Dea – Hospital Specialist Palliative Care Team 2005) (Table 5.6). Details of the basis of the cost estimated are provided in Appendix 12.

Table 5.6 Cost parameters used within the model

Costs	Value	Source	Distribution, and values used to define the distribution
Initial Op			
Open	£ 5852	See Section 5.1	Triangular with high and low based on IQR. IQR £4968-£6272
Relative cost of laparoscopic	1.05	See Section 5.1	Lognormal; sd 0.33
Emergency Operation	£1615	NRC. HRG F42,	Triangular with high and low based on IQR. IQR 1132-2322
Re-operation (as open)	£5852	See Section 5.1	Triangular with high and low based on IQR. IQR £4968-£6272
Outpatient visit	£99	King 2005	
CT scan	£73	NRC, CT (other)	Triangular with high and low based on IQR. IQR 56 – 91
Colonoscopy	£622	NRC HRG 35.	Triangular with high and low based on IQR. IQR 370-868.
Surgery for hernia	£1689	NRC HRG F72	Triangular with high and low based on IQR. IQR 1306-2234.
Non-operative management following recurrence	£1216	Expert advice	

Estimation of Quality Adjusted Life Years (QALYs)

No suitable utility data required to estimate QALYs were identified in any of the economic evaluations identified in Chapter 4. Potential utility data were sought from a focused search of the Harvard Cost Utility Database[118] and a search for relevant studies conducted as part of the search for economic evaluations (see Chapter 4 for methods). However, despite this search little usable data were identified. The CLASICC Trial, which has not yet fully reported, is using the EQ-5D instrument collected at baseline, two weeks, three, six, 18 and 36 months post operation. These data will be collected from the first 500 patients randomised to the trial (approximately 340 laparoscopic and 170 conventional patients). Until such data are obtained then reliable utilities data applicable to the UK will not be available. In the interim, data were taken from one published study which has used the EQ-5D questionnaire.[119] This study was conducted in Norway and recruited a total of 95 patients from 1993 to 1996. The aim of the study was to assess the cost-effectiveness of adjuvant chemotherapy in the treatment of Dukes' B and C colorectal cancer after surgical resection. The quality of life of the participants was assessed using a questionnaire which included: the EuroQol questionnaire, a simple quality of life scale and the global quality of life measure of the EORTC QLQ-C30. It reported a median quality of life value of 0.83 (0-1 scale) in all patients and measures.

From this limited data it has been assumed that the recovery from surgery was associated with a value of 0.83, it has been assumed that by definition the time spent free from disease is associated with a value of one. The value associated with the other states (except death) was also 0.83. As such data are very limited, the estimates of QALYs should be treated with caution.

5.3.2 Assessment of cost-effectiveness

The base-case analysis was based on the costs and outcomes faced by a cohort of 65 year olds (the mean age of patients receiving a surgical resection of colorectal cancer in England and Wales). Within the economic model two different outcomes are presented: the incremental cost per additional life year and incremental cost per QALY. Data on these two outcomes are presented in two ways. First, mean costs, life years or QALYs for the alternative interventions are presented and incremental cost per additional life year or QALYs calculated where appropriate. The second way in which the cost-effectiveness of the alternative interventions is presented is in terms of cost effectiveness acceptability curves (CEACs).[120] CEACs have been used to illustrate the uncertainty caused by the statistical variability in the model's parameter estimates. 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 or QALY.

5.3.3 Sensitivity analysis and subgroup analysis

Sensitivity analysis focused on varying assumptions or parameters in the base-case model.

Assumption of equal survival and disease-free survival

[redacted] In this analysis it has been assumed that the relative effect size for these two parameters is one. There is of course some uncertainty surrounding this and a similar distribution to that used in the base-case analysis has been used.

Costs

Source of cost data

Data regarding the costs of procedures were made available from other sources. This sensitivity analysis explored the cost estimates for laparoscopic and open surgical procedures for colorectal cancer from an unpublished paper by Franks and colleague (Franks, Thames Valley University,

2005). [redacted]. The paper by Franks and colleague (Franks, Thames Valley University, 2005) is summarised and critiqued in Chapter 4 [redacted]The first sensitivity analysis, with regards to this cost data, utilised the revised costs estimated from Franks and colleague (Franks, Thames Valley University, 2005). [redacted]

Additional cost data

Currently, the cost data has not taken into account the extra cost which preoperative preparation for laparoscopic resection might incur and essentially assumes the same approach is used for both methods of resection. These costs could include such aspects as the necessity of a CT scanner for preoperative staging as opposed to an ultrasound scanner. This sensitivity analysis assessed the impact on cost of extra assessment which may be required to determine suitable laparoscopic candidates. All patients treated by laparoscopic resection are assumed to incur an additional cost of

a CT scan to allow for preoperative staging and all patients whose resection was undertaken via the open method are assumed to incur the additional cost of an ultrasound scan preoperatively. The cost of an ultrasound scan was taken from the National Reference costs. A triangular distribution was defined for this cost based on the interquartile range of costs reported for this HRG. Mean cost of £32 with interquartile range of £26 to £39.

Changes to the re-operation rate for recurrent disease

An estimate of the number of re-operations that might take place given recurrent disease was based on data from one centre (5%). As a result, the re-operation rate was changed in the sensitivity analysis to either a "high" rate of 10% or a "low" rate of 1%. The distributions surrounding this parameter remained similar.

Changes to the relative effect size of the re-operation rate for recurrent disease

No data were available to identify the difference in re-operation rates between laparoscopic resection and open resection. The base-case analysis assumed the relative effect size for this difference would be one as it was deemed unlikely that the initial method of resection would affect management subsequent to a recurrence. As this estimate was solely based on expert opinion, this sensitivity analysis allowed the relative effect size for the rate of re-operation to change from 0.5 to two. Thus, the rate of re-operation for laparoscopic resection, in comparison with open resection, was made to decrease to half the rate and increase to double the rate of open resection. A similar distribution to that used in the base-case analysis has been used.

Combination of previous two analyses

The relative effect size for the re-operation rate for recurrent disease was assumed to be one in the base-case analysis. This analysis combines the high and low estimates of rates of re-operation from the previous sensitivity analysis with different estimates of the relative effect size of the re-operation rate for laparoscopic compared to open resection. The low re-operation rate (1%) was combined with a relative effect size of 0.5. The higher re-operation rate (10%), was combined with a relative effect size equal to two. Similar distributions to those used in the base-case analysis were used.

Changes to the rate of mortality for non-operative management of recurrent disease

The risk of death for patients with non-operative recurrent disease was based on the interpretation of the survival curve from the study by Benoist.[114] A constant mortality rate of 0.2 was used for the

base-case analysis however the mortality rate at six monthly intervals was also estimated from the 24 month study period. This analysis uses the high and low values for the mortality rate for non-operative management of recurrent disease, 0.31 and 0.11 respectively. A distribution similar to that used in the base-case analysis was utilised.

Changes to the relative effect size of mortality for non-operative management of recurrent disease

The mortality rates for patients receiving non-operative management for recurrent disease was assumed to be the same for the two interventions as it was deemed unlikely that the initial method of resection would affect this rate of mortality. The relative effect size was therefore assumed to be one in the base-case analysis. This analysis considered the implications of a relative effect size of 0.5 or 1.5, meaning the mortality rate for patients in the laparoscopic arm could decrease by half and increase by 50% in comparison with patients in the open arm. A relative rate of two (as opposed to 1.5) was not calculated as mortality became greater than one.

Combination of previous two analyses

The relative effect size for the mortality of non-operative management of recurrent disease was assumed to be one in the base-case analysis. This analysis combines the high and low estimates of survival from the previous sensitivity analysis with high and low estimates of the relative effect size of mortality for laparoscopic compared to open resection. The low mortality rate of 0.11 was combined with a relative effect size of 0.5. The higher mortality rate, 0.31, was combined with a relative effect size equal to 1.5. A similar distribution to that used in the base-case analysis has also been used.

Changes to the rate of hernia

No specified rate for the occurrence of hernias, associated with laparoscopic resection, could be found. The relative effect size of a hernia for laparoscopic compared with open resection was assumed to be one. This analysis allowed the relative effect size for the rate of re-operation to change from 0.5 to two. Thus, the rate of hernia following laparoscopic surgery, in comparison with open surgery, was made to decrease to half the rate and increase to double the rate.

Utilities

Use of alternative data to estimate QALYs

Although utilities data required to estimate QALYs was sparse, alternative data were identified by Petrou and Campbell.[121] This study aimed to test the hypothesis that when stabilisation of disease (colorectal cancer) is achieved, chemotherapy can bring positive quality of life benefits. These data were derived from the responses of 30 nurses in the UK experienced in the oncological care of colorectal cancer patients. The nurses, acting on behalf of patients, assessed the values of various health states associated with the treatment of metastatic colorectal cancer. The health states defined by Petrou and Campbell, and those defined within the model, are shown below in Table 5.7. Two variations for the value of non-operative management were used (progressive disease and terminal disease) to assess what difference these alternative values might make to the results.

Table 5.7 Alternative utility values (1)

Utilities		**Value**
Health States defined by Petrou	*Health States defined within the economic model*	
Best Possible Health	Disease-free and Disease-free after successfully treated recurrence	100
Worst Possible Health	Dead	0
Stable Disease	Initial Operation and Recur	95
Progressive Disease (PD)	Non-operative management (1)	57.5
Terminal Disease (TD)	Non-operative management (2)	10

Further to the above sensitivity analysis, a second sensitivity analysis using utility data from a recently published NICE appraisal, which addressed the use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer, has also been included to ascertain what differences in QALY values might be apparent.[122] Utility estimates for patients with Dukes' Stage III colon cancer were sought as part of the systematic review and the estimates used in the assessment of quality of life for this report are shown in Table 5.8. It should be noted that the utility values used for the analysis carried out by Pandor and colleagues are from a number of sources and their usefulness are discussed in the aforementioned review by Pandor and colleagues.[122] As in the previous analysis, two variations for the value of non-operative management were used ("adjuvant chemotherapy without side effects" and "on palliative chemotherapy") to assess what difference these alternative values might make to the results. It should be noted that these utility estimates should be treated with care as the study population does not include surgical patients or patients

with Dukes' Stage I or II cancer. Further, the study population for this review only refers to patients with colon cancer, therefore, excluding rectal cancer.

Table 5.8 Alternative utility values (2)

	Utilities	**Value**
Health States defined by NICE Assessment Report	*Health States defined within the economic model*	
In remission	Initial Operation, Recurrence, Disease-free and Disease-free after successfully treated recurrence	0.92
On palliative chemotherapy	Non-operative management (1)	0.24
On adjuvant chemotherapy (without significant side effects)	Non-operative management (2)	0.70

5.3.4 Subgroup analysis

The model parameters, with respect to survival and disease-free survival, were adjusted in order to estimate relative cost-effectiveness for patients given their stage of cancer. In terms of stage of disease, little stage-dependent data were available however the meta-analysis conducted by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) provided some limited data by stage which were modelled to illustrate the impact that different stages of disease might have on recurrence and mortality rates. Estimation of the risk of death was based on the survival curves from Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005), for patients with stages I, II and III disease for both open and laparoscopic resection, reproduced in Figure 3.2. These data provided estimates of survival up to three years post surgery. Overall survival for each six month time period up to 36 months was estimated from these curves. From these data a mortality rate for each six-month cycle length was calculated. A constant mortality rate was assumed based on the mean value at each six month time period.

Estimation of the risk of recurrence, either local or metastatic disease, was based on data on disease-free survival for stages I, II and III, also provided by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). These data were estimated using the same methods as for the risk of death described above. As with the risk of death a constant risk of recurrence was assumed. Figure 3.2 shows the survival curves for disease-free and overall survival by stage from Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). The top panel shows disease-free survival. Subtle differences between the two procedures by stage can be seen though these should be treated with caution as the number of people contributing to this data at three years is unknown. No confidence intervals are provided in the paper by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005), therefore distributions allowing the uncertainty surrounding these parameters could not be explored. The results, therefore, are expressed purely as a deterministic analysis.

5.3.5 Results

The results of the deterministic analyses of incremental cost per Life Year (LY) and incremental cost per QALY are reported in Tables 5.9 and 5.10 respectively.

Table 5.9 Results of the deterministic model for a 25-year time horizon (life years)

Scenario	Procedure	Cost (£)	Life years	Incremental cost (£)	Incremental life years	Incremental cost per life year
Base-case	Open	9613	15.35			
	Laparoscopic	9876	15.30	263	-0.05	Dominated
Equal Survival	Open	9613	15.35			
	Laparoscopic	9903	15.35	290	0	Dominated

Table 5.10 Results of the deterministic model for a 25-year time horizon (QALYs)

Scenario	Procedure	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY
Base-case	Open	9613	14.68			
	Laparoscopic	9876	14.63	263	-0.05	Dominated
Equal Survival	Open	9613	14.68			
	Laparoscopic	9903	14.68	290	0	Dominated

Laparoscopic resection is dominated by open resection over the 25-year time horizon considered. The point estimates of the incremental cost-effectiveness provided in the above two tables do not provide any indication of the uncertainty that surrounds the model parameters. The uncertainty surrounding the precision of many of the parameter estimates is reflected in the likelihood that the two surgical interventions are cost-effective at different threshold values for society's willingness to pay for a life year and a QALY. Figures 5.2 and 5.3 report the CEACs comparing laparoscopic to open surgery in terms of life years and QALYs respectively.

Figure 5.2 **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)**

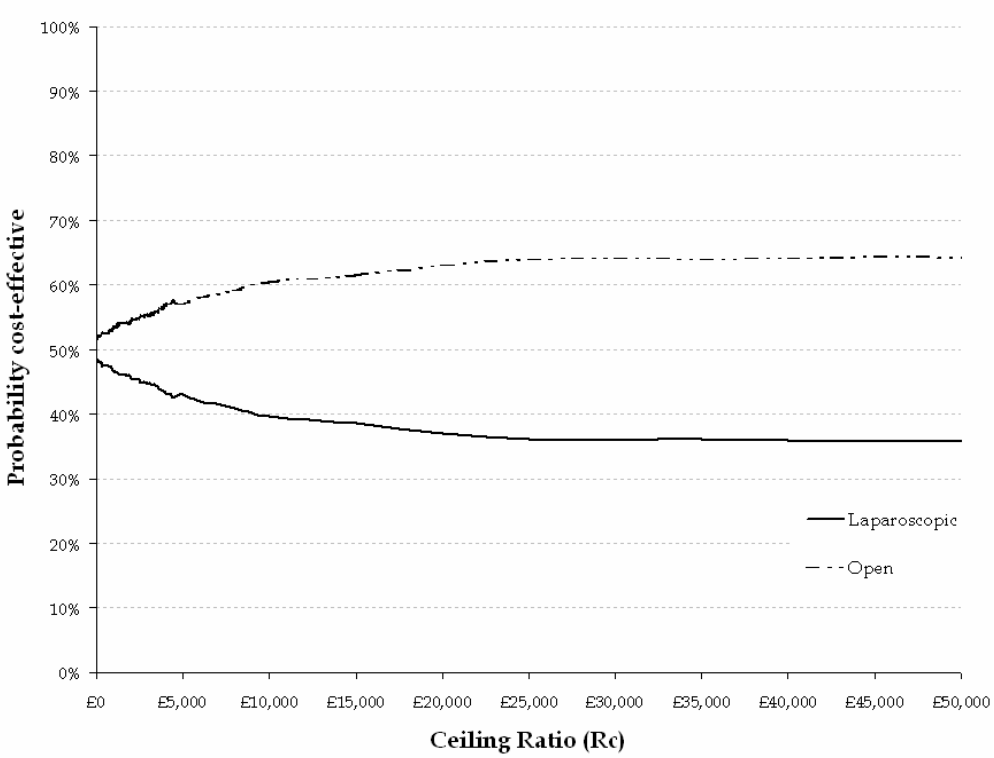
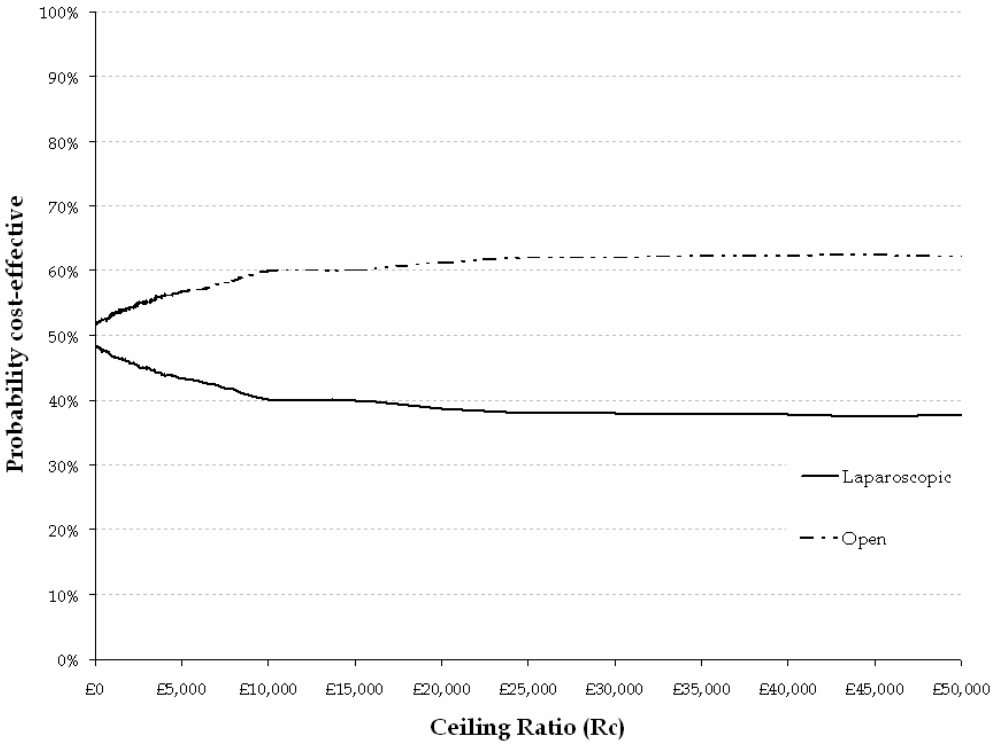


Figure 5.3 **Cost-effectiveness acceptability curve showing society's willingness to pay for a QALY for the comparison of laparoscopic with open surgery (Base-case analysis)**



The results, presented for both life years and QALYs, are driven by very small differences in survival and disease-free survival observed at three years follow-up (see Chapter 3). An alternative interpretation of the data on survival and disease-free survival is that there are no meaningful differences (see Figure 3.1 and results of meta-analysis reported in Chapter 3). Figures 5.4 and 5.5 report alternative analyses for life years and QALYs respectively that make this assumption.

Figure 5.4 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

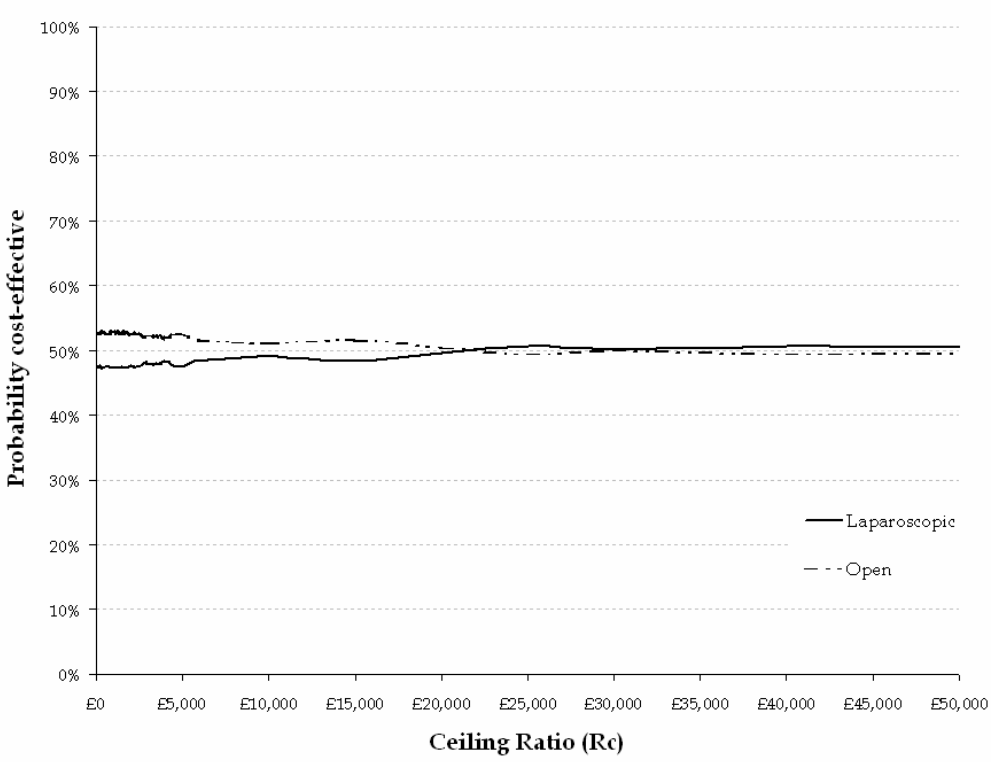
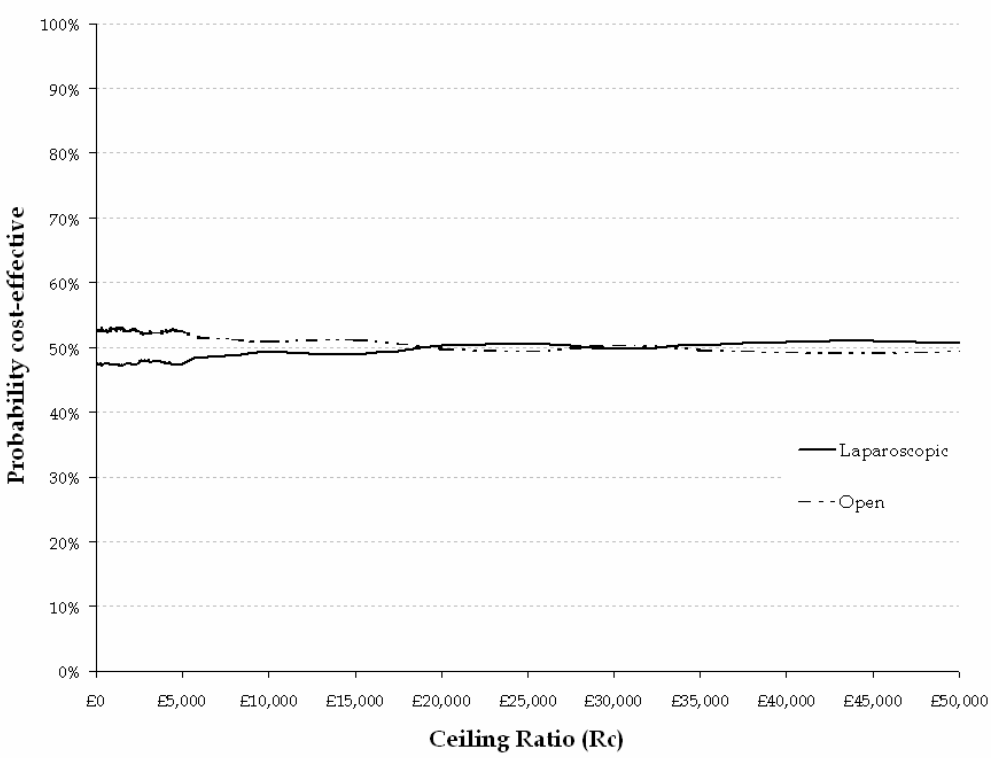


Figure 5.5 Cost-effectiveness acceptability curve showing society's willingness to pay for a QALY for the comparison of laparoscopic with open surgery assuming equal survival and disease-free survival



As Figures 5.4 and 5.5 illustrate, the likelihood that laparoscopic surgery might be considered cost-effective is very similar to the likelihood that open surgery would be considered cost-effective.

The estimates of QALYs for the analysis presented in Figures 5.3 and Figure 5.5 do not capture the QALY gain that might be associated with an earlier recovery. Some indication of the relevance of any QALY gain associated with earlier recovery can be gained by looking at what value for this QALY gain is implied should it be judged that laparoscopic surgery was worthwhile. Assuming a threshold value for society's willingness to pay for a QALY of £30,000 and given the mean incremental cost of laparoscopic surgery of £263 (base-case analysis) and £290 (equal mortality and disease-free survival) then the implied value of the QALY gain would need to be 0.009 and 0.010 respectively. In a comparison between laparoscopic and open hernia repair the observed gain in QALYs was 0.006 at three months.[123]

5.3.6 Sensitivity analysis

Alternative and additional costs data

Changes surrounding the use of alternative cost data provided by a draft paper from a subset of patients from the CLASICC trial produced interesting results. In the first sensitivity analysis using estimates from Franks and colleague (Franks, Thames Valley University, 2005), cost data for the two interventions were re-estimated using the methods described in section 5.3.3. [redacted]

The second sensitivity analysis used the cost estimates for open resection from Franks and colleague (Franks, Thames Valley University, 2005) but utilised the difference in length of stay between open and laparoscopic surgery from the review of effectiveness. [redacted]

A cost analysis taking into account the cost for preoperative staging of disease with respect to each intervention was also performed (see section 5.3.3). An increased difference in cost of £40 between laparoscopic and open resection was observed and relatively little impact on the likelihood that laparoscopic resection would be considered cost-effective. This is as would be expected given the difference in cost for these two imaging modalities (£73 for a CT scan and £32 for an ultrasound scan; taken from the National Reference Costs).

Table 5.11 Sensitivity analysis around changes in costs (life years)

Sensitivity Analysis	Procedure	Cost (£)	Life years	ICER (£)	Probability 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	9613	15.351		60.4%	63.0%	64.0%	64.2%
	Laparoscopic	9876	15.298	(Dominated)	39.6%	37.0%	36.0%	35.8%
Equal Survival	Open	9613	15.351		51.0%	50.3%	49.9%	49.5%
	Laparoscopic	9903	15.351	(Dominated)	49.0%	49.7%	50.1%	50.5%
Cost Data from CLASICC (1)	Open	[redacted]	15.351		[redacted]	[redacted]	[redacted]	[redacted]
	Laparoscopic	[redacted]	15.298	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Data from CLASICC (2) using length of stay data from the review of effectiveness	Laparoscopic	[redacted]	15.298		[redacted]	[redacted]	[redacted]	[redacted]
	Open	[redacted]	15.351	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional cost data for preoperative staging	Open	9646	15.351		61.7%	65.9%	66.6%	66.7%
	Laparoscopic	9949	15.298	(Dominated)	38.3%	34.1%	33.4%	33.3%

BC = base-case
ICER = Incremental cost effectiveness ratio

Table 5.12 Sensitivity analysis around changes in costs (QALYs)

Sensitivity Analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability 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	9613	14.679		59.9%	61.2%	62.0%	62.2%
	Laparoscopic	9876	14.630	(Dominated)	40.1%	38.8%	38.0%	37.8%
Equal Survival	Open	9613	14.679		50.8%	49.8%	50.2%	49.3%
	Laparoscopic	9903	14.679	(Dominated)	49.2%	50.2%	49.8%	50.7%
Cost Data from CLASICC (1)	Open	[redacted]	14.679		[redacted]	[redacted]	[redacted]	[redacted]
	Laparoscopic	[redacted]	14.630	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Data from CLASICC (2) using length of stay data from the review of effectiveness	Laparoscopic	[redacted]	14.630		[redacted]	[redacted]	[redacted]	[redacted]
	Open	[redacted]	14.679	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional cost data for preoperative staging	Open	9646	14.679		60.9%	65.2%	66.1%	65.5%
	Laparoscopic	9949	14.630	(Dominated)	39.1%	34.8%	33.9%	34.5%

BC = base-case
ICER = Incremental cost effectiveness ratio

Changes in the rates of re-operations

Changing the rate at which patients with recurrent cancer receive a further surgical resection had little effect on cost-effectiveness in comparison to the base-case analysis (Table 5.13 for life years and Table 5.14 for QALY results). This would be expected given the similarities in mortality and disease-free survival along with the assumption of no difference in re-operation rates between the two surgical approaches. Changing the relative risk of a re-operation was shown to markedly influence the likelihood that laparoscopic surgery would be cost-effective. For example, adopting a relative risk of 0.5 (i.e. patients originally receiving laparoscopic surgery are less likely to be operated on for recurrent disease than patients who originally receive an open surgery) reduced the likelihood that laparoscopic surgery would be considered cost-effective. This is due to the strong assumption that patients who receive a re-operation for subsequent disease would, if the operation were successful, have the same mortality and disease-free survival as someone following the initial surgery (Table 5.13 for life years and Table 5.14 for QALY results). A further sensitivity analysis was conducted to examine the interaction between the baseline risk of a re-operation and the relative risk of re-operation (Table 5.13 for life years and Table 5.14 for QALY results). Allowing a higher rate of operations for recurrent disease and increasing the chance that patients who originally received laparoscopic surgery would receive an operation for any recurrent disease would greatly increase the likelihood that laparoscopic resection would be considered cost-effective. Given the model assumptions, this is as would be expected.

Table 5.13 Sensitivity analysis around changes in the risk of re-operation for recurrent disease (life years)

Sensitivity Analysis	Procedure	Cost (£)	Life years	ICER (£)	Probability 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	9613	15.351		60.4%	63.0%	64.0%	64.2%
	Laparoscopic	9876	15.298	(Dominated)	39.6%	37.0%	36.0%	35.8%
Equal Survival	Open	9613	15.351		51.0%	50.3%	49.9%	49.5%
	Laparoscopic	9903	15.351	(Dominated)	49.0%	49.7%	50.1%	50.5%
Re-operation rate 1% - (BC=5%)	Open	9567	15.173		60.1%	64.9%	66.0%	66.2%
	Laparoscopic	9830	15.122	(Dominated)	39.9%	35.1%	34.0%	33.8%
Re-operation rate 10% - (BC=5%)	Open	9671	15.574		60.7%	64.5%	64.5%	64.7%
	Laparoscopic	9933	15.518	(Dominated)	39.3%	35.5%	35.5%	35.3%
RR of 0.5 for re-operation rate (BC=1)	Open	9613	15.351		75.0%	81.0%	81.3%	83.2%
	Laparoscopic	9847	15.188	(Dominated)	25.0%	19.0%	18.7%	16.8%
RR of 2 for re-operation rate (BC=1)	Open	9613	15.351		28.1%	22.6%	20.8%	19.0%
	Laparoscopic	9933	15.518	1921	71.9%	77.4%	79.2%	81.0%
RR of 0.5 for re-operation rate (BC=1) & 1% rate of re-operation (BC=5%)	Open	9567	15.173		64.7%	69.1%	70.0%	71.4%
	Laparoscopic	9825	15.100	(Dominated)	35.3%	30.9%	30.0%	28.6%
RR of 2 for re-operation rate (BC=1) & 10% rate of re-operation (BC=5%)	Open	9671	15.574		9.7%	4.4%	2.8%	1.8%
	Laparoscopic	10047	15.957	980	90.3%	95.6%	97.2%	98.2%

BC = base-case
ICER = Incremental cost effectiveness ratio

Table 5.14 Sensitivity analysis around changes in the risk of re-operation for recurrent disease (QALYs)

Sensitivity Analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	9613	14.679		59.9%	61.2%	62.0%	62.2%
	Laparoscopic	9876	14.630	(Dominated)	40.1%	38.8%	38.0%	37.8%
Re-operation rate 1% - (BC=5%)	Open	9567	14.492		59.1%	63.2%	64.2%	64.7%
	Laparoscopic	9830	14.446	(Dominated)	40.9%	36.8%	35.8%	35.3%
Re-operation rate 10% - (BC=5%)	Open	9671	14.912		59.7%	63.0%	62.6%	62.4%
	Laparoscopic	9933	14.860	(Dominated)	40.3%	37.0%	37.4%	37.6%
RR of 0.5 for re-operation rate (BC=1)	Open	9613	14.679		75.2%	80.9%	80.9%	82.2%
	Laparoscopic	9847	14.515	(Dominated)	24.8%	19.1%	19.1%	17.8%
RR of 2 for re-operation rate (BC=1)	Open	9613	14.679		26.5%	20.4%	18.4%	16.7%
	Laparoscopic	9933	14.860	1761	73.5%	79.6%	81.6%	83.3%
RR of 0.5 for re-operation rate (BC=1) & 1% rate of re-operation (BC=5%)	Open	9567	14.492		63.4%	67.6%	69.1%	69.9%
	Laparoscopic	9825	14.423	(Dominated)	36.6%	32.4%	30.9%	30.1%
RR of 2 for re-operation rate (BC=1) & 10% rate of re-operation (BC=5%)	Open	9671	14.911		8.6%	3.4%	1.4%	1.1%
	Laparoscopic	10047	15.320	920	91.4%	96.6%	98.6%	98.9%

BC = base-case
ICER = Incremental cost effectiveness ratio

Non-operative mortality rates for recurrent disease

As might be expected, changes in the baseline level of mortality associated with recurrent disease had little effect on the likelihood that laparoscopic surgery would be considered cost-effective (Table 5.15 for life years and Table 5.16 for QALY results). The model was highly sensitive to the assumption that survival for patients in the state of non-operative management of recurrent disease would in anyway be influenced by the choice of initial surgery. Combining changes in the baseline level of non-operative mortality and in the relative risk between laparoscopic and open surgery provided a similar finding to changes in relative risk alone (Table 5.15 for life years and Table 5.16 for QALY results).

Risk of hernia

One area where limited data were available was on the risk of hernia (and on other morbidities associated with the method of surgery). Even assuming a 50% fewer or twice the number of hernias occurring after open surgery, little effect on the cost-effectiveness of laparoscopic surgery was shown. This was because the baseline risk of hernia was low and the only impact on cost-effectiveness was through cost i.e. the incidence and treatment of a hernia had no effect on utility (Table 5.17 for life years and Table 5.18 for QALY results).

Alternative utility values

The data available on utilities was very limited but some alternative utility values were available from Petrou and Campbell and also from a recently published NICE appraisal review.[121,122] As described in Section 5.3.3, values were available for the health states in the model (although data relevant to recovery from surgery and longer term morbidities associated with the method of surgery, such as hernias, were not available). However, two alternative values were available for non-operative management from Petrou and Cambell.[121] In the first sensitivity analysis non-operative management was assigned the value estimated by this study for progressive disease.[121] In this analysis laparoscopic surgery was still dominated but was associated with a slightly higher probability of being considered cost-effective (Table 5.19). In the second analysis non-operative management was assigned the value estimated by Petrou and Campbell for terminal disease.[121] In this analysis laparoscopic surgery was again dominated but slightly more likely to be considered cost-effective in comparison to the analysis using the value for progressive disease. The reason for this is that, in the base-case analysis, patients receiving open surgery have a slightly worse disease-free survival compared to laparoscopic surgery. Hence, they are more likely to spend time in this state and incur the lower utilities associated with this state.

Further alternative utility data taken from the NICE appraisal regarding the use of oxaliplatin and capecitabine on the treatment of Stage III patients with colon cancer also provided alternative estimates of utility values to allow further estimation of QALYs.[122] Two separate values for the non-operative management of recurrent disease were, again, used within the model as outlined in section 5.3.3. The first sensitivity analysis using utilities from this review used the low rate of 0.24 for the non-operative management state (see Table 5.19). This state related to those on palliative chemotherapy from the NICE review. In this analysis, laparoscopic was still dominated by open and the difference in QALYs between the two interventions remained similar to the results using utility values from Petrou and Campbell.[121] This serves to highlight that the only factor driving these differences is that of the small differences in survival and disease-free survival at three years. The number of QALYs gained in this analysis, for both interventions are, however, less than those using data from Petrou and Cambell. This is because the value for the disease-free and disease-free after a successfully treated recurrence states were assumed to have the same value as that for the initial operation and for recurrence i.e. they were not assumed to be in full health with a utility score equal to one so could not incur the higher utility when in these states. The results from the second sensitivity analysis using the utility values from the NICE review used a value of 0.7 for the non-operative management state, which was classified by the NICE review,[122] as patients on adjuvant chemotherapy (see Table 5.19). Once again, laparoscopic is dominated by open resection and is slightly less likely to be considered cost-effective in comparison with the value for palliative chemotherapy. This is due to the fact that patients receiving open surgery have a slightly worse disease-free survival compared to laparoscopic surgery and are therefore more likely to spend time in the non-operative management state. Hence, they have a greater chance of accruing the extra QALYs associated with this state when it has the higher utility value of 0.7.

Table 5.15 Sensitivity analysis associated with non-operative management for recurrent disease (life years)

Sensitivity Analysis	Procedure	Cost (£)	Life years	ICER (£)	Probability 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	9613	15.351		60.4%	63.0%	64.0%	64.2%
	Laparoscopic	9876	15.298	(Dominated)	39.6%	37.0%	36.0%	35.8%
Equal Survival	Open	9613	15.351		51.0%	50.3%	49.9%	49.5%
	Laparoscopic	9903	15.351	(Dominated)	49.0%	49.7%	50.1%	50.5%
High mortality rate of Non OM (0.31). (BC=0.2)	Open	8924	14.520		58.3%	60.6%	61.6%	61.9%
	Laparoscopic	9193	14.475	(Dominated)	41.7%	39.4%	38.4%	39.1%
Low mortality rate for Non OM (0.11) (BC=0.2)	Open	10961	17.120		66.5%	71.5%	73.4%	73.2%
	Laparoscopic	11211	17.049	(Dominated)	33.5%	28.5%	26.6%	26.8%
RR of 0.5 for mortality for Non OM state (BC=1)	Open	9613	15.351		0.0%	0.0%	0.0%	0.0%
	Laparoscopic	11467	17.405	903	100.0%	100.0%	100.0%	100.0%
RR of 1.5 for mortality for Non OM state (BC=1)	Laparoscopic	9237	14.530		0.8%	0.1%	0.1%	0.1%
	Open	9613	15.350	456	99.2%	99.9%	99.9%	99.9%
RR of 0.5 for Non OM mortality (BC=1) & low (0.11) mortality rate for Non OM state (BC=0.2)	Open	10961	17.120		0.0%	0.0%	0.0%	0.0%
	Laparoscopic	13247	20.021	788	100.0%	100.0%	100.0%	100.0%
RR of 1.5 for Non OM mortality (BC=1) & high (0.31) mortality rate for Non OM state (BC=0.2)	Laparoscopic	8745	13.961		2.3%	0.8%	0.5%	0.4%
	Open	8924	14.520	321	97.7%	99.2%	99.5%	99.6%

BC = base-case
OM = Operative management
ICER = Incremental cost effectiveness ratio

Table 5.16 Sensitivity analysis associated with non-operative management for recurrent disease (QALYs)

Sensitivity Analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	9613	14.679		59.9%	61.2%	62.0%	62.2%
	Laparoscopic	9876	14.630	(Dominated)	40.1%	38.8%	38.0%	37.8%
Equal Survival	Open	9613	14.679		50.8%	49.8%	50.2%	49.3%
	Laparoscopic	9903	14.679	(Dominated)	49.2%	50.2%	49.8%	50.7%
High rate of Non OM mortality (0.31). (BC=0.2)	Open	8924	13.989		57.7%	60.2%	60.5%	60.6%
	Laparoscopic	9193	13.947	(Dominated)	42.3%	39.8%	39.5%	39.4%
Low mortality rate for Non OM (0.11) (BC=0.2)	Open	10961	16.146		64.1%	69.8%	70.1%	71.1%
	Laparoscopic	11211	16.084	(Dominated)	35.9%	30.2%	29.9%	28.9%
RR of 0.5 for mortality for Non OM state (BC=1)	Open	9613	14.680		0.0%	0.0%	0.0%	0.0%
	Laparoscopic	11467	16.379	1,090	100.0%	100.0%	100.0%	100.0%
RR of 1.5 for mortality for Non OM state (BC=1)	Laparoscopic	9237	13.989		1.7%	0.6%	0.3%	0.1%
	Open	9613	14.679	546	98.3%	99.4%	99.7%	99.9%
RR of 0.5 for Non OM mortality (BC=1) & low (0.11) mortality rate for Non OM state (BC=0.2)	Open	10961	16.146		0.0%	0.0%	0.0%	0.0%
	Laparoscopic	13247	18.551	951	100.0%	100.0%	100.0%	100.0%
RR of 1.5 for Non OM mortality (BC=1) & high (0.31) mortality rate for Non OM state (BC=0.2)	Laparoscopic	8745	13.520		3.7%	2.0%	1.6%	1.3%
	Open	8924	13.989	383	96.3%	98.0%	98.4%	98.7%

BC = base-case
OM = Operative management
ICER = Incremental cost effectiveness ratio

Table 5.17 Sensitivity analysis around changes in the risk of hernia (life years)

Sensitivity Analysis	Procedure	Cost (£)	Life years	ICER (£)	Probability 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	9613	15.351		60.4%	63.0%	64.0%	64.2%
	Laparoscopic	9876	15.298	(Dominated)	39.6%	37.0%	36.0%	35.8%
Equal Survival	Open	9613	15.351		51.0%	50.3%	49.9%	49.5%
	Laparoscopic	9903	15.351	(Dominated)	49.0%	49.7%	50.1%	50.5%
RR of 0.5 for hernia rate (BC=1)	Open	9613	15.351		60.0%	62.5%	63.4%	63.9%
	Laparoscopic	9823	15.298	(Dominated)	40.0%	37.5%	36.6%	36.1%
RR of 2 for hernia rate (BC=1)	Open	9613	15.351		61.9%	64.1%	64.7%	64.9%
	Laparoscopic	9982	15.298	(Dominated)	38.1%	35.9%	35.3%	35.1%

BC = base-case
ICER = Incremental cost effectiveness ratio

Table 5.18 Sensitivity analysis around changes in the risk of hernia (QALYs)

Sensitivity Analysis	Procedure	Cost (£)	Life years	ICER (£)	Probability 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	9613	14.679		59.9%	61.2%	62.0%	62.2%
	Laparoscopic	9876	14.630	(Dominated)	40.1%	38.8%	38.0%	37.8%
Equal Survival	Open	9613	14.679		50.8%	49.8%	50.2%	49.3%
	Laparoscopic	9903	14.679	(Dominated)	49.2%	50.2%	49.8%	50.7%
RR of 0.5 for hernia rate (BC=1)	Open	9613	14.679		58.5%	60.3%	61.6%	61.9%
	Laparoscopic	9823	14.630	(Dominated)	41.5%	39.7%	38.4%	38.1%
RR of 2 for hernia rate (BC=1)	Open	9613	14.679		60.8%	62.3%	63.1%	62.8%
	Laparoscopic	9982	14.630	(Dominated)	39.2%	37.7%	36.9%	37.2%

BC = base-case
ICER = Incremental cost effectiveness ratio

Table 5.19 Sensitivity analysis around changes in the use of alternative utility values (QALYs)

Sensitivity Analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	9613	14.679		59.9%	61.2%	62.0%	62.2%
	Laparoscopic	9876	14.630	(Dominated)	40.1%	38.8%	38.0%	37.8%
Equal Survival	Open	9613	14.679		50.8%	49.8%	50.2%	49.3%
	Laparoscopic	9903	14.679	(Dominated)	49.2%	50.2%	49.8%	50.7%
Alternative QALY-Petrou. Non OM utility score 0.575 (see Table 5.7)	Open	9613	14.246		57.9%	59.6%	60.4%	60.1 %
	Laparoscopic	9876	14.203	(Dominated)	42.1%	40.4 %	39.6%	39.9%
Alternative QALY-Petrou. Non OM utility score 0.10 (see Table 5.7)	Open	9613	13.095		56.0%	56.6%	56.4%	56.3%
	Laparoscopic	9876	13.064	(Dominated)	44.0%	43.4%	43.6%	43.7%
Alternative QALY-Pandor. Non OM utility score 0.24 (see Table 5.8)	Open	9613	12.477		56.2%	57.7%	57.5%	57.4%
	Laparoscopic	9876	12.444	(Dominated)	43.8%	42.3%	42.5%	42.6%
Alternative QALY-Pandor. Non OM utility score 0.70 (see Table 5.8)	Open	9613	13.591		59.0%	60.5%	61.6%	61.9%
	Laparoscopic	9876	13.547	(Dominated)	41.0%	39.5%	38.4%	38.1%

BC = base-case
OM = Operative management
ICER = Incremental cost effectiveness ratio

5.3.7 Results of subgroup analysis

A deterministic analysis was performed to assess the cost effectiveness for each intervention by stage of cancer (Table 5.20 for life years and Table 5.21 for QALYs). The input parameters for mortality and recurrence, by stage of disease, were obtained from the survival curves taken from Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) (see Figure 3.2). The results are limited and do not reflect the degree of statistical uncertainty which might surround the mortality and recurrence parameters. [redacted] (Bonjer, QE 11 Health Sciences Center, Halifax, 2005) though some difference in mean costs and effects between the stage of disease can be seen from the results below (Table 5.20 for life years and Table 5.21 for QALYs). Curiously for both life years and QALYs, it appears that patients with stage III disease, treated laparoscopically, actually had improved overall and disease-free survival compared to open patients as this was the only instance where neither intervention clearly dominated the other. The results for patients with stage I are broadly consistent with the base-case analysis with a similar cost and quality of life difference between the two interventions (Table 5.20 for life years and Table 5.21 for QALYs). Patients with stage II colorectal cancer appear to be worse off when treated laparoscopically compared with being treated with open surgery with an increased cost and decreased effectiveness. Clinical opinion normally suggests that patients whose disease progression is the least advanced (patients with early stages of cancer) might be the best candidates for laparoscopic surgery. The evidence from the subgroup analysis performed is inconclusive and appears not be consistent with this assumption. The data used to allow this analysis should be treated cautiously and further randomised evidence and/or meta-analyses with data on stage dependent outcomes is warranted for any conclusions to be reached with regard to the suitability of laparoscopic candidates by stage of disease.

Table 5.20 Deterministic results of subgroup analysis for different stages of cancer (life years)

Scenario	Procedure	Cost (£)	Life years	Incremental cost (£)	Incremental life years	Incremental cost per life year
Base-case	Open	9613	15.35			
	Laparoscopic	9876	15.30	263	-0.05	Dominated
Equal Survival	Open	9613	15.35			
	Laparoscopic	9903	15.35	290	0	Dominated
Stage I	Open	8994	24.04			
	Laparoscopic	9247	23.63	253	-0.41	Dominated
Stage II	Open	9458	16.84			
	Laparoscopic	9764	14.67	306	-2.17	Dominated
Stage III	Open	9802	11.14			
	Laparoscopic	9812	13.11	10	1.97	5

Table 5.21 Deterministic results of subgroup analysis for different stages of cancer (QALYs)

Scenario	Procedure	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY
Base-case	Open	9613	14.68			
	Laparoscopic	9876	14.63	263	-0.05	Dominated
Equal Survival	Open	9613	14.68			
	Laparoscopic	9903	14.68	290	0	Dominated
Stage I	Open	8994	23.50			
	Laparoscopic	9247	23.10	253	-0.40	Dominated
Stage II	Open	9458	16.20			
	Laparoscopic	9764	14.03	306	-2.18	Dominated
Stage III	Open	9802	10.43			
	Laparoscopic	9812	12.45	10	2.02	5

5.4 Summary of evidence on cost-effectiveness

The results presented in the balance sheet suggest that if it is assumed that there is no difference in long-term outcomes then a judgement is required as to whether the shorter recovery associated with laparoscopic resection is worth the additional cost of £250 to £300 per patient. [redacted]

The available data were explicitly synthesised in an economic model. In the base-case of this model, and almost all of the sensitivity analyses, (making many of the same assumptions about survival and disease-free survival as the base-case analysis), laparoscopic surgery was dominated (i.e. no more effective but more costly) by open surgery. However, the likelihood that laparoscopic surgery might be considered cost-effective varied between 30% and 50% regardless of whether outcomes were measured in life years or QALYs. If an assumption were made of equal survival and disease-free survival then the mean estimates of incremental cost-effectiveness still suggest laparoscopic surgery is dominated. Although, as costs and outcomes are similar, both approaches had a similar likelihood of being considered cost-effective.

A major concern with this analysis is that few data were available on the utilities. More importantly the model fails, because of lack of data, to include the QALY gain that might be associated with an earlier recovery following laparoscopic surgery. The implied value of the QALY gain would need to be 0.009 and 0.010 respectively. In a comparison between laparoscopic and open groin hernia repair the observed gain in QALYs was 0.006.[123] It could be argued that as open resection of colorectal cancer involves a larger incision than open repair of inguinal hernia, the magnitude of QALY gain for laparoscopic compared with open resection might be greater than that observed for hernia repair. What this fundamentally illustrates is that relatively small differences in QALYs may, in strict economic terms, be key to conclusions. This is especially the case when it is remembered that a single day in full health is equal to 0.00274 QALYs.

Similarly, little data were available on morbidities associated with the method of surgery such as hernia and persisting pain. The risk of such outcomes along with their associated management costs and utilities may, as with the evaluation of surgery for inguinal hernia,[124] be central to determining relative cost-effectiveness.

The model was also sensitive to the patient pathways and their associated probabilities, costs and utilities following recurrent disease. In the context of the available data, which suggested similar mortality and disease-free survival, this is likely to be unimportant especially if the patient pathway following recurrence is not influenced by the initial choice of surgery. Should further data become available suggesting the contrary, however, then the sensitivity analysis suggest that the results produced by the model would be sensitive to the management of recurrent disease and further work to develop this aspect of the model might be warranted.

The analysis was repeated for different stages of disease and results were broadly similar to the base-case analysis. Further evidence to allow data synthesis with regards to outcomes by stage is warranted.

6. IMPLICATIONS FOR OTHER PARTIES

6.1 Quality of life for the family and carers

The data reported in Chapter 3 and summarised in Section 5.1 suggest that laparoscopic resection is associated with some short-term benefit but takes longer to perform. There is no evidence of a difference in long term outcomes measured by either surrogate endpoints (e.g. lymph node retrieval and resection margins) or final outcomes (e.g. death, disease-free survival and hernia for three years after surgery). Laparoscopic surgery is therefore an approach that offers patients some short-term advantages without compromising safety or long-term outcomes. Furthermore, should the short-term benefits of laparoscopic surgery be realised and associated with a quicker recovery, this may reduce the time and effort that a patient's family or other carers devote to care following discharge from hospital.

6.2 Financial impact for the patient and others

Although the mean age of patients receiving surgery for colorectal cancer is past the age of retirement, a significant proportion of patients will still be in employment. Faster recovery following surgery might result in earlier return to work. People who would otherwise experience financial hardship as a result of being away from work would benefit from the shorter recovery period of laparoscopic surgery. Employers might benefit by having their employees back to work earlier.

It has been argued that an enhanced recovery programme may offer advantage in terms of earlier discharge. If so, such policies may be associated with some transfer of cost from the NHS to the families and carers of patients compared with conventional discharge policies. Whether such an effect occurs is not clear and a recent Cochrane review reported that evidence on cost shifting was limited.[125]

7 IMPLICATIONS FOR THE NHS

7.1 Training

Currently few surgeons routinely perform laparoscopic surgery within the UK. Training courses and a preceptorship programme have been organised by relevant professional groups in collaboration with industry. It has been argued that such training should reduce operation time and conversion rates (Ethicon Endo-surgery, Submission to NICE, 2005) and possibly improve other outcomes. Despite such programmes, it will take time to increase the number of surgeons capable of providing laparoscopic surgery for colorectal cancer. The pool of surgeons within the UK with the necessary experience to act as a preceptor (experience of at least 100 such resections) is small. (Ethicon Endo-surgery, Submission to NICE, 2005). However, there are an increasing number of training courses and schemes available for surgeons wishing to develop the necessary skills.

HALS may be technically easier to perform (and hence easier to learn) than laparoscopic surgery. However, few data are available to assess its role as a substitute or complement to laparoscopic surgery is unclear.

7.2 Fair access and equity issues

Laparoscopic equipment does not appear to be a restriction, because it is available in the majority of NHS hospitals where colorectal resections take place. An issue will be matching the distribution of appropriately skilled surgeons with the distribution of colorectal cancer surgery within the UK.

7.3 Resource transfers between primary and secondary care

The potentially quicker recovery associated with laparoscopic surgery may result in less call on primary care services compared with open surgery although earlier discharge from hospital may negate this. The implementation of an enhanced recovery programme, as described by Basse and colleagues,[38] for laparoscopic or open surgery may result in a shift in balance of care from secondary to primary care irrespective of type of surgery performed. Given the experience of early discharge schemes for other conditions, the magnitude of such a shift is likely to be modest in cost terms but the shift of work may not be accompanied by any additional resource.[126]

7.4 Budgetary impact on the NHS

The budget impact of increasing use of laparoscopic surgery from current level of provision of open surgery is estimated as part of Section 2.3.10. As outlined in that section, the additional cost of increasing laparoscopic surgery to 25% of all resections may range from less than £100,000 from the current level of provision of 0.1% of all resections, to an additional cost of £2.1 million.

Such estimates are subject to considerable uncertainty. Furthermore, they do not include long-term costs (although this review suggests they will not differ between treatments) or differences in the cost of pre-surgery which may differ between laparoscopic and open resection. One reason for a difference in pre-surgery costs would be if laparoscopic surgery were limited to less complicated cases. If this occurs then such cases would need to be identified. This may require routine CT staging of the tumour although an increasing number of open operations already require such detailed imaging. However, in some centres, due to the limited availability of CT, an ultrasound is performed instead. Thus, any increase in use of laparoscopic surgery may lead to increased demand for CT imaging.

An enhanced recovery programme may result in shorter length of stay; however cost saving is only realised if beds are closed as a consequence. In practice, the freed bed-days may be used to provide other desirable care (providing additional benefit at further cost). This is in addition to the cost of establishing the enhanced recovery programme. Such a programme may not therefore result in reduced overall costs to the NHS.

8. DISCUSSION

8.1 Main results

As stated in Chapter 1 current guidance from NICE on the use of laparoscopic surgery for colorectal cancer is that open rather than laparoscopic surgery is the preferred procedure and that laparoscopic surgery should only be undertaken as part of a randomised controlled trial.[1] This guidance was based on a technology assessment review conducted in 2000.[21]

The 2000 review included data from five RCTs and 18 non-randomised comparisons. It found some evidence of short-term benefits for laparoscopic resection. In particular, it found that the use of analgesia and length of stay were less following laparoscopic surgery. The additional cost of laparoscopic resection was estimated to be approximately £200 per patient. There was insufficient evidence to judge whether the procedures differed in respect of long-term outcomes such as survival or disease-free survival.

Long-term outcome remains the most important issue. There were concerns that cure rates may be less after laparoscopic surgery, with the possibility of port site metastases. However, early trial results suggested better long-term results after laparoscopic surgery, possibly due to less disruption to the immune system.

This updated review identified 19 RCTs and one individual patient data meta-analysis of four of the largest trials comparing laparoscopic with open surgery. Data from the RCTs related to 4568 patients. The long-term evidence was enhanced by the individual patient data meta-analysis, providing evidence on survival and disease-free survival up to three years after surgery.

Although the results are associated with some uncertainty, laparoscopic surgery is likely to be more costly than open surgery. The magnitude of the extra cost from studies appears to be about £250 to £300 per patient. Although only limited data are available, the costs of laparoscopic surgery were sensitive to the additional costs of the equipment required for laparoscopic surgery and the extent of reduction in length of stay compared with open surgery. The other likely cost driver is the extra theatre costs associated with the longer operating time.

The results of the updated review of data for short-term outcomes have not fundamentally changed the overall picture: convalescence is more rapid after laparoscopic surgery and this is reflected in less postoperative pain, shorter hospital stay, and more rapid return to usual activities. Few cases of wound and port site recurrences were reported. The major change since the 2000 review has been in the evidence on recurrence, disease-free survival and overall survival. [redacted] The updated review presented in this report also attempted to assess relative effectiveness in terms of differences in wound related morbidities such as incisional and port-site hernias, and persisting pain. Few data were identified for hernia and none on persisting pain.

The results of the updated review along with results of the individual patient meta-analyses have been incorporated into the economic evaluation outlined in Chapter 5. The balance sheet approach illustrates the trades-offs that have to be taken into account when making decisions about which type of surgery to use. Assuming there are no differences in long-term outcomes, a judgement is required as to whether the short-term benefits following laparoscopic surgery are worth the estimated additional £250 to £300 per patient.

The base-case analysis suggests that laparoscopic resection is 'dominated' in terms of incremental cost per life year and incremental cost per QALY. These findings reflect two things (1) the similarity in survival and disease-free survival between laparoscopic and open surgery; and (2) the very limited data on utilities which do not capture the short-term benefits associated with laparoscopic surgery. There is a likelihood of between 40% and 50% that laparoscopic surgery would be considered cost-effective at an incremental cost per life year or QALY that society might be willing to pay. The 50% likelihood of being cost-effective occurs under the assumption of no difference in survival or disease-free survival [redacted]

There were no utility data available to model the gain in QALYs associated with more rapid recovery. However, it was possible to estimate the implied value for the QALY gain associated with an earlier recovery that would be needed for laparoscopic surgery to be considered cost-effective. The results of the sensitivity analyses suggest that, should society be willing to pay £30,000 per QALY, then earlier recovery following laparoscopic surgery

would need to be associated with an increase of QALYs of between 0.009 to 0.010 QALYs compared with open surgery. To put these figures in context, in the MRC Laparoscopic Groin Hernia trial, laparoscopic repair was found to be associated with a mean gain in QALYs at a three month follow-up of 0.00583 QALYs (i.e. about two-thirds the threshold for laparoscopic colorectal cancer).[123] Arguably, it might be expected that the differences in recovery between laparoscopic and open surgery for colorectal cancer would be greater than between laparoscopic and open surgery for inguinal hernia. Nevertheless, a judgement is required as to whether the magnitude of additional QALYs identified by the implied value calculation can plausibly be provided by laparoscopic surgery. Furthermore, it should be noted that this implied valuation indicates their relatively small differences in QALYs, which cannot be identified with the data available, may be crucial determinants of conclusions. For example, the difference in QALYs would be equivalent to an additional three to four days of full health.

Little evidence was available on the relative merits of HALS or the use of an enhanced recovery programme for both laparoscopic and open surgery. The limited evidence available would suggest that overall HALS might be expected to provide similar costs and outcomes to laparoscopic surgery. It has been suggested that HALS may be best thought of as complementary to laparoscopic surgery with a role for particular cases rather than as a substitute (Ethicon Endo-surgery submission to NICE, 2005).

With respect to the role of enhanced recovery, the one economic evaluation (based on an RCT) that formally compared laparoscopic to open surgery in the context of such a programme, still found that the mean length of stay between the two procedures was less for laparoscopic surgery. However, such an approach appeared to offer advantages in terms of freeing up bed days for other uses following both forms of surgery. The precise magnitude of any difference in length of stay between laparoscopic and open surgery is important as it has a significant impact on both the incremental cost and cost-effectiveness. For example, should there be no difference in length of stay the incremental cost of laparoscopic surgery would be approximately £700; the cost of the two forms of surgery would be equivalent if the length of stay was approximately four days less for laparoscopic surgery (a greater difference than suggested by the results of the systematic review presented in Chapter 3).

There were relatively few data for any of the subgroups. The data that were available suggest that there may be important differences between colon and rectal cancer. However, this is tentative, and it was impossible to judge whether or not there are potentially

important differences between treatments within clinical subgroups of colorectal cancer patients.

8.2 Assumptions, limitations and uncertainties

The systematic review of effectiveness identified considerably more RCTs than were available for the review in 2000.[21] Unfortunately for many of the review outcomes the data were sparse. For example, only one RCT (from Hong Kong) reported data on return to usual activities.[53] Furthermore, even where data were available it was not always reported in a format suitable for inclusion in the meta-analysis. Nonetheless, the direction and magnitude of effect of these data appeared to be consistent and had it been possible to include the data in the meta-analysis the precision of the estimate available would have been increased.

Several limitations must be noted when interpreting the results of the review of effectiveness (Chapter 3). An extensive literature search was conducted and both published and unpublished data were sought. Despite these efforts, it is possible that some unpublished studies may have been missed. The impact on direction of effect is unknown. The criteria for inclusion and exclusion of patients vary considerably between the studies. For example, some trials exclude patients with advanced disease while other trials include only patients with colon cancer. This therefore limited our subgroup analysis. Hence, the results might not be generalisable to all groups of patients who might undergo laparoscopic surgery. Differences in patient group and variation in operative technique and treatment protocols existed between studies. However, the review attempted to identify and explore sources of heterogeneity. In most trials, outcome assessors and patients were not blinded. This might have influenced some of the outcomes. Moreover, quality of life and pain scores were reported using a variety of instruments and therefore comparisons were difficult. Furthermore, in most trials, around 20% of participants randomised to laparoscopic surgery had open surgery; this could have blunted any true differences between the two approaches. Despite these limitations, the overall findings obtained from these trials were similar.

The best available evidence on disease-free survival and overall survival are likely to come from the individual patient data meta-analyses conducted by Bonjer and colleagues (Bonjer, QE 11 Health Sciences Center, Halifax, 2005). This meta-analysis did not include all the data from all the available RCTs and it only had a follow-up of three years. [redacted] Nonetheless, had the data from the other trials been incorporated it is

likely that the precision of the estimates would have been improved. The biggest limitation of this review is that the data available relate to at most a three-year time horizon. More long-term follow-up data are therefore required before it is certain that there is no difference in longer-term recurrence and survival.

The data available were very limited for some of the outcomes and also for the subgroups and insufficient to draw firm conclusions about the relative effectiveness of the techniques being compared. Further studies would be useful to address these deficiencies in the evidence base.

There was little information on the longer-term risks of wound related morbidity. Insufficient data were available to incorporate the risk of and the different types of hernia (port site and incisional hernias) into the economic model. In studies comparing laparoscopic to open surgery for other conditions the risks (and associated costs and utilities) of these wound related morbidities have been central determinants of cost-effectiveness. Further data are needed on the risks of outcomes, such as hernias and persisting pain (along with their costs of management and associated effects on utility).

Very meagre data were available for the comparison of HALS and open surgery. The paucity of data highlights the need for more studies for this comparison.

In common with other laparoscopic procedures, laparoscopic surgery for colorectal cancer is technically more difficult than open surgery. The cost effectiveness (and also almost certainly the safety) of laparoscopic surgery will be influenced by where operators are on their learning curves. The effect of learning may explain why some trial patients randomised to laparoscopic surgery actually received open surgery ("opposite method initiated") and why so many trial patients allocated to laparoscopic surgery were converted during the procedure from laparoscopic to open surgery. Increased experience in selecting which patients are suitable for laparoscopic surgery as well as improving operator expertise might be expected to reduce both these rates.

In addition, the systematic review was conducted on an intention to treat basis. Therefore, any reduction in the rate at which patients undergoing laparoscopic surgery are converted to open surgery might be expected to increase the difference observed between laparoscopic and open surgery.

As with any economic evaluation a number of assumptions have been made. These assumptions have mostly been made in response to the very limited data available. For example, as mentioned above, the economic evaluation did not differentiate between port site and incisional hernia, which may in fact differ in terms of cost of treatment and effect on patients' well-being. Similarly, no usable data with which to differentiate the two interventions were available for such aspects as rates for re-operations, following a recurrence. As a result, these rates were assumed to be the same which may not be justified given the lack of data to support this.

One concern about the economic model is the quantity and quality of data available. In particular, data on two key components: cost and utilities were very limited. In the case of costs the data available were subject to considerable imprecision, as it had been derived from a small RCT.[40] Alternative cost data from the CLASICC trial was also explored within the economic model, in sensitivity analysis, and produced similar results to the base-case analysis (Franks, Thames Valley University, 2005). It should be noted that the data from CLASICC are preliminary and may be subject to change. They should therefore be treated with caution. With respect to utilities, data were almost entirely absent and the results presented in terms of incremental cost per QALY presented in Chapter 5 should be treated with extreme caution. This is because data on the potential QALY gain that might be apparent after laparoscopic resection e.g. shorter hospitalisation, earlier return to usual activities and less postoperative pain; are nonexistent making the results with regard to quality of life extremely tenuous. Additional relevant data may soon be available from the UK-based CLASICC trial in which data are being collected on costs and QALYs (based on responses to the EQ 5D). A revised economic analysis based on the best available data on effectiveness from the systematic review should be conducted once data on costs and utilities from CLASICC are available.

The nature of the data available also had an impact on the economic evaluation. Data on survival and disease-free survival were only available for a three year time horizon. In the economic model it was assumed that such data could be extrapolated up to a 25 year time horizon. Having data available for a longer time horizon would greatly strengthen the results of the economic model. An important clinical outcome, not explicitly incorporated into the economic model, is conversion due to lack of useable data. There is very little data on the impact that conversion might have on cost and both short and long term effects. Another area where the paucity of data might have impacted on results is recurrence of disease. The model has not allowed recurrence of disease to be split by type i.e. residual

disease, local recurrence, wound and port-site recurrence. As a result, important differences by type of recurrence, and therefore method of surgical resection, could not be observed. It should be noted, however, that the three year disease-free survival data used within the analysis does suggest no difference in rates though longer term data is needed to substantiate this. A further area in which the data available has been limited is the management of patients following a recurrence. The likelihood that should a recurrence occur, and the likelihood that a re-operation would be performed, could not be differentiated between the two forms of resection. Similarly the likelihood of non-operative management for patients with recurrent disease also could not be differentiated between the two forms of resection. If differences are found to lie in these areas in the future then these costs and consequences will have to be addressed. Finally, the rates of mortality in the economic model were assumed to be constant over time which is unrealistic given the time horizon of the model (25 years). Nonetheless, as the available data suggested no difference in survival at three years the effect of changing mortality rates over time would not be expected to have much effect on relative efficiency. Should longer term data become available that suggests a difference in survival, further work to develop this aspect of the model estimates would be warranted.

9. CONCLUSIONS

9.1 Implications for the NHS

- The use of laparoscopic surgery within the NHS will depend on judgements about the balance between additional cost, shorter recovery and apparently similar long-term effectiveness at three years.
- Laparoscopic surgery costs (approximately £250 to £300 per patient) more than open surgery (the current standard). This higher cost is associated with longer operation times. Furthermore, the additional equipment cost is not fully compensated by the reductions in length of stay.
- Laparoscopic surgery is associated with short-term benefits in terms of less postoperative pain and more rapid recovery.
- Overall and disease-free survival appear to be similar after each type of procedure at three years.
- There is a scarcity of data relating to HALS. The one small RCT identified reports similar outcomes to laparoscopic surgery.
- An enhanced recovery programme offers the possibility of freeing bed days. It also reduces the difference in length of stay between laparoscopic and open surgery and therefore reduces one of the advantages of laparoscopic surgery.
- Should the use of laparoscopic surgery increase, this would require surgeons to become proficient in the technique. Rates of conversion between laparoscopic and open surgery are associated with a 'learning curve'. Appropriate training, such as the preceptorship programme developed by professional organisations, is needed for both patient selection and the technical aspects of the procedure.
- If laparoscopic surgery is to be increased, long-term audit is required for quality assurance purposes.

9.2 Implications for patients and carers

- Laparoscopic surgery is less invasive than open surgery and likely to reduce the recovery period, while providing similar long-term outcomes compared with open surgery.
- Laparoscopic (or open surgery) may be provided in the context of an enhanced recovery programme, which leads to a shorter hospital stay. This is a benefit only if there is no increased burden of care after discharge. There is no evidence to clarify this.

9.3 Implications for research

- Direct measurements of utilities from recovery through to the long term are required to confirm the study findings. These data should become available from the CLASICC Trial.
- Better data on the resources and costs of both laparoscopic and open surgery are required. Again, although data from a preliminary analysis conducted as part of the CLASICC Trial has been used to inform sensitivity analysis, more detailed data should become available when this trial is completed.
- Further long-term follow-up of all RCT cohorts is required.
- Bonjer and colleagues should be encouraged to extend their individual patient data meta-analysis in terms of both follow-up and inclusion of other relevant studies by involving other relevant groups, as has been done for other laparoscopic procedures.
- In other evaluations of laparoscopic surgery, the relative risk of wound related morbidity has played an important part in assessing relative effectiveness and cost-effectiveness. Further data are needed on the risks of outcomes, such as hernias and persisting pain (along with their costs of management and associated effects on utility).
- If HALS is to be adopted widely, methodologically sound RCTs comparing HALS with both laparoscopic and open surgery are necessary.
- Further research is required relating to the alternative surgical approaches for the different location and stages of colon and rectal cancer, taking account of surgical competence.
- Further research is required on the effectiveness and cost-effectiveness of an enhanced recovery programme for both open and laparoscopic surgery compared with conventional open surgery.
- Laparoscopic surgery for colorectal cancer is technically challenging and performance is likely to improve with experience. This issue is important, and further methodologically robust research is warranted.

10 REFERENCES

1 National Institute for Clinical Excellence. *Guidance on the use of laparoscopic surgery for colorectal surgery. Technology appraisal guidance no 17* [document on the Internet]. National Institute for Clinical Excellence [accessed June 2005]. Available from: http://www.nice.org.uk/pdf/guidancelapcolcanc.pdf

2 Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;**350**(20):2050-9.

3 Guillou P.J, Quirke P, Thorpe H, Walker J, Jayne D, Smith AM et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;**365**:1718-26.

4 Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005;**6**(7):477-84.

5 Seeley R, Stephens T, Tate P, editors. *Anatomy and physiology*. 6th ed. Boston, Mass.: McGraw-Hill Education; 2003.

6 Phillips R, editor. *Colorectal surgery*. London: W B Sauders; 1998.

7 Smith JA, King PM, Lane RH, Thompson MR. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. *Br J Surg* 2003;**90**(5):583-92.

8 *Referral guidelines for bowel cancer* [document on the Internet]. Association of Coloproctology of Great Britain & Ireland [accessed June 2005]. Available from:http://www.acpgbi.org.uk/download/GUIDELINES-bowelcancer.pdf

9 *Globocan 2002 database* [website on the Internet]. International Agency for Research on Cancer [accessed April 2005]. Available from: http://www-dep.iarc.fr/

10 Rowan, S., Wood, H., Cooper, N., Quinn, M. *Update to Cancer Trends for England & Wales 1950-1999* [document on the Internet]. National Cancer Intelligence Centre, UK Office for National Statistics [accessed June 2005]. Available from: http://www.statistics.gov.uk/downloads/theme_health/CancerTrendsUpdates.pdf

11 Card T, Logan R. Colorectal cancer: prevention and early diagnosis. *Medicine* 2003;**31**(2):60-4.

12 Wanebo HJ, editor. *Colorectal cancer*. St Louis: Mosby; 1993.

13 *Hospital episode statistics* [website on the Internet]. NHS Health and Social Care Information Centre [accessed June 2005]. Available from:http://www.hesonline.nhs.uk/Ease/servlet/DynamicPageBuild?siteID=1802&categoryID=192&callingCatID=325

14 Sanderson H, Walker A, Young D. *Colorectal cancer*. In: Stevens A, Raferty J, Mant J, Simpson S, editors. Health care needs assessment: the epidemiologically based needs assessment reviews. Oxford: Radcliffe Publishing; 2004. p. 449-502.

15 *Mortality statistics: general. Review of the Registrar General on deaths in England and Wales 2002* [document on the Internet]. National Statistics, UK Office of National Statistics [accessed June 2005]. Available from: http://www.statistics.gov.uk/downloads/theme_health/DH1_35_2002/DH1no35.pdf

16 *Bowel (colorectal) cancer* [website on the Internet]. Cancer Research UK [accessed April 2005]. Available from: http://info.cancerresearchuk.org/cancerstats/types/bowel/?a=5441

17 Fitzpatrick, D. A. and Gavin, A. T. *Survival of cancer patients in Northern Ireland 1993-1996* [document on the Internet]. Northern Ireland Cancer Registry, Belfast [accessed June 2005]. Available from : http://www.qub.ac.uk/nicr/pdf/survivalreport/colorectal.pdf

18 Sprangers MA, Taal BG, Aaronson NK, te VA. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. *Dis Colon Rectum* 1995;**38**(4):361-9.

19 Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. *J Clin Oncol* 2004;**22**(23):4829-36.

20 Rauch P, Miny J, Conroy T, Neyton L, Guillemin F. Quality of life among disease-free survivors of rectal cancer. *J Clin Oncol* 2004;**22**(2):354-60.

21 Vardulaki, K. A., Bennett-Lloyd, B. D., Parfitt, J., Normond, C., Paisley, S., Darzi, A. et al. *A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer* [document on the Internet]. National Institute for Clincial Excellence [accessed June 2005]. Available from: http://www.nice.org.uk/pdf/HTAreportonlapsurgcoloreccanc.pdf

22 Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002;**359**(9325):2224-9.

23 Chapman A, deNichilo D, Babidge W, Maddern G, Hewett P, Levitt M et al. *Systematic review of laparoscopic-assisted resection of colorectal malignancies. ASERNIP-S Report No 8.* Adelaide, South Australia: ASERNIP-S; 2000.

24 Sgambati SA, Ballantyne GH. *Minimally invasive surgery for diseases of the colon & rectum: the legacy of an ancient tradition.* In: Jager RM, Wexner S, editors. Laparoscopic colorectal surgery. New York: Churchill Livingstone; 1996. p. 13-23.

25 Fazio VW, Lopez-Kostner F. Role of laparoscopic surgery for treatment of early colorectal carcinoma. *World J Surg* 2000;**24**(9):1056-60.

26 Romanelli JR, Kelly JJ, Litwin DE. Hand-assisted laparoscopic surgery in the United States: an overview. *Semin Laparosc Surg* 2001;**8**(2):96-103.

27 Darzi A. Hand-assisted laparoscopic colorectal surgery. *Semin Laparosc Surg* 2001;**8**(2):153-60.

28 Litwin DEM, Darzi A, Jakimowicz J, Kelly JJ, Arvidsson D, Hansen P et al. Hand-assisted laparoscopic surgery (HALS) with the handport system: Initial experience with 68 patients. *Ann Surg* 2000;**231**(5):715-23.

29 Veldkamp R, Gholghesaei M, Bonjer HJ, Meijer DW, Buunen M, Jeekel J et al. Laparoscopic resection of colon cancer: consensus of the European Association of Endoscopic Surgery (EAES). *Surg Endosc* 2004;**18**(8):1163-85.

30 Shah PR, Joseph A, Haray PN. Laparoscopic colorectal surgery: learning curve and training implications. *Postgrad Med J* 2005;**1**:527-40.

31 Dulucq, J. L., Wuntringer, P, Stabilini, C. *Laparoscopic rectal resection with anal sphincter preservation for rectal cancer: long-term outcome.* Surg Endosc [serial on the Internet] 12th October 2005, DOI:10.1007/s00464-005-0081-1. Available from: http://www.springerlink.com/

32 D'Annibale A, Morpurgo E, Fiscon V, Trevisan P, Sovernigo G, Orsini C et al. Robotic and laparoscopic surgery for treatment of colorectal diseases. *Dis Colon Rectum* 2004;**47**(12):2162-8.

33 Koh DC, Wong KS, Sim R, Ng YP, Hu ZQ, Cheong DM et al. Laparoscopic-assisted colon and rectal surgery - lessons learnt from early experience. *Ann Acad Med Singapore* 2005;**34**(3):223-8.

34 Schoetz DJ, Jr., Bockler M, Rosenblatt MS, Malhotra S, Roberts PL, Murray JJ et al. "Ideal" length of stay after colectomy: whose ideal? *Dis Colon Rectum* 1997;**40**(7):806-10.

35 Sokolovic E, Buchmann P, Schlomowitsch F, Szues TD. Comparison of resource utilization and long-term quality-of- life outcomes between laparoscopic and conventional colorectal surgery. *Surg Endosc* 2004;**18**(11):1663-7.

36 Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH. 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery. *Br J Surg* 2001;**88**(11):1533-8.

37 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutrit* 2005;**24**(3):466-77.

38 Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum* 2004;**47**(3):271-7.

39 Basse L, Raskov HH, Hjort JD, Sonne E, Billesbolle P, Hendel HW et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* 2002;**89**(4):446-53.

40 King PM. Open versus laparoscopic surgery for colorectal cancer: a randomised study embedded within an enhanced recovery programme. *Br J Surg* In press 2005.

41 Sheldon TA, Cullum N, Dawson D, Lankshear A, Lowson K, Watt I et al. What's the evidence that NICE guidance has been implemented? Results from a national evaluation using time series analysis, audit of patients' notes, and interviews. *BMJ* 2004;**329**(7473):999.

42 Harinath G, Shah PR, Haray PN, Foster ME. Laparoscopic colorectal surgery in Great Britain and Ireland - Where are we now? *Colorectal Dis* 2005;**7**(1):86-9.

43 Oxman AD, Guyatt GH. The science of reviewing research. *Ann NY Acad Sci* 1993;**703**:125-33.

44 Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. *JAMA* 1994;**272**(17):1367-71.

45 Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**(12):1235-41.

46 Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Systematic reviews of trials and other studies. *Health Technol Assess* 1998;**2**(19):1-276.

47 Araujo SE, da Silva eSousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP et al. Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. *Rev Hosp Clin Fac Med Sao Paulo* 2003;**58**(3):133-40.

48 Curet MJ, Putrakul K, Pitcher DE, Josloff RK, Zucker KA. Laparoscopically assisted colon resection for colon carcinoma: perioperative results and long-term outcome. *Surg Endosc* 2000;**14**(11):1062-6.

49 Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M. Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. *Surg Endosc* 2003;**17**(4):636-40.

50 Hewitt PM, Ip SM, Kwok SP, Somers SS, Li K, Leung KL et al. Laparoscopic-assisted vs. open surgery for colorectal cancer: comparative study of immune effects. *Dis Colon Rectum* 1998;**41**(7):901-9.

51 Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW, Jr. Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. *J Laparoendosc Adv Surg Tech A* 2004;**14**(6):329-34.

52 Kim SH, Milsom JW, Gramlich TL, Toddy SM, Shore GI, Okuda J et al. Does laparoscopic vs. conventional surgery increase exfoliated cancer cells in the peritoneal cavity during resection of colorectal cancer? *Dis Colon Rectum* 1998;**41**(8):971-8.

53 Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS et al. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. *Lancet* 2004;**363**(9416):1187-92.

54 Milsom JW, Bohm B, Hammerhofer KA, Fazio V, Steiger E, Elson P. A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. *J Am Coll Surg* 1998;**187**(1):46-54.

55 Neudecker J, Junghans T, Ziemer S, Raue W, Schwenk W. Prospective randomized trial to determine the influence of laparoscopic and conventional colorectal resection on intravasal fibrinolytic capacity. *Surg Endosc* 2003;**17**(1):73-7.

56 Schwenk W, Bohm B, Haase O, Junghans T, Muller JM. Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* 1998;**383**(1):49-55.

57 Stage JG, Schulze S, Moller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB et al. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg* 1997;**84**(3):391-6.

58 Tang C-L, Eu K-W, Tai B-C, Soh JGS, MacHin D, Seow-Choen F. Randomized clinical trial of the effect of open versus laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer. *Br J Surg* 2001;**88**(6):801-7.

59 Vignali A, Braga M, Zuliani W, Frasson M, Radaelli G, Di C, V. Laparoscopic colorectal surgery modifies risk factors for postoperative morbidity. *Dis Colon Rectum* 2004;**47**(10):1686-93.

60 Zhou ZG, Hu M, Li Y, Lei WZ, Yu YY, Cheng Z et al. Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer. *Surg Endosc* 2004;**18**(8):1211-5.

61 Bohm B, Junghans T, Neudecker J, Schwenk W. Hepatic and renal function following laparoscopic and conventionell resection of colorectal cancer - Results from a prospective randomized trial. *Viszeralchirurgie* 1999;**34**(1):20-4.

62 Braga M, Vignali A, Gianotti L, Zuliani W, Radaelli G, Gruarin P et al. Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. *Ann Surg* 2002;**236**(6):759-66.

63 Delgado S, Lacy AM, Valdecasas JCG, Balague C, Pera M, Salvador L et al. Could age be an indication for laparoscopic colectomy in colorectal cancer? *Surg Endosc* 2000;**14**(1):22-6.

64 Delgado S, Lacy AM, Filella X, Castells A, Garcia-Valdecasas JC, Pique JM et al. Acute phase response in laparoscopic and open colectomy in colon cancer: randomized study. *Dis Colon Rectum* 2001;**44**(5):638-46.

65 Hasegawa H, Watanabe M, Kabeshima Y, Yamamoto S, Kitajima M. Short-term results of a randomised controlled trial of laparoscopic vs. open colectomy for colorectal cancer. *Colorectal Dis* 2001;**3**(1 Suppl 1):8.

66 Janson M, Bjorholt I, Carlsson P, Haglind E, Henriksson M, Lindholm E et al. Randomized clinical trial of the costs of open and laparoscopic surgery for colonic cancer. *Br J Surg* 2004;**91**(4):409-17.

67 Lacy A. Laparoscopic assisted colectomy (LAC) for colon cancer: results of a randomized controlled trial. *Gastroenterology* 2001;**120**(5 Suppl 1):A35.

68 Lacy AM, Garcia-Valdecasas JC, Pique JM, Delgado S, Campo E, Bordas JM et al. Short-term outcome analysis of a randomized study comparing laparoscopic vs open colectomy for colon cancer. *Surg Endosc* 1995;**9**(10):1101-5.

69 Lacy AM, Delgado S, Garcia-Valdecasas JC, Castells A, Pique JM, Grande L et al. Port site metastases and recurrence after laparoscopic colectomy. A randomized trial. *Surg Endosc* 1998;**12**(8):1039-42.

70 Lacy AM, Garcia-Valdecasas JC, Delgado S, Fanelli RD. Laparoscopic-assisted colectomy is associated with a disease-free survival advantage for patients with advanced stage nonmetastatic colon cancer. *Evid-based Gastroenterol* 2002;**3**(3):96-8.

71 Leung KL. Systemic cytokine response after laparoscopic-assisted resection of rectosigmoid carcinoma. *Ann Surg* 2000;**231**(4):506-11.

72 Leung KL, Tsang KS, Ng MH, Leung KJ, Lai PB, Lee JF et al. Lymphocyte subsets and natural killer cell cytotoxicity after laparoscopically assisted resection of rectosigmoid carcinoma. *Surg Endosc* 2003;**17**(8):1305-10.

73 Nelson H. Laparoscopic colectomy for colon cancer--a trial update. *Swiss Surg* 2001;**7**(6):248-51.

74 Nelson H. Laparoscopically assisted colectomy is as safe and effective as open colectomy in people with colon cancer. *Cancer Treat Rev* 2004;**30**(8):707-9.

75 Neudecker J, Junghans T, Ziemer S, Raue W, Schwenk W. Effect of laparoscopic and conventional colorectal resection on peritoneal fibrinolytic capacity: A prospective randomized clinical trial. *Int J Colorectal Dis* 2002;**17**(6):426-9.

76 Ordemann J, Jacobi CA, Schwenk W, Stosslein R, Muller JM. Cellular and humoral inflammatory response after laparoscopic and conventional colorectal resections: Results of a prospective randomized trial. *Surg Endosc* 2001;**15**(6):600-8.

77 Schwenk W, Bohm B, Muller JM. Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial. *Surg Endosc* 1998;**12**(9):1131-6.

78 Schwenk W, Bohm B, Muller JM. Influence of laparoscopic or conventional colorectal resection on postoperative quality of life. *Zentralbl Chir* 1998;**123**(5):483-90.

79 Schwenk W, Bohm B, Witt C, Junghans T, Grundel K, Muller JM. Pulmonary function following laparoscopic or conventional colorectal resection: a randomized controlled evaluation. *Arch Surg* 1999;**134**(1):6-12.

80 Schwenk W. Inflammatory response after laparoscopic and conventional colorectal resections - results of a prospective randomized trial. *Langenbecks Arch Surg* 2000;**385**(1):2-9.

81 Stocchi L, Nelson H, Sargent D, Larson D, Fleshman J, Stryker S et al. Morbidity following laparoscopic-assisted vs. open colectomy: Results from a multicenter prospective randomized trial. *Dis Colon Rectum* 2005;**48**(3):636-7.

82 Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G, Clinical Outcomes of Surgical Therapy (COST) Study Group. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* 2002;**287**(3):321-8.

83 Winslow ER, Fleshman JW, Birnbaum EH, Brunt LM. Wound complications of laparoscopic vs open colectomy. *Surg Endosc* 2002;**16**(10):1420-5.

84 Wu FP. Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients. *Dis Colon Rectum* 2003;**46**(2):147-55.

85 Wu FP, Hoekman K, Sietses C, von Blomberg BM, Meijer S, Bonjer HJ et al. Systemic and peritoneal angiogenic response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. *Dis Colon Rectum* 2004;**47**(10):1670-4.

86 Young-Fadok TM, Sargent DJ, Nelson H, Fleshman JW. Conversion does not adversely affect oncologic outcomes after laparoscopic colectomy for colon cancer: Results from a multicenter prospective randomized trial. *Dis Colon Rectum* 2005;**48**(3):637-8.

87 Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. *Br J Surg* 2005;**92**:1124-32.

88 Sjoerdsma W, Meijer DW, Jansen A, den Boer KT, Grimbergen CA. Comparison of efficiencies of three techniques for colon surgery. *J Laparoendosc Adv Surg Tech A* 2000;**10**(1):47-53.

89 Quah HM, Jayne DG, Eu KW, Seow-Choen F. Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer. *Br J Surg* 2002;**89**(12):1551-6.

90 Color Study Group. COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer. *Dig Surg* 2000;**17**(6):617-22.

91 Hazebroek EJ, Color Study Group. COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer. *Surg Endosc* 2002;**16**(6):949-53.

92 Figueredo A, Rumble RB, Maroun J, Earle CC, Cummings B, McLeod R et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. *Bmc Cancer* 2003;**3**(1):26, Oct 6.

93 Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent - the GILDA trial. *Surg Oncol* 2004;**13**(2-3):119-24.

94 Liang JT, Lai HS, Huang KC, Chang KJ, Shieh MJ, Jeng YM et al. Comparison of medial-to-lateral versus traditional lateral-to-medial laparoscopic dissection sequences for resection of rectosigmoid cancers: randomized controlled clinical trial. *World J Surg* 2003;**27**(2):190-6.

95 Hand-assisted laparoscopic surgery vs standard laparoscopic surgery for colorectal disease: a prospective randomized trial. HALS Study Group. *Surg Endosc* 2000;**14**(10):896-901.

96 Basse L, Madsen JL, Billesbolle P, Bardram L, Kehlet H. Gastrointestinal transit after laparoscopic versus open colonic resection. *Surg Endosc* 2003;**17**(12):1919-22.

97 Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Ann Surg* 2005;**241**(3):416-23.

98 Bergamaschi R, Tuech JJ, Cervi C, Arnaud J-P. Re-establish pneumoperitoneum in laparoscopic-assisted sigmoid resection? Randomized trial. *Dis Colon Rectum* 2000;**43**(6):771-4.

99 Braga M, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C et al. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. *Dis Colon Rectum* 2002;**45**(8):1070-7.

100 Braga M, Vignali A, Frasson M, Zuliani W, Civelli V, Di Carlo V. Laparoscopic vs open colectomy: Postoperative morbidity, long- term complications and quality of life in randomized trial. *Dis Colon Rectum* 2005;**48**(3):636.

101 Kang JC, Jao SW. Hand-assisted laparoscopic colectomy versus open colectomy: A prospective, randomized study. *Dis Colon Rectum* 2004;**47**(6):1019.

102 Kang JC, Chung MH, Chao PC, Yeh CC, Hsiao CW, Lee TY et al. Hand-assisted laparoscopic colectomy vs open colectomy: a prospective randomized study. *Surg Endosc 18(4):577-81,* 2004;**18**(4):577-81.

103 Liang JT, Shieh MJ, Chen CN, Cheng YM, Chang KJ, Wang SM. Prospective evaluation of laparoscopy-assisted colectomy versus laparotomy with resection for management of complex polyps of the sigmoid colon. *World J Surg* 2002;**26**(3):377-83.

104 Targarona EM, Gracia E, Garriga J, Martinez-Bru C, Cortes M, Boluda R et al. Prospective randomized trial comparing conventional laparoscopic colectomy with hand-assisted laparoscopic colectomy: applicability, immediate clinical outcome, inflammatory response, and cost. *Surg Endosc* 2002;**16**(2):234-9.

105 *Improving access to cost-effectiveness information for health care decision making: the NHS Economic Evaluation Database. CRD Report No 6.* 2nd ed. York: NHS Centre for Reviews & Dissemination; 2001.

106 Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;**44**(11):1271-8.

107 Mulrow CD, Cook DJ. *Systematic review: synthesis of best evidence for healthcare.* Philadelphia,PA: American College of Physicians; 1998.

108 Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. *JAMA* 2002;**287**(21):2809-12.

109 Zheng MH, Feng B, Lu AG, Li JW, Wang ML, Mao ZH et al. Laparoscopic versus open right hemicolectomy with curative intent for colon carcinoma. *World J Gastroenterol* 2005;**11**(3):323-6.

110 Delaney CP, Kiran RP, Senagore AJ, Brady K, Fazio VW. Case-matched comparison of clinical and financial outcome after laparoscopic or open colorectal surgery. *Ann Surg* 2003;**238**(1):67-72.

111 Gibson M, Byrd C, Pierce C, Wright F, Norwood W, Gibson T et al. Laparoscopic colon resections: a five-year retrospective review. *Am Surg* 2000;**66**(3):245-8.

112 *Hospital episode statistics* [database on the Internet]. UK Department of Health [accessed August 2005]. Available from:URL: http://www.dh.gov.uk/PublicationsAndStatistics/Statistics/HospitalEpisodeStatistics/fs/en

113 Mulrow CD. *Rationale for systematic reviews.* In: Chalmers I, Alvarez G, editors. Systematic reviews. London: BMJ Publishing Group; 1995.

114 Benoist S, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. *Br J Surg* 2005;**92**(9):1155-60.

115 Iversen GR. *Bayesian statistical inference.* Thousand Oaks, CA: Sage Publications; 1984.

116 *NHS reference costs* [database on the Internet]. UK Department of Health [accessed August 2005]. Available from: http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en

117 *Management of colorectal cancer. SIGN publication no 67.* Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2003.

118 *Cost Effectiveness Analysis (CEA) Registry* [database on the Internet]. Harvard School of Public Health [accessed August 2005]. Available from: http://www.hsph.harvard.edu/cearegistry

119 Norum J, Vonen B, Olsen JA, Revhaug A. Adjuvant chemotherapy (5-fluorouracil and levamisole) in Dukes' B and C colorectal carcinoma. A cost-effectiveness analysis. *Ann Oncol* 1997;**8**(1):65-70.

120 Van Hout B, Al M, Gordon G. Costs, effects and C/E ratios alongside a clinical trial. *Health Econ* 1994;**3**(5):309-19.

121 Petrou S, Campbell N. Stabilisation in colorectal cancer. *Int J Palliat Nurs* 1997;**3**(5):275-80.

122 Pandor, A, Eggington, S, Paisley, S, Tappenden, P, Sutcliffe, P. *The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer* [document on the Internet]. National Institute for Health and Clinical Excellence [accessed October 2005]. Available at: http://www.nice.org.uk/pdf/Assessment_Report_(CiC_removed).pdf

123 MRC Laparoscopic Groin Hernia Trial Group. Cost-utility analysis of open versus laparoscopic groin hernia repair: results from a multicentre randomized clinical trial. *Br J Surg* 2001;**88**(5):653-61.

124 McCormack K, Wake B, Perez J, Fraser.C., Cook J, McIntosh E et al. Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation. *Health Technol Assess* 2005;**9**(14):1-218.

125 Shepperd S, Iliffe S. Hospital at home versus in-patient hospital care. *The Cochrane Database of Systematic Reviews* 2005;Issue 3. Art. No.: CD000356. DOI: 10.1002/14651858.CD000356.pub2.

126 Scott A, Vale L. Increased general practice workload due to a primary care led National Health Service: The need for evidence to support rhetoric. *Br J Gen Pract* 1998;**48**(428):1085-8.

127 Patankar SK, Larach SW, Ferrara A, Williamson PR, Gallagher JT, DeJesus S et al. Prospective comparison of laparoscopic vs. open resections for colorectal adenocarcinoma over a ten-year period. *Dis Colon Rectum* 2003;**46**(5):601-11.

128 Champault GG, Barrat C, Raselli R, Elizalde A, Catheline JM. Laparoscopic versus open surgery for colorectal carcinoma: a prospective clinical trial involving 157 cases with a mean follow-up of 5 years. *Surg Laparosc Endosc Percutan Tech* 2002;**12**(2):88-95.

129 *British National Formulary* [publication on the Internet]. British Medical Association/Royal Pharmaceutical Society of Great Britain [accessed March 2005]. Available from: http://www.bnf.org/bnf/