Health Technology Assessment 2006; Vol. 10: No. 45

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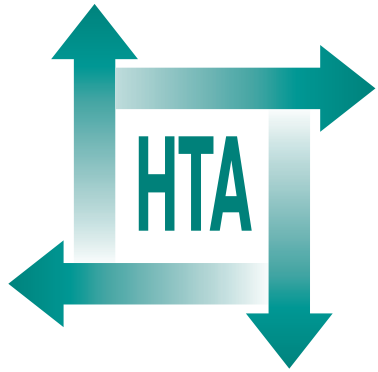
November 2006

Health Technology Assessment
NHS R&D HTA Programme



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Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation

A Murray,[1*] T Lourenco,[1] R de Verteuil,[1,2] R Hernandez,[2] C Fraser,[1] A McKinley,[3] Z Krukowski,[3] L Vale[1,2] and A Grant[1]

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Declared competing interests of authors: Z Krukowski received a travel grant from Autosuture (Tyco Healthcare) and the Royal College of Surgeons approximately 10 years ago. In the last 2 years he has advised Ethicon Endo-Surgery, Tyco Healthcare and Karl Storz Endoscopy (UK) Ltd on the development of new laparoscopic equipment. He 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. A McKinley was awarded a training fellowship from Ethicon Endo-Surgery in 2005. The fellowship covered travel and accommodation expenses for two trips to Hamburg. One trip was for a 2-day international laparoscopic colorectal meeting. The other was for a short visit ($2^1/_2$ days) to operate in the wet laboratory there, a facility not available in the UK. The clinical department of both Z Krukowski and A McKinley use, among others, Ethicon Endo-Surgery, Tyco Healthcare, KeyMed (Medical & Industrial Equipment) Ltd and Richard Wolf UK Ltd equipment for both open and laparoscopic procedures. A Grant attended a single meeting organised by Ethicon Endo-Surgery in 2003 to discuss possibilities for meta-analysis of trials of laparoscopic surgery for colorectal cancer. 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 Endo-Surgery.

Published November 2006

This report should be referenced as follows:

Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2006;**10**(45).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/44/01. The protocol was agreed in May 2005. The assessment report began editorial review in May 2006 and was accepted for publication in June 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

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Abstract

Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation

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Objective: The aim of this study was 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.

Data sources: Electronic databases were searched from 2000 to May 2005. A review of economic evaluations was undertaken by the National Institute for Health and Clinical Excellence in 2001. This review was updated from 2000 until July 2005.

Review methods: Data from selected studies were extracted and assessed. Dichotomous outcome data from individual trials were combined using the relative risk method and continuous outcomes were combined using the Mantel–Haenszel weighted mean difference method. Summaries of the results from individual patient data (IPD) meta-analyses were also presented. An economic evaluation was also carried out using a Markov model incorporating the data from the systematic review. The results were first presented as a balance sheet for comparison of the surgical techniques. It was then used to estimate cost-effectiveness measured in terms of incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) for a time horizon up to 25 years.

Results: Forty-six reports on 20 studies [19 randomised controlled trials (RCTs) and one IPD 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, with 10 having less than 100 participants. The total numbers of trial participants who underwent laparoscopic or open surgery were 2429 and 2139, respectively. 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. 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 was found to be more costly and no more effective than open surgery. With respect to incremental cost per QALY, few data were available to differentiate between laparoscopic and open surgery. The results of the base-case analysis indicate that there is an approximately 40% chance that laparoscopic surgery is the more cost-effective intervention at a threshold willingness to pay for a QALY of £30,000. A second analysis assuming equal mortality and disease-free survival found that there was an approximately 50% likelihood at a similar threshold value. Broadly similar results were found in the sensitivity analyses. A threshold analysis was performed to investigate the magnitude of QALY gain associated with quicker recovery following laparoscopic surgery required to provide an incremental cost per QALY of £30,000. The implied number of additional QALYs required would be 0.009–0.010 compared with open surgery.

Conclusions: Laparoscopic resection is associated with a quicker recovery (shorter time to return to usual activities and length of hospitalisation) and no evidence of a difference in mortality or disease-free survival up to 3 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 in terms of both patient selection and performing the technique. 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. In terms of relative cost-effectiveness, 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 3 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 long-term follow-up of the RCT cohorts would be very useful further research and ideally these data should be incorporated into a wider IPD meta-analysis. Data on the long-term complications of surgery such as incisional hernias and differences in outcomes such as persisting pain would also be valuable. Once available, further data on both costs and utilities 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. Research relating to the effect of experience on performance is also required.

Contents

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	COlon cancer Laparoscopic or Open Resection Study Group
COST	Clinical Outcomes of Surgical Therapy Study Group
CT	computed tomography
EORTC QLQ-3D	European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire
HALS	hand-assisted laparoscopic surgery
HRG	Health Care Resource Group
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
IQR	interquartile range
NICE	National Institute for Health and Clinical Excellence
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
TNM	tumour, lymphatic nodes metastasis
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Previous guidance from the National Institute for Health and Clinical Excellence (NICE) 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.

Objective of the study

The aim of this study was 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 allowed, possible differential effects were explored within a number of subgroups. The subgroups relate to the location of the cancer, the stage of the cancer and age at diagnosis.

Description of proposed service

In laparoscopic surgery, ports are inserted through which the laparoscopic instruments are manipulated. In practical terms, a totally laparoscopic procedure and a laparoscopically assisted procedure are considered comparable because of the size of incisions involved and hereafter are jointly described as laparoscopic surgery. In 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. 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 primary resection of tumours. However, there is significant morbidity associated with this procedure. Laparoscopic surgery is less invasive and may lead to more rapid recovery. 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 reduced tissues trauma 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 operation length, the cost of materials and the effect of surgeon experience on patient outcomes.

This review assesses the clinical effectiveness and cost-effectiveness of laparoscopic surgery 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 possible differential effects within predefined subgroups relating to the location of the cancer, the stage of the cancer and age at diagnosis were explored, although limited data were available.

Methods

Effectiveness

Electronic searches were undertaken from 2000 to May 2005 to identify published and unpublished trials of laparoscopic compared with open surgery for colorectal cancer. Systematic reviews and other evidence-based reports were identified and their lists of references searched. Selected conference proceedings were searched.

All RCTs and quasi-RCTs were eligible for inclusion if they compared laparoscopic surgery or HALS with open surgery for colorectal cancer. Also eligible were individual patient data (IPD) meta-analyses of such studies, where they provided additional data.

Two reviewers independently extracted data and assessed study quality. Dichotomous outcome data from individual trials were combined using the relative risk method and continuous outcomes

were combined using the Mantel–Haenszel weighted mean difference method. Summaries of the results from IPD meta-analyses were also presented.

Cost-effectiveness

A review of economic evaluations was undertaken by NICE in 2001. This review was updated from 2000 until July 2005. Quality assessment and data abstraction were conducted according to the guidelines for reviewers for the NHS Economic Evaluation Database.

An economic evaluation was also carried out using a Markov model incorporating the data from the systematic review. This model was first used to present a balance sheet for comparison of the surgical techniques. It was then used to estimate cost-effectiveness measured in terms of incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) for a time horizon up to 25 years.

Results

Number and quality of studies

In total, 46 reports on 20 studies (19 RCTs and one IPD 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, with 10 having less than 100 participants. The total numbers of trial participants who underwent laparoscopic or open surgery were 2429 and 2139, respectively.

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. 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 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 appeared more costly and no more effective than open surgery. With respect to incremental cost per QALY, few data were available to differentiate between laparoscopic and open surgery. The results of the base-case analysis indicate that there is an approximately 40% chance that laparoscopic surgery is the more cost-effective intervention at a threshold willingness to pay for a QALY of £30,000. A second analysis assuming equal mortality and disease-free survival found that there was an approximately 50% likelihood at a similar threshold value.

Sensitivity analyses

Broadly similar results were found in the sensitivity analyses. A threshold analysis was performed to investigate the magnitude of QALY gain associated with quicker recovery following laparoscopic surgery required to provide an incremental cost per QALY of £30,000. The implied number of additional QALYs required would be 0.009–0.010 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 3-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 and the data used to estimate QALYs were highly suspect. The UK-based multicentre Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial is due to report its economic evaluation soon and a draft version of a cost analysis conducted alongside the CLASICC trial was incorporated within the economic model as sensitivity analysis. The results of this analysis are not contained in this report as the data were supplied in confidence. Nevertheless, it is expected that this study will provide additional data on costs and will provide utility scores relevant to the UK.

Conclusions

Summary of benefits

Laparoscopic resection is associated with a quicker recovery (shorter time to return to usual activities

and length of hospitalisation) and no evidence of a difference in mortality or disease-free survival up to 3 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 in terms of both patient selection and 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

In terms of relative cost-effectiveness, 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 3 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.

Other important issues regarding implications

Should the use of laparoscopic surgery be increased from its current level of 0.1% 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. Owing 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 may not lead to reduced total costs to the NHS.

Notes on the generalisability of the findings

The 19 trials were conducted in a wide range of settings but data relating to the subgroups were limited. With respect to the 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 were available from the IPD meta-analysis identified as part of the review, this study only reported data from four RCTs for up to 3 years. The long-term follow-up of the RCT cohorts would be very useful and ideally these data should be incorporated into a wider IPD meta-analysis.

Few data were available on the long-term complications of surgery such as incisional hernias. Given the apparent similarity between the procedures in survival and disease-free survival, attention might be given to identifying differences in 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.

Chapter 1

Aim of the review

Previous guidance from the National Institute for Health and Clinical Excellence (NICE) on the use of laparoscopic surgery for colorectal cancer was that open rather than laparoscopic surgery was 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). This meta-analysis included data describing 1536 participants with follow-up for death and disease-free survival for 3 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.

Chapter 2
Background

Description of underlying health problem

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 1.5–1.8 m long and consists of four parts: the ascending, transverse, descending and 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 1* provides further details of the mode of presentation.

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% whereas incidence has increased slowly (*Figure 1*).

The overall incidence of colorectal cancer is higher in men than in women (*Figure 2*). In the UK, the male to female ratios for colonic and rectal cancer are 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]

The mean age at diagnosis for colorectal cancer in the UK is 65 years.[13] As *Figure 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* gives further details specific for England, Scotland, Wales and Northern Ireland.

A small subgroup of colorectal cancer is caused by inherited predisposition; however, it is estimated that over 75% of cases arise 'sporadically' (*Figure 3*). Diet, including over-nutrition, high meat and fat consumption, deficiencies in

TABLE 1 *Modes of presentation of patients with colorectal cancer*[8]

Mode of presentation[a]	Proportion of all patients with colorectal cancer (%)
Common modes of presentation of patients with established cancer	
Rectal bleeding associated with a change in bowel habit	35
Abdominal or rectal mass	30
Iron deficiency anaemia below 100 g/l	30
Intestinal obstruction	20
Change in bowel habit as a single symptom	10
Uncommon symptomatic presentations of patients with 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] A patient can present with more than one symptom.

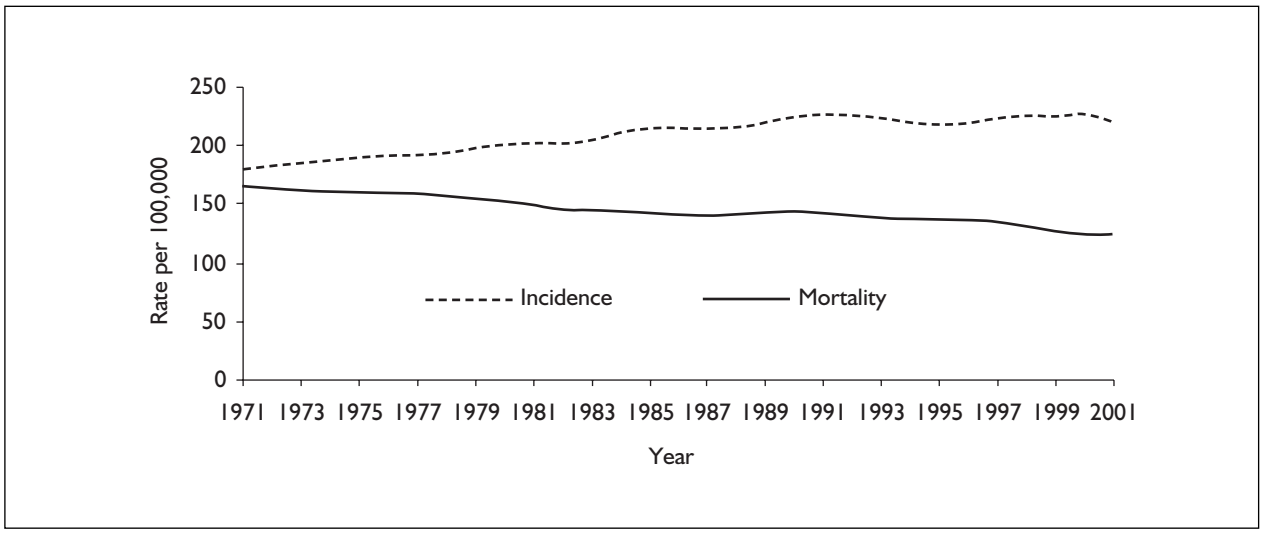

FIGURE 1 *Incidence and mortality rates over time in England and Wales, 1971–2001 (data specific to males only)*[10]

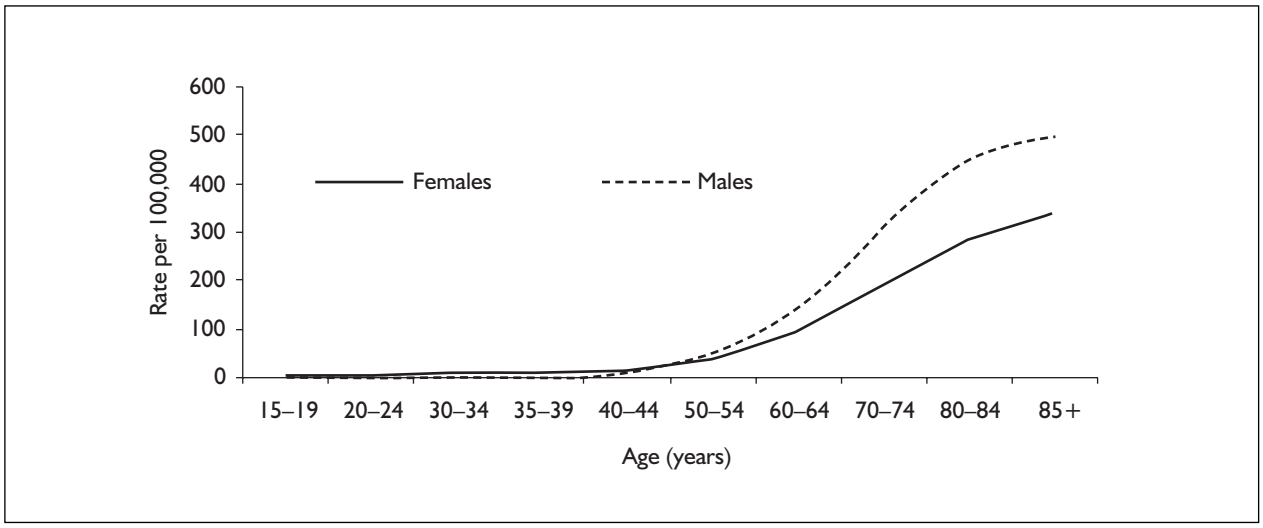

FIGURE 2 *Frequency distribution of new cases by age group, England and Wales, 2001*[10]

TABLE 2 *Death rates per 100,000 population for colorectal cancer in 2002 for England, Wales, Scotland and Northern Ireland*[15]

	Age (years)					
	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

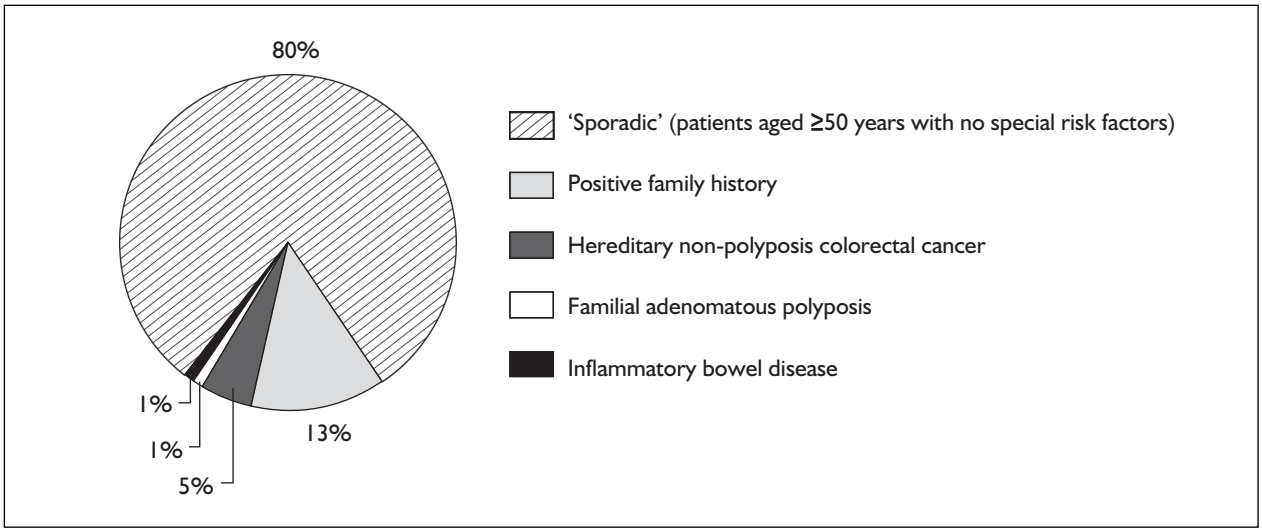

FIGURE 3 *Risk factors associated with new cases of colorectal cancer*[11]

vegetables, key minerals and vitamins, is a major risk factor.[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 submucosa 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] (TNM: classification of malignant tumours, where T stands for tumour, N for lymphatic nodes and M for metastasis).

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 3–6 months after surgery.[20]

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 are performed as elective procedures. However, up to 30% of primary resections present as an emergency (*Table 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 and 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, intra- 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

TABLE 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)[a]
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
1999–2000	32,725	29.0	50.0	65.5	32	17.1
1998–99	32,580	24.8	50.0	66	33	17.0

[a] Over this period, the median length of hospital stay has remained at 13 and 14 days for colon and rectal cancer, respectively.

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 a 5-cm distal longitudinal margin. Whenever possible, this is followed by anastomosis, suturing or stapling the proximal colon to the rectum/anus.

According to the 2003–4 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 periods surveyed, there was a relative decrease in the number of primary resections performed (*Table 3*).[13]

Description of new intervention

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 procedure and a laparoscopically assisted procedure are considered comparable because of the size of incisions involved. Hand-assisted laparoscopic surgery (HALS) is a different concept and is discussed 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.

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 this report laparoscopic and laparoscopically assisted surgery are collectively called laparoscopic surgery.

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]

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 and the study has not considered a subgroup analysis for the comparison of alternative forms of resection in patients presenting as emergencies.

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.

Personnel involved

The number of staff employed in laparoscopic operations is usually similar to that 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 (30–50) are required for the surgeon to obtain proficiency.[29]

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 to be 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 programme' 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 programme is characterised by a highly scripted pre- 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 2 hours on the day of surgery and for 6 hours each day from then on.[37]

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.

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 UK (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.

Expected costs

The current use of laparoscopic colorectal surgery is low but there is the potential for its use to increase dramatically. The expected costs of adopting laparoscopic surgery based on different degrees of diffusion are illustrated in *Table 4*. The total direct costs to the NHS are based on mean costs 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 3*.

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. First, the costs of both

TABLE 4 *Cost of surgery for colorectal cancer*

Proportion 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	1238.1
20.0	185.2	1653.6
25.0	185.6	2069.0

laparoscopic and open surgery are not known precisely. Second, the calculations have assumed a fixed operation cost and therefore 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.

Chapter 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 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 in addition to 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.

Methods for reviewing effectiveness

Search strategy

Electronic searches were undertaken to identify published and unpublished reports of RCTs and systematic reviews evaluating the effectiveness of laparoscopic surgery and HALs 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 Week 1, 2005), EMBASE (2000–Week 19, 2005), BIOSIS (2000–May 2005), Science Citation Index (2000–27 May 2005), MEDLINE Extra (11 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.

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 with open surgery for colorectal cancer. UK registries, providing data for a minimum of 3 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 3 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. Other subgroups, such as gender or grade of cancer, might have been considered. In the former case it was not expected that gender would greatly influence the results and in the latter case it was not expected that there would be any data.

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
- postoperative 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.

Other outcomes such as postoperative bowel recovery were also considered. However, they were not included as outcomes as they were felt to be surrogates for length of stay and postoperative recovery.

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. With respect to outcomes data, the authors' definitions of outcomes were used. Such definitions may vary between included studies but would be consistent within studies and hence would still be useful when estimating relative effect sizes.

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 nine-item checklist (Appendix 4) developed by Oxman and colleagues.[43,44] Primary RCTs were assessed using the Delphi criteria list[45] (Appendix 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. This statistic was used as it was more appropriate for use in the economic model developed in Chapter 5. Continuous outcomes were combined using the inverse variance weighted mean difference (WMD) method; 95% confidence intervals (CIs) and p-values were calculated for the estimates of RR and WMD. All results are reported using a fixed-effects model. χ^2 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.

Owing to the lack of uniformity of the data presented in 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.

Results

Quantity and quality of research available

Number of studies identified

The results of the searches are summarised in *Table 5*. The numbers retrieved from the

TABLE 5 *Search results*

Database	No. retrieved
MEDLINE/EMBASE/MEDLINE Extra multifile search (after deduplication in Ovid)	167
Science Citation Index	14
BIOSIS	3
CENTRAL	70
Journals@Ovid Full Text	35
Health Management Information Consortium	34
Cochrane Database of Systematic Reviews	24
Database of Abstracts of Reviews of Effectiveness	30
HTA database	12
National Research Registry	1
Current Controlled Trials	1
Clinical Trials	10
Selected from conference abstracts	581
Total retrieved	**982**

TABLE 6 *Papers selected for full assessment*

Assessment	No. 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**

TABLE 7 *Included reports*

Source	Primary reports	Secondary reports
Identified from searches (2000–5)	13	20
Pre-2000 (original review)	3	2
Pre-2000 (not in original review)	2	4
Unpublished	2	0
Total	**20**	**26**

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.

A total of 982 reports were identified from the various searches, of which 167 (157 full-text papers and 10 abstracts) were selected for full assessment. *Table 6* details the numbers of these that were included and excluded.

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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005).[40]

Hence, 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 7*. The list of included studies (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal

TABLE 8 *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

communication, 2005)[2–4,22,40,47–60] and associated references[61–86] are listed in Appendix 6.

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 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 10 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 8* 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 (SDs), interquartile ranges or 95% CIs).[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]

The quality assessment scores of the individual patient data meta-analyses are tabulated in Appendix 7 (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). **[Academic-in-confidence information removed.]**

Characteristics of included studies

Appendix 8 provides details of the characteristics of the RCTs, which are summarised in *Table 9*. 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,[50,53] 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 10 fewer than 100. The total number of participants allocated to laparoscopic surgery was 2429 and to open resection 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 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 who 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

TABLE 9 *Summary of the baseline characteristics*

Study ID	Comparators	No. of participants	Age (years)[a]	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[b]	326/301	536/0
	Open	546	71[b]	336/285	546/0
COST, 2004[2]	Laparoscopic	435	70[b]	223/212	435/0
	Open	428	69[b]	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[b]	4/4	8/0
	Open	8	70[b]	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[b]	8/11	19/0
	Open	19	65[b]	10/8	18/0
King, 2006[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[b]	26/29	48/7[c]
	Open	54	69[b]	36/18	50/4[c]
Neudecker, 2003[55]	Laparoscopic	14	62[b]	7/7	14/0
	Open	16	64[b]	10/6	16/0
Schwenk, 1998*a*[56]	Laparoscopic	30	64	14/16	23/7
	Open	30	65	16/14	23/7
Stage, 1997[57]	Laparoscopic	15	72[b]	8/7	15/0
	Open	14	73[b]	5/9	14/0
Tang, 2001[58]	Laparoscopic	118	64[b]	61/57	118/0
	Open	118	62[b]	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

NR, not reported.
[a] Age is given as mean, unless otherwise stated.
[b] Median.
[c] Some colon patients were actually upper rectum.

a specific location and its stage, for each participant group as a whole, and did not report outcomes within each participant group separately. However, 10 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[40] to 72.3 years[60] compared with 44[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 was not 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) included patients from four of the above trials: Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC), the COlon cancer Laparoscopic or Open Resection Study Group (COLOR), the Clinical Outcomes of Surgical Therapy Study Group (COST) and Lacy and colleagues.[2–4,22] **[Academic-in-confidence information removed.]**

Description of surgery received

'Opposite' method initiated

The 'opposite' method to the one to which the patient was randomised was initiated in 46/1173 (3.9%) of those randomised to laparoscopic resections (*Table 10*). Rates varied between the trials that reported this information. **[Academic-in-confidence information removed.]**

Number of ports

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 11*). **[Academic-in-confidence information removed.]**

Surgeon prior experience

Ten of the RCTs reported that surgeons performing the procedures were experienced in laparoscopic 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.

TABLE 10 *'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 (unpublished)[a]	**[Academic-in-confidence information removed]**					

[a] Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy trials.

TABLE 11 *Conversions*

Study ID	No. of conversions	No. of 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, 2006[40]	3	41	7
Leung, 2004[53]	47	203	23
Stage, 1997[57]	3	18	16
Tang, 2001[58]	15	118	13
Bonjer, 2005 (unpublished)[a]	**[Academic-in-confidence information removed]**		

[a] Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy trials.

Assessment of effectiveness

Table 12 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.

Duration of operation

Of the 19 eligible studies, 16 (n = 4125) provided information on the duration of operation (*Table 13*). 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 13*). 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 the study by Leung and colleagues[53] all participants suffered from rectal or sigmoid cancers, in that by Lacy and colleagues[22] all participants had colon cancer and in that by Schwenk and colleagues[56] both groups were included. Furthermore, the study by Leung and colleagues[53] had many more participants with TNM Stage IV than the other two studies.

Blood loss

Blood loss data were not reported in a form sufficiently similar to allow for a quantitative synthesis (*Table 14*). 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 ($p = 0.039$). The largest trial that provided data reported a median difference in blood loss of 75 ml.[4] The other trials are broadly consistent with this.

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

Of the 19 included studies, three reported abdominal wound breakdown.[4,40,47] In two studies, the proportion of patients who had an abdominal

TABLE 12 *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 of hospital stay**	**Postoperative 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[83a]						✓				✓													✓		
Weeks, 2002[82a]																✓				✓					
Curet, 2000[48]	✓	✓			✓	✓			✓		✓			✓	✓			✓			✓				
Hasegawa, 2003[49]	✓	✓	✓		✓	✓			✓		✓				✓	✓					✓				
Hewitt, 1998[50]	✓					✓									✓	✓									
Kaiser, 2004[51]	✓	✓			✓				✓		✓				✓	✓		✓	✓		✓				
Kim, 1998[52]																					✓				
King, 2006[40]	✓	✓	✓	✓					✓		✓			✓	✓	✓				✓					
Lacy, 2002[22]	✓	✓	✓		✓		✓				✓			✓	✓	✓		✓	✓		✓	✓			
Leung, 2004[53]	✓	✓	✓		✓			✓	✓		✓			✓	✓		✓	✓	✓		✓	✓	✓		
Milsom, 1998[54]					✓			✓													✓				
Neudecker, 2003[55]	✓																								
Schwenk, 1998a[56]	✓										✓														
Schwenk, 1998b[77a]						✓									✓	✓									
Schwenk, 1998c[78a]																				✓					
Stage, 1997[57]	✓	✓			✓	✓		✓	✓						✓	✓					✓				
Tang, 2001[58]	✓		✓			✓			✓		✓														
Vignali, 2004[59]					✓																				
Zhou, 2004[60]	✓	✓	✓					✓							✓	✓		✓			✓				

[a] Additional reports of the same study.

TABLE 13 *Duration of operation*

Study ID	Laparoscopic		Open		*p*-Value	Comments
	n	Duration (minutes)	*n*	Duration (minutes)		
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, 2006[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)

IQR, interquartile range.

TABLE 14 *Blood loss*

Study ID	Laparoscopic		Open		*p*-Value	Comments
	n	Blood loss (ml)[a]	*n*	Blood loss (ml)[a]		
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, 2006[40]	41	11 (27%)	19	18 (95%)	<0.001	Number with blood loss >100 ml
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)

[a] Except for King, 2006[40] (see 'Comments' column).

wound breakdown appeared to be higher in the open group;[4,40] however, the CIs 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 15*). Seven studies[3,47,49,51,53,54,57] showed more lymph nodes retrieved in the open group than in the laparoscopic group, 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) **[Academic-in-confidence information removed]**.

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

TABLE 15 *Lymph node retrieval (number)*

Study ID	Laparoscopic		Open		*p*-Value	Comments
	n	Number	*n*	Number		
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 (unpublished)[a]	**[Academic-in-confidence information removed]**					Mean

[a] Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy trials.

proximal, distal and circumferential disease-free margins during histological examination. In rectal cancer, the distal and circumferential margins are particularly important.

Table 16 gives 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) using other definitions, which were not always well described (*Table 17*). Furthermore, whereas 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, $p = 0.53$).

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 95% CI was wide (Appendix 9, comparison 01:06: 96/1620 versus 86/1348, RR 0.86, 95% CI 0.64 to 1.14, $p = 0.29$).

TABLE 16 *Resection margins*

Study ID	Laparoscopic		Open		*p*-Value	Comments
	n	Value	*n*	Value		
Proximal resection margins						
COLOR, 2005[4]	526	0	538	1	1.0	No. of positive resection margins
COST, 2004[2]	435	13 (2–78)	428	12 (3-50)	0.38	Median (range) (cm)
Distal resection margins						
COLOR, 2005[4]	526	1	538	1	1.0	No. of positive resection margins
COST, 2004[2]	435	10 (2–40)	428	11 (1–42)	0.09	Median (range) (cm)
Leung, 2004[53]	203	4.5 (3.0)	200	4.5 (2.7)	0.97	Mean (SD) (cm)
Circumferential resection margins						
CLASICC, 2005[3]	439	46 (10.5%)	228	20 (8.8%)	0.45	No. of positive resection margins
Colon	246	16 (0.4%)	131	6 (4.6%)	0.8	
Rectum	193	30 (0.5%)	97	14 (14.4%)		
COLOR, 2005[4]	526	9 (1.7%)	538	8 (1.5%)	1.0	No. of positive resection margins

TABLE 17 *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 (unpublished)[a]	**[Academic-in-confidence information removed]**							

[a] Individual patient data meta-analysis including patients from COLOR, COST, CLASICC and Lacy trials.

Urinary tract infection

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 compared with the open group, but again the 95% CI 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) provided information on operative and 30-day mortality. **[Academic-in-confidence information removed.]** 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 one reported 28-day mortality[4] (the last 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 95% CI was 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 18*). The

TABLE 18 *Length of hospital stay*

Study ID	Laparoscopic		Open		*p*-Value	Comments
	n	Stay (days)	n	Stay (days)		
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, 2006[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[56])	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.

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 18*). 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,[60] where the average age of participants was lower than in 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 WMD 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 7 days regardless of the type of surgery.

Postoperative pain

Five studies included a measure of postoperative pain (*Table 19*).[3,53,57,77,82] Between the first day and 2 weeks postoperation, four studies favoured the laparoscopic group[3,53,57,77] and one did not show

TABLE 19 *Postoperative pain – pain scores*

Study ID	Measure	Laparoscopic		Open		*p*-Value	Comments
		n	Pain score	*n*	Pain score		
CLASICC, 2005[3]	EORTC QLQ-C30 (pain) at 2 weeks postoperation	526	40	268	35	NS	Estimated from graph
	EORTC QLQ-C30 (pain) at 3 months postoperation	526	21	268	19	NS	Estimated from graph (back to baseline)
Leung, 2004[53]	VAS at 1 day postoperation	203	4.6 (2.4)	200	5.4 (2.3)	0.003	Mean (SD)
Schwenk, 1998b[77] (Schwenk, 1998a[56])	VAS at rest at 1 day postoperation	30	17.5 (0–50)	30	26 (0–50)	0.2	Median (range)
	Cumulative VAS score during rest for first week postoperation	30	161 (17–729)	30	252 (123–441)	0.07	Median (range)
Stage, 1997[57]	VAS at rest at 1 day postoperation	15	15	14	16	NS	Estimated from graph
	VAS at rest at 5 days postoperation	15	0	14	5	NS	Estimated from graph
	VAS at rest 30 days postoperation	15	0	14	0	NS	Estimated from graph
Weeks, 2002[82] (COST, 2004)	Pain distress at 2 days postoperation	203	2 (1–3)	198	2 (1–3)	NS	Median (IQR)
	Pain distress at 2 weeks postoperation	201	1 (1–2)	194	1 (1–2)	NS	Median (IQR)
	Pain distress at 2 months postoperation	199	1 (1–1)	180	1 (1–2)	NS	Median (IQR)

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (100: better); VAS, visual analogue score (0: better); NS, not significant.

any differences between the two interventions[82] (Sign test, $p = 0.125$). Three studies measured pain at 1–3 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 20*). 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, $p = 0.031$).

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 4–365 days) was lower than that in the open group (mean 44 days, range 7–198 days, $p = 0.002$).

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 21*).[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 the quality of life scores were similar in both the laparoscopic and open groups;[40] however, this was a randomised study embedded within an enhanced recovery programme (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 20 *Postoperative pain – analgesic requirement*

Study ID	Measure	Laparoscopic		Open		*p*-Value	Comments
		n	Value	*n*	Value		
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 (postoperative 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, 2006[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)

TABLE 21 *Quality of life*

Study ID	Measure	Laparoscopic	Open	Comments
CLASICC, 2005[3]	EORTC QLQ-C30	55	52	Estimated from graph at 2 weeks
King, 2006[40]	EORTC QLQ-C30	NR	NR	Scores were similar at 2 weeks
Schwenk, 1998c[78] (Schwenk, 1998a[56])	EORTC QLQ-C30	NR	NR	Scores favours laparoscopic at 1 and 4 weeks ($p = 0.05$)
Weeks, 2002[82]	QLI	1 (0–2)	1 (0–2)	
(COST, 2004)	Global QoL	80 (70–90)	75 (60–90)	Median (IQR) at 2 weeks

Global QoL, Global quality of life (0, death; 100, excellent health); QLI, quality of life index (0, normal functioning; 1, moderately impaired functioning; 2, severely impaired functioning).

Overall survival

Seven RCTs[2,3,22,48,51,53,60] (Guillou PJ, University of Leeds: personal communication, 2005) and one individual patient data meta-analysis (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 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 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[22] (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). Figure 2 of their study is reproduced here as *Figure 4* **[Academic-in-confidence information removed]**. Bonjer and colleagues did not include all the RCTs; 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 those 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. Four studies slightly favoured laparoscopic resection[2,22,48,53] and one slightly favoured open resection.[51] 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 3-year follow-up of the CLASICC trial. Only preliminary unpublished data from this trial were obtained; as these data were supplied as academic-in-confidence, they have not been included in this report (Guillou PJ, University of Leeds: personal communication, 2005).

FIGURE 4 [Academic-in-confidence information removed]

Disease-free survival

Five RCTs[2,22,51,53] (Guillou PJ, University of Leeds: personal communication, 2005) and one meta-analysis (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) provided information on disease-free survival. **[Academic-in-confidence information removed.]** Further data were available from the CLASICC trial; however these data were preliminary and unpublished. As these data were supplied as academic-in-confidence, they have not been included in this report (Guillou PJ, University of Leeds, personal communication, 2005). 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 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 3 to 108 months. **[Academic-in-confidence information removed.]**

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 22*). Eight studies provided information on

TABLE 22 *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]	Laparoscopic, median 52.7 (IQR 38.9); open median 49.2 (IQR 35.4)	0/167	0/170	

port-site recurrence.[22,49,51–54,57,60] Of 483 patients, three were found to have a port-site recurrence (*Table 23*).[22,60]

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, one of which was a port-site hernia, but this difference was not statistically significant (Appendix 9, comparison 01:14).

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 with open resection for cancer Stages I, II or III ($p > 0.05$). The meta-analysis of individual patient data compared

TABLE 23 *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]	Laparoscopic, median 52.7 (IQR 38.9); open, median 49.2 (IQR 35.4)	0/167
Milsom, 1998[54]	Laparoscopic, 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

FIGURE 5 [Academic-in-confidence information removed]

overall and disease-free survival for patients undergoing laparoscopic with open resection by stage of cancer (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). **[Academic-in-confidence information removed.]**

Age

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

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 postoperative 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 95% CIs. Operative and 30-day mortality were also statistically similar in both groups. **[Academic-in-confidence information removed.]** 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 operation and length of stay displayed significant heterogeneity. Consistency in 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

TABLE 24 *Summary of the clinical effect size from meta-analysis*

Outcome	No. of trials	Effect size	95% CI	*p*-Value
Duration of operation	3	39.65[b]	31.64 to 47.67	<0.001
Lymph node retrieval	3	–0.41[b]	–1.42 to 0.59	0.42
Length of hospital stay	4	–2.58[b]	–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[c]	0.74 to 1.73	0.58
Abdominal wound breakdown	3	0.63[c]	0.26 to 1.52	0.30
Positive resection margins	4	1.15[c]	0.74 to 1.77	0.53
Wound infection	9	0.86[c]	0.64 to 1.14	0.29
Urinary tract infection	7	1.15[c]	0.66 to 1.98	0.62
30-day mortality	3	0.57[c]	0.25 to 1.29	0.18
Operative mortality	4	0.84[c]	0.29 to 2.47	0.75
Overall survival	7	1.03[c]	0.98 to 1.09	0.28
Disease-free survival	5	1.01[c]	0.95 to 1.07	0.83
Recurrence[a]	7	0.92[c]	0.74 to 1.14	0.44
Recurrence – wound	4	1.97[c]	0.18 to 21.62	0.58
Hernia	2	1.49[c]	0.76 to 2.9	0.29

[a] Total number of recurrences when reported as it is by the author.
[b] Weighted mean difference.
[c] Relative risk.

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 24*. A summary of clinical effect for other outcomes is given in *Table 25*.

TABLE 25 *Summary of clinical effect size for other outcomes*

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

[a] (*n*) Studies that reported statistically significant results at the 0.05 level.

Chapter 4

Systematic review of economic evaluations

Methods

Search strategies

Studies that reported both costs and outcomes of laparoscopic and/or HALS techniques compared with 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 and 2005.

Databases searched were MEDLINE (2000–May Week 2, 2005), EMBASE (2000–Week 21, 2005), MEDLINE Extra (23 May 2005), Science Citation Index (2000–27 May 2005), NHS Economic Evaluation Database (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 and references of consultees' submissions. Full details of the search strategies used are documented in Appendix 1.

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 with 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.

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*
   (a) author and year
   (b) the interventions studied
   (c) the type of economic evaluation
   (d) the country of origin and currency reported.
2. *The intervention, study design and main outcomes*
   (a) fuller description of treatment
   (b) numbers receiving or randomised to each intervention
   (c) outcomes studied.
3. *Sources of data*
   (a) effectiveness data
   (b) mortality and co-morbidity (if measured)
   (c) cost data
   (d) quality of life (if measured).
4. *Methods and study perspective*
5. *Results*
   (a) costs
   (b) benefits
   (c) incremental cost-effectiveness ratio (ICER)
   (d) 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.

Quality assessment strategy

One economist assessed included studies using the NHS Economic Evaluation Database 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[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:

1. Is it unlikely that important relevant studies were missed?
2. Were the inclusion criteria used to select articles appropriate?
3. Was the assessment of studies reproducible?

4. Were the design and/or methods and/or topic of included studies broadly comparable?
5. How reproducible are the overall results?
6. Will the results help resource allocation in healthcare?

Each stem (1–6) was answered by one of the following: 'Impossible to judge', 'No', 'Partly', 'Yes'.

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 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 with those drawn from the consultee submissions and similarities and differences highlighted.

Where relevant data were available from studies which were unpublished but for which the authors were seeking publication, these data have been treated as academic-in-confidence and not reported.

Results

Number of studies identified

The results of the literature searches are presented in *Table 26*. The number of reports retrieved from the searches in the Science Citation Index and Journals@Ovid Full Text are the totals after deduplication against the results of the MEDLINE/EMBASE multifile search.

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[40] (Franks PJ, Thames Valley University: personal communication, 2005). 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 'Summary of results and discussion' (p. 34).[104]

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 with open resection for colorectal cancer[40] (Franks PJ, Thames Valley University: personal communication, 2005). One of these was in the context of an enhanced recovery programme.[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 10 Swedish centres.[66] The fourth study was based on a single-centre cohort-matched study conducted in China (*Table 27*).[109] Two studies considered costs from a societal perspective[40,66] whereas the others adopted a hospital perspective (*Table 27*).[53,109] The fifth study was described as a cost analysis (data supplied as academic-in-confidence has not been presented in this report) (Franks PJ, Thames Valley University: personal communication, 2005).

TABLE 26 *Results of searching for studies on cost-effectiveness*

Database	Hits screened	Selected for full assessment
MEDLINE/EMBASE/MEDLINE Extra multifile search (after deduplication in Ovid)	256	28
Science Citation Index	63	5
NHS Economic Evaluation Database	5	0
HTA Database	30	3
Heath Management Information Consortium	35	2
Selected from conference abstracts	3	3
Total	**392**	**41**

TABLE 27 *Characteristics of the included studies*

Study ID	Design	Sample	Follow-up (months)	Perspective
Franks, 2005, (unpublished) (UK)	Multicentre RCT (CLASICC)	Laparoscopic: 452 Open: 230	3	Stated as hospital (NHS) but societal
Janson, 2004[66] (Sweden)	Single-centre from a multicentre RCT	Laparoscopic: 98 Open: 112	36	Societal
King, 2006[40] (UK)	Single-centre RCT	Laparoscopic: 43 Open: 19	3	Societal
Leung, 2004[53] (Hong Kong)	Single-centre RCT	Laparoscopic: 203 Open: 200	52.7 (mean) 49.2 (mean)	Hospital
Zheng, 2005[109] (China)	Single-centre cohort-matched	Laparoscopic: 30 Open: 34	27 (mean) 26 (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, 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[40,53,66,109] (Franks PJ, Thames Valley University: personal communication, 2005).[40,53,66,109]

Patient group, study sample and study design

The sample sizes in four of the five studies were modest (*Table 27*). 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 27*). The outcome measures also varied between studies (*Table 28*).

Methods of economic analysis

The four trial-based papers[40,53,66] (Franks PJ, Thames Valley University: personal communication, 2005) presented details on which items were included in the cost calculations, whereas 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 PJ, Thames Valley University: personal communication, 2005), whereas no unit costs were reported in the other two studies.[53,109] Discounting was performed only in the Swedish study whereas it was actually relevant in all studies with a follow-up greater than 12 months. Indirect costs were calculated in three of the studies using the human capital approach (time off paid work)[40,60] (Franks PJ, Thames Valley University: personal communication, 2005). Three papers did not use any summary measure of health benefits[40,53,109] and left the results disaggregated. One study focused on costs alone (Franks PJ, Thames Valley University: personal communication, 2005). In the study by Janson and colleagues, the mean cost for reoperated patients for each arm of the trial was presented (although it is not reported in this chapter).[66]

One-way sensitivity analysis was performed in three studies. Changes in perioperative, equipment, recovery, intensive care unit and hospital costs were considered in the study by Franks and colleagues (Franks PJ, Thames Valley University: personal communication, 2005). They also considered a subgroup analysis by location of cancer (colon or rectum). 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]

Results

The results of the included studies are summarised in *Table 29*. The results of the study

TABLE 28 *Outcome measures used in the included studies*

Study ID	End-points
Franks, 2005 (unpublished) (UK)	None specified
Janson, 2004[66] (Sweden)	Complication rate (e.g. anastomotic leak, bowel perforation, wound rupture, ileus, postoperative bleeding, incarcerated abdominal hernia, endoscopic dilation, closure loop ileostomy) Reoperations Mortality 3-year survival
King, 2006[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 Postoperative 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

by Franks and colleagues were provided as academic-in-confidence and have been removed from this report.

In the study by Janson and colleagues, total costs, 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 than the open group (€9474 versus €7235; $p = 0.018$), as were the costs related to the first admission and the costs of primary surgery.[66]

In King and colleagues' study, 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 postoperative costs such as reoperations and productivity cost savings resulting from the earlier return to usual activities.[40]

Similarly, the health service costs in the study by Leung and colleagues were also higher for laparoscopic than for open surgery and this difference, as with the other two RCT-based

TABLE 29 *Cost data reported in the included studies*[a]

Study ID		Laparoscopic	Open	Difference (%)	*p*-Value
Janson, 2004[66] (Sweden)	Total cost[b]	€11,660	€9,814	€1,846 (18.8)	$p = 0.104$
Perspective: societal	Total costs, excluding productivity losses[b]	€9,474	€7,235	€2,239 (30.9)	$p = 0.018$
	First admission[b]	€6,931	€5,375	€1,556 (28.9)	$p = 0.015$
	Primary surgery[b]	€3,493	€2,322	€1,171 (50.4)	$p = 0.001$
King, 2006[40] (UK)	Total cost	£6,433	£6,790	–£357 (–5.3)	95% CI: –2167 to 2992
Perspective: societal	Total costs – indirect costs	£5,985	£6,068	–83 (–1.4%)	NA
	Theatre costs	£2,885	£1,964	£921 (46.9)	95% CI: 1251 to 586
Leung, 2004[53] (Hong Kong) Perspective: hospital	Direct costs[c]	US$9,297	US$7,148	US$2,149 (30.1)	$p < 0.001$
Zheng, 2005[109] (China) Perspective: hospital	Total cost of operation and drugs[d]	CNY 11,499 (SD: 2,619)	CNY 10,228 (SD: 2,373)	CNY 1,271 (12.4)	$p = 0.131$

NA, not available.
[a] The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence.
[b] €1 ≈ £0.67.
[c] US$1 ≈ £0.55.
[d] CNY = Chinese yuan (renminbi); CNY 1 ≈ £0.067.

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 (~£67); www.bloomberg.com, accessed 24 August 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]

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 Zheng and colleagues'[109] study, see Appendix 11. Only one measure of effectiveness was common across all four studies: complications. *Table 30* reports the number of complications (see *Table 28* 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.

Using the data presented in *Tables 29* and *30*, the incremental cost per complication avoided can be calculated (*Table 31*).

Based on mean data for costs and complications open surgery is dominant (i.e. less costly and more effective) in one study[66] whereas in another laparoscopic surgery is dominant.[40] For the two studies laparoscopic surgery could avoid a complication at a cost of US$76,872[53] and CNY 10,008[109] (approximately £42,000 and £780, respectively).

One study conducted a subgroup analysis by location of disease (colon or rectum) (Franks PJ, Thames Valley University: personal communication, 2005). The results of this analysis were supplied on an academic-in-confidence basis and are not presented in this report.

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

The cost-effectiveness review submitted by the 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 latter[109] were included in this review. All studies included in the

TABLE 30 *Number of complications reported in the included studies*[a]

Study ID		Laparoscopic	Open	Difference (%)	*p*-value
Janson, 2004[66] (Sweden)	Total complications	33 (33%)	26 (23.2%)	7 (9.8)	NR
	First admission	21 (21%)	18 (16.1%)	3 (4.9)	NR
	After discharge	12 (12%)	8 (7.1%)	4 (4.9)	NR
King, 2006[40] (UK)	Major morbidity	6 (15%)	5 (26%)	1 (–11)	Odds 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)	NR
Zheng, 2005[109] (China)	Major complications	5 (16.7%)	10 (29.4%)	–5 (–12.7)	$p = 0.23$

NR, not reported.
[a] The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence.

TABLE 31 *Incremental cost per complication avoided*[a]

Study ID	Incremental cost	Difference in complications (%)	ICER
Janson, 2004[66] (Sweden) Perspective: societal	€1,846	–10%	Open dominates
Janson, 2004[66] (Sweden) Perspective: Health Service	€2,239	–10%	Open dominates
King, 2006[40] (UK) Perspective: societal	–£357	11%	Laparoscopic dominates
King, 2006[40] (UK) Perspective: NHS	–£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

[a] The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence.

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.

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 costs for the laparoscopic procedure were statistically significantly higher than those for open surgery. The mean total cost of laparoscopic surgery appeared to be greater than that for open surgery in all studies except that of 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 Endo-Surgery was a brief presentation of some of the key issues in the consideration of laparoscopic surgery (submission to NICE by Ethicon Endo-Surgery, July 2005). It did not contain a systematic review or 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 3-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 affect 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.

Data reporting a detailed subgroup analysis by location of disease supplied by Franks and colleagues were provided as academic-in-confidence and have not been included in this report.

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 the 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 provide no evidence of a difference in complication rates. Data from Franks and colleagues supplied as academic-in-confidence have not been presented in this report. In addition, the data from Zheng and colleagues were for 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 PJ, Thames Valley University: personal communication, 2005), Janson and colleagues[66] and King and colleagues[40] considered indirect costs whereas the other two studies considered only direct costs from surgery and hospital stay.[53,109] The costing methodology was also poorly described in these last two studies. For example, Zheng and colleagues reported only final cost figures and no details on the way in which calculations were performed.[109]

The extent to which the costs from the three non-UK studies would be applicable to the UK is unclear. One UK study had a very small sample size, and it was based on a single centre.[40] Further data relevant to the UK were also provided by the study by Franks and colleagues, but these data were supplied as academic-in-confidence and are not presented in this report. The study by Janson and colleagues[66] was larger and the relative difference in cost between the two interventions (see *Table 29*) may help inform decision-makers in the UK. However, the relatively short follow-up in both studies indicates that a modelling exercise

TABLE 32 *Summary of results from Taragona and colleagues*[104]

Intervention	Operation time (minutes): mean (range)	Conversions[a]	Operation cost[a]
Laparoscopic (n = 27)	135 (109–240)	6	€1959±593
HALS (n =27)	120 (70–300)	2	€2035±512

[a] No statistically significant differences.

with a longer time horizon might add valuable information for decision-making.

In addition to the studies comparing laparoscopic with 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.

The study found no evidence of a statistically significant difference in terms of operation time or conversion rates (*Table 32*). The authors also did not find any statistically significant differences in terms of bowel sounds, refeeding, overall morbidity rates, reoperation 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 a minimally invasive approach, maintains all the oncological features of conventional laparoscopic surgery, and does not increase the cost".

Conclusions

This chapter has presented the overall evidence available on cost-effectiveness analyses of laparoscopic surgery for colorectal cancer compared with open surgery, based on a systematic review of the literature and on the revision of the review submitted by the ALSGBI. 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 are likely to be imprecise and unreliable when compared with the data available from a systematic review of effectiveness (Chapter 3). Hence, 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 that compared HALS with open surgery. Evidence comparing laparoscopic with hand-assisted laparoscopic surgery is very limited and provides no evidence for a difference in either costs or effects.

Chapter 5

Economic evaluation

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.

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 patient parameter.

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- and the long-term health effects of the different forms of resection. Data on the costs of resection were 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; postoperative costs; chemotherapy and radiotherapy costs; and follow-up costs at 3 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 were 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[40] was broadly consistent with the findings of the systematic review of effectiveness. Therefore, the data reported for theatre costs in this study were 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. This study 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 33*.

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 a 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 1-day stay for both procedures) and a surgical ward (the remainder of the stay). Both ward costs were taken from King and colleagues.[40]

Postoperative costs

The postoperative costs estimated by King and colleagues[40] included the use of medications in addition to 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 postoperative complications. Therefore, it has been assumed that the cost of open resection for this element is the same as that of 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 3 months from the initial operation. Follow-up costs were collected via patient-completed questionnaires after 2 weeks and 3 months of 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 33*.

Estimation of total costs

Table 34 summarises the estimates of the costs 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.

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 6*).

The threshold analysis suggests that should laparoscopic resection be associated with a length of stay that is on average just over 4 days less than open surgery, then the costs of the two surgeries would be equivalent. A difference of this magnitude was rarely observed in 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 1 day).

Results

Table 35 presents the balance sheet for the comparison of laparoscopic with open surgery for colorectal cancer.

As *Table 35* 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 3-year follow-up. With respect to cost, although differences are non-significant, it is likely that

TABLE 33 *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 of laparoscopic to combined cost of open and laparoscopic resection	0.595	NA	NA
Range of 95% 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	NA	NA
Cost per day (surgical ward)	£162	NA	NA
Chemotherapy and radiotherapy cost			
Laparoscopic resection	£175.5	Triangular	Derived using data below
Open resection	£176.5	Triangular	Derived using data below
Ratio of laparoscopic to combined cost of open and laparoscopic resection	0.499	NA	NA
Range of 95% 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 of laparoscopic to combined cost of open and laparoscopic resection	0.377	NA	NA
Range of 95% CI around mean difference in cost		£234	NA NA

HDU, high-dependency unit; NA, not applicable.

TABLE 34 *Estimates of costs 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 3 months	360	594	–234
Total cost	**6117**	**5852**	**265**
			95% CI –3829 to 4405[a]

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

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 95% CI are sufficiently wide 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 3 years. A judgement is required as to whether the findings with respect to survival and

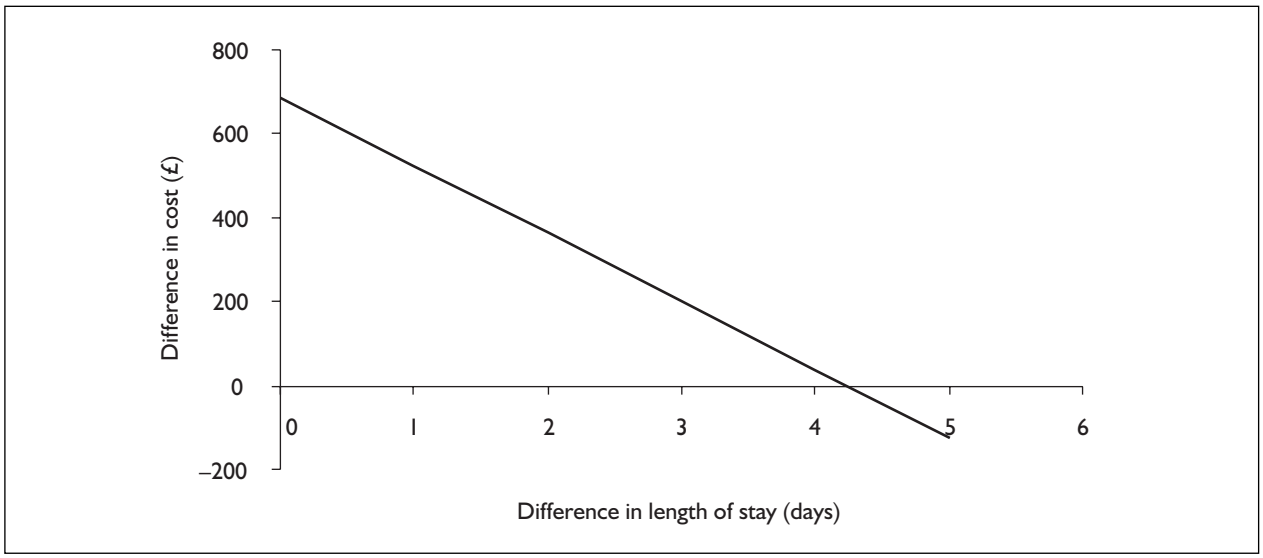

FIGURE 6 *Threshold analysis on effect of differences in length of stay on cost*

disease-free survival will persist in 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.

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 (*Figure* 7). 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 reoperation 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. All costs are presented in UK pounds sterling for 2004 and costs and benefits are discounted at 6 and 1.5%, respectively.

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.
- Death.

A cost per patient for each health state in the Markov model was calculated using the methods outlined below. The main cost components in the model are the initial operative procedure and the costs of any subsequent reoperation or management. It has been assumed that if a recurrence occurred and a reoperation 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 postoperative complications have 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 reoperation 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

TABLE 35 *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 minutes 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 75 ml per operation)		9 (4 in MA)
Less time away from usual activities (32 vs 44 days)		1
Less postoperative pain and analgesia (1 day less on average)		5 and 6
No statistically significant difference in:		
Cost (mean difference £265, 95% CI –3829 to 4405)[a]		
Anastomotic leakage (RR 1.13, 95% CI 0.74 to 1.73)		8
Abdominal wound breakdown (RR 0.63, 95% CI 0.26 to 1.52)		3
Wound infection (RR 0.89, 95% CI 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

MA, patients' data meta-analysis by Bonjer and colleagues (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005).

[a] 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.

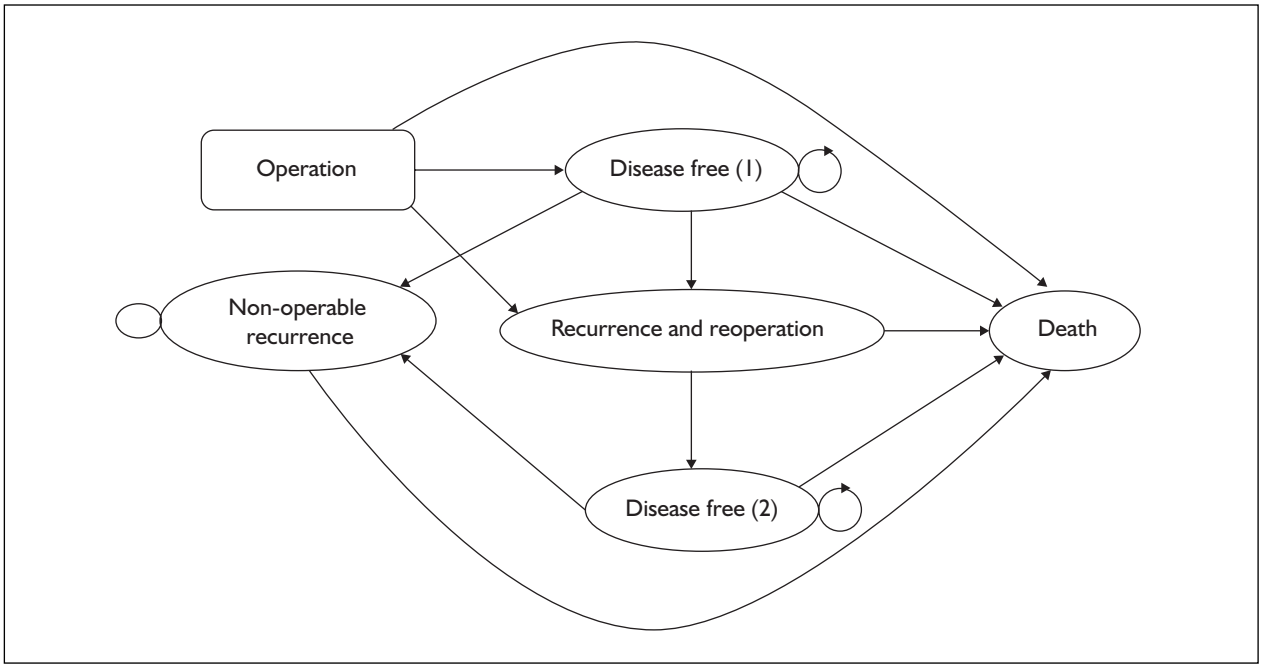

FIGURE 7 *Markov model for the comparison of alternative methods of resection*

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 6 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 13.

Estimation of model parameters

Baseline parameters

Where quantitative synthesis was possible, the outputs of the systematic review of effectiveness (Chapter 3) were presented as RRs for dichotomous variables and WMDs 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, although 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 here as *Figure 4* (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). These data provided estimates of survival up to 3 years post-surgery. Overall survival for open resection for each 6-month period up to 36 months was estimated from these curves. From these data, a mortality rate for each 6-month cycle length was calculated. As interpreting rates from these curves is an imprecise method, and the mortality rates for each 6-month period were similar, a constant mortality rate was assumed (*Table 36*).

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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 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 36*).

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 ages of the chemotherapy and resection groups were 61 and 60 years, respectively. Although this study currently provides 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 time period of 24 months, divided into 6-month periods, was estimated from this curve. A mortality rate for each 6-month cycle length was calculated and, from this, a constant mortality rate was obtained. Based on these data, a mortality rate for inoperable cancer with the value of 0.2 was calculated and is shown in *Table 36*. 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 reoperation for a postoperative complication and the risk of a reoperation 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

TABLE 36 *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	$\alpha = 5.4$, $\beta = 21.6$
Other probabilities			
Emergency operation rate	0.019	Triangular	IQR 0.008–0.034
Risk of hernia	0.003	Triangular	IQR 0.002–0.012
Reoperation rate (after recurrence)	0.05	Beta	$\alpha = 15$, $\beta = 285$

of the different types 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 ALSGBI (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 36*).

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 reoperation, it was believed, based on clinical opinion, that the risk of reoperation 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 reoperation is equal to the risk of an anastomotic leakage. The baseline risk of an anastomotic leakage was based on the rates reported in the open arms of those trials identified by the systematic review of effectiveness (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 36*).

Should the cancer recur, the patients might have a reoperation. 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 14–15 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.

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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). The relative effect size of death for laparoscopic compared with open resection was derived from the estimate of 3-year survival reported by Bonjer and colleagues. **[Academic-in-confidence information removed.]** These estimates of an absolute difference were converted into a relative effect size for laparoscopic surgery (*Table 37*). The 95% CIs 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. **[Academic-in-confidence information removed.]** The same methods used to estimate the relative difference in mortality were used to estimate the

TABLE 37 *Relative effect sizes used in the model*[a]

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		
Other probabilities				
Emergency operation rate	1.13	0.74	1.73	Log-normal
Risk of hernia	1	1	1	
Reoperation rate (after recurrence)	1	1	1	

[a] Absolute parameter values for each intervention were derived by applying the relative effect sizes to estimates of the absolute rate for open resection (*Table 36*) with the relative rates reported in this table.

relative difference in recurrence and an associated distribution (*Table 37*).

It was assumed that the RR of mortality faced by a patient with non-curative cancer was one (*Table 37*). 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 RR of an emergency operation. For the same reason as described above, the RR 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 37*). The statistical imprecision surrounding the point estimate was characterised by log-normal distributions for RRs due to the methods used to derive these relative effects.

Two other relative effect sizes required for the model are the RR of hernia and the RR of a reoperation after a recurrence. In both cases an RR 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, an RR 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 37*).

Table 37 details the point estimates of the relative effect sizes used in the model. Also included in the table are the 95% CIs 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.

Resource use and costs

The main cost component included in the model is the costs associated with the initial operation. The method used to derive the cost for open resection is described in the section 'Methods' (p. 37). 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 of 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 log-normal 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 6 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]

TABLE 38 *Cost parameters used within the model*

Costs	Value (£)	Source	Distribution, and values used to define the distribution
Initial operation			
Open	5852	Earlier[a]	Triangular with high and low based on IQR. IQR £4968–6272
Relative cost of laparoscopic resection	1.05	Earlier[a]	Lognormal; SD 0.33
Emergency operation	1615	NRC. HRG F42	Triangular with high and low based on IQR. IQR £1132–2322
Reoperation (as open)	5852	Earlier[a]	Triangular with high and low based on IQR. IQR £4968–6272
Outpatient visit	99	King, 2006[40]	
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	

[a] See the section 'Introduction' (p. 35)

A triangular distribution was defined for this cost based on the interquartile range of costs reported for this HRG (*Table 38*). The cost of an outpatient visit made at 6 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 Costs and a distribution for this cost was defined using the same method as 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 and 24 months postoperatively. Patients would also be reviewed and undergo colonoscopy after 3 years and then subsequent colonoscopy every 5 years, until aged approximately 70 years. The cost of a colonoscopy was taken from the National Reference Costs and based on HRG F35 (an endoscopic or intermediate procedure for the large intestine). The distribution for this cost was defined using the same method as 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 at 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 Costs. The cost used related to HRG F72 (abdominal hernia procedures at age less than 70 years) and a distribution for this cost was defined using the same method used for emergency surgery (*Table 38*).

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 would cost the same as the initial open surgical resection as, based on expert opinion, it was deemed unlikely that any reoperation would be performed laparoscopically. In addition to the cost of a reoperation, patients might receive medications for the control of symptoms if surgery was not indicated. The cost for a typical regime of care for a patient was defined following consultation with a Macmillan Cancer Nurse (O'Dea F, Hospital Specialist Palliative Care Team, Grampian University Hospital NHS Trust: personal communication, 2005) (*Table 38*). Details of the basis of the cost estimated are provided in Appendix 12.

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, few usable data were identified. The CLASICC Trial, which has not yet fully reported, is using the EQ-5D instrument collected at baseline, 2 weeks and 3, 6, 18 and 36 months postoperation. 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, 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 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 EQ-5D 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 these limited data, assuming 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 quality-adjusted life-years (QALYs) should be treated with caution.

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 the 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.

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

[Academic-in-confidence information removed.]
One interpretation of all the evidence available on overall survival and disease-free survival is that there is no difference between laparoscopic and open resection. 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.

Use of pooled estimate for relative difference in survival and disease-free survival from meta-analysis conducted as part of review of effectiveness

As part of the systematic review of effectiveness, a pooled analysis of outcomes of interest was conducted where data allowed it. Two such pooled estimates were derived for overall survival and disease-free survival. As such, it was therefore possible to conduct a sensitivity analysis using these estimates in place of those provided by Bonjer and colleagues (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005). From the meta-analysis conducted as part of the review of effectiveness, the relative effective sizes in terms of mortality and recurrence rates for laparoscopic compared with open resection were 0.97 (SD 0.03) and 0.99 (SD 0.03), respectively. Given the nature of the data, a normal distribution was assigned to the parameters.

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 colleagues (Franks PJ, Thames Valley University: personal communication, 2005). This paper is a cost-analysis and reports cost data for a subset of the patients entered into the CLASICC trial; the paper is summarised and critiqued in Chapter 4. The method used to derive the cost for open resection was the same as the method used to determine the costs for the base-case analysis described in the section 'Methods' (p. 35). The first sensitivity analysis, with regard to this cost

data, utilised the revised costs estimated from Franks and colleagues. A second sensitivity analysis was performed using the WMD in length of stay reported in Chapter 3, which was applied to the length of stay for open resection from Franks and colleagues. The data used to conduct this sensitivity analysis was supplied as academic-in-confidence and has not been included in this report.

Additional cost data

Currently, the cost data have not taken into account the extra cost which preoperative preparation for laparoscopic resection might incur and essentially assume that the same approach is used for both methods of resection. These costs could include such aspects as the necessity for 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. The mean cost was £32 with an interquartile range of £26–39.

Changes to the reoperation rate for recurrent disease

An estimate of the number of reoperations that might take place given recurrent disease was based on data from one centre (5%). As a result, the reoperation 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 reoperation rate for recurrent disease

No data were available to identify the difference in reoperation rates between laparoscopic resection and open resection. The base-case analysis assumed that 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 based solely on expert opinion, this sensitivity analysis allowed the relative effect size for the rate of reoperation to change from 0.5 to two. Hence the rate of reoperation 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 was used.

Combination of previous two analyses

The relative effect size for the reoperation 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 reoperation from the previous sensitivity analysis with different estimates of the relative effect size of the reoperation rate for laparoscopic compared with open resection. The low reoperation rate (1%) was combined with a relative effect size of 0.5. The higher reoperation rate (10%) was combined with a relative effect size of 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 and colleagues.[114] A constant mortality rate of 0.2 was used for the base-case analysis; however, the mortality rate at 6-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 were 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 that the mortality rate for patients in the laparoscopic arm could decrease by 50% 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

TABLE 39 *Alternative utility values (1)*

Utilities		Value
Health states defined by Petrou and Campbell[121]	**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

TABLE 40 *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

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 with 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 of 1.5. A similar distribution to that used in the base-case analysis was also 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 reoperation 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 were 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,[121] and those defined within the model, are shown in *Table 39*. 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.

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 40*. 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 is 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

TABLE 41 *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 42 *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

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.

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, few stage-dependent data were available; however, the meta-analysis conducted by Bonjer and colleagues (Bonjer J, QE II Health Sciences Centre, Halifax, NS: personal communication, 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 for patients with Stages I, II and III disease for both open and laparoscopic resection, **[Academic-in-confidence information removed]**. These data provided estimates of survival up to 3 years post-surgery. Overall survival for each 6-month period up to 36 months was estimated from these curves. From these data, a mortality rate for each 6-month cycle length was calculated. A constant mortality rate was assumed based on the mean value at each 6-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 J, QE II Health Sciences Center, Halifax, NS: personal communication, 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. **[Academic-in-confidence information removed.]** No CIs were provided by Bonjer and colleagues, hence, distributions allowing the uncertainty surrounding these parameters could not be explored. The results, therefore, are expressed purely as a deterministic analysis.

Results

The results of the deterministic analyses of incremental cost per life-year and incremental cost per QALY are reported in *Tables 41* and *42*, respectively.

Laparoscopic resection is dominated by open resection over the 25-year time horizon considered. The point estimates of the incremental cost-effectiveness provided in *Tables 41* and *42* 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 8* and *9* report the

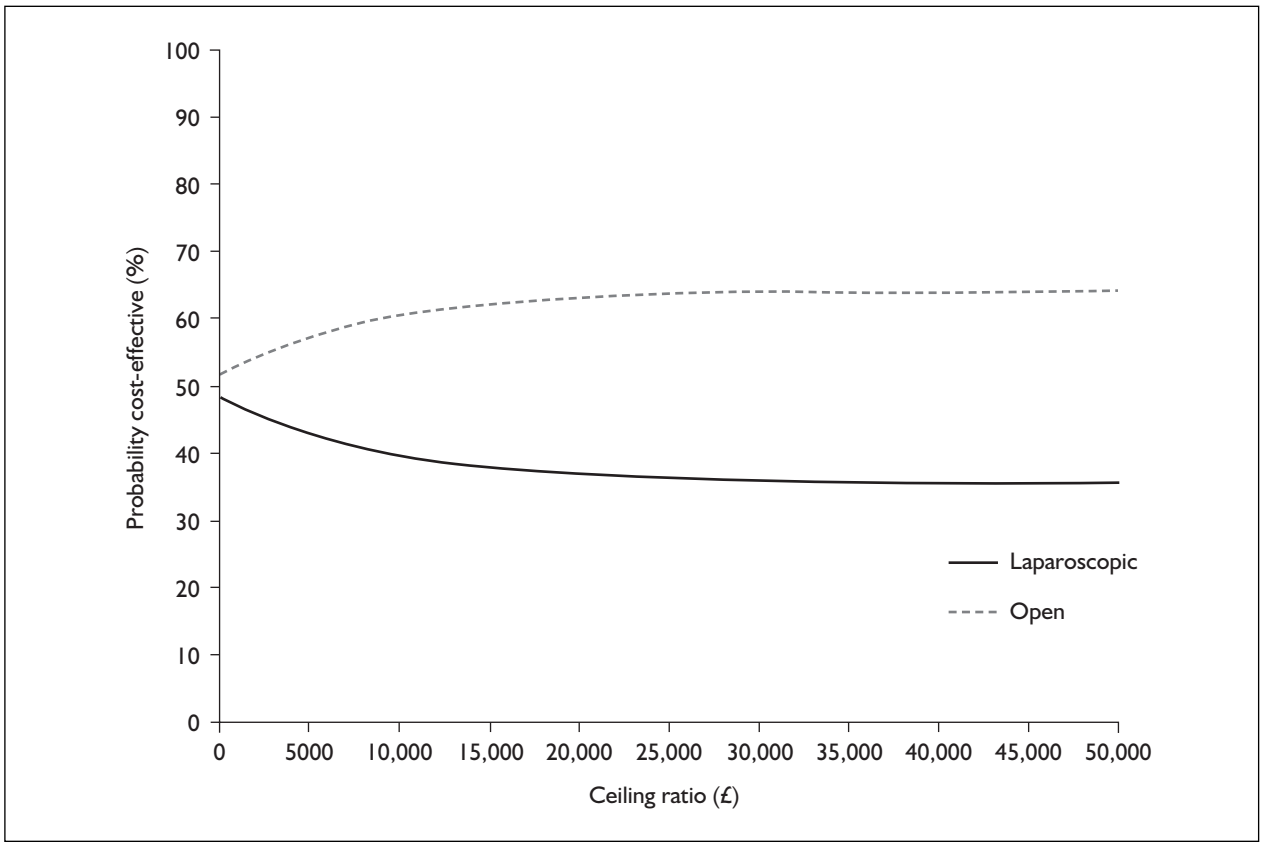

FIGURE 8 *CEACs showing society's willingness to pay for a life-year for the comparison of laparoscopic with open surgery (base-case analysis)*

CEACs comparing laparoscopic with open surgery in terms of life-years and QALYs, respectively.

The results presented for both life-years and QALYs are driven by very small differences in survival and disease-free survival observed at 3 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 4* and results of meta-analysis reported in Chapter 3). *Figures 10* and *11* report alternative analyses for life years and QALYs respectively that make this assumption.

As *Figures 10* and *11* 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 9* and *11* do not capture the QALY gain that might be associated with an earlier recovery. Some indication of the relevance of any QALY obtained associated with earlier recovery can be obtained 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 3 months.[123]

Sensitivity analysis

Use of pooled estimate for relative difference in mortality and recurrence from meta-analysis conducted as part of review of effectiveness

The use of the pooled estimates from the systematic review of effectiveness led to laparoscopic surgery having a much greater chance of being considered cost-effective. Laparoscopic surgery was found to be more costly (by approximately £300) but more effective (see *Table 43* for life-years and *Table 44* for QALYs).

Alternative and additional costs data

Changes surrounding the use of alternative cost data provided by a draft paper from a subset of

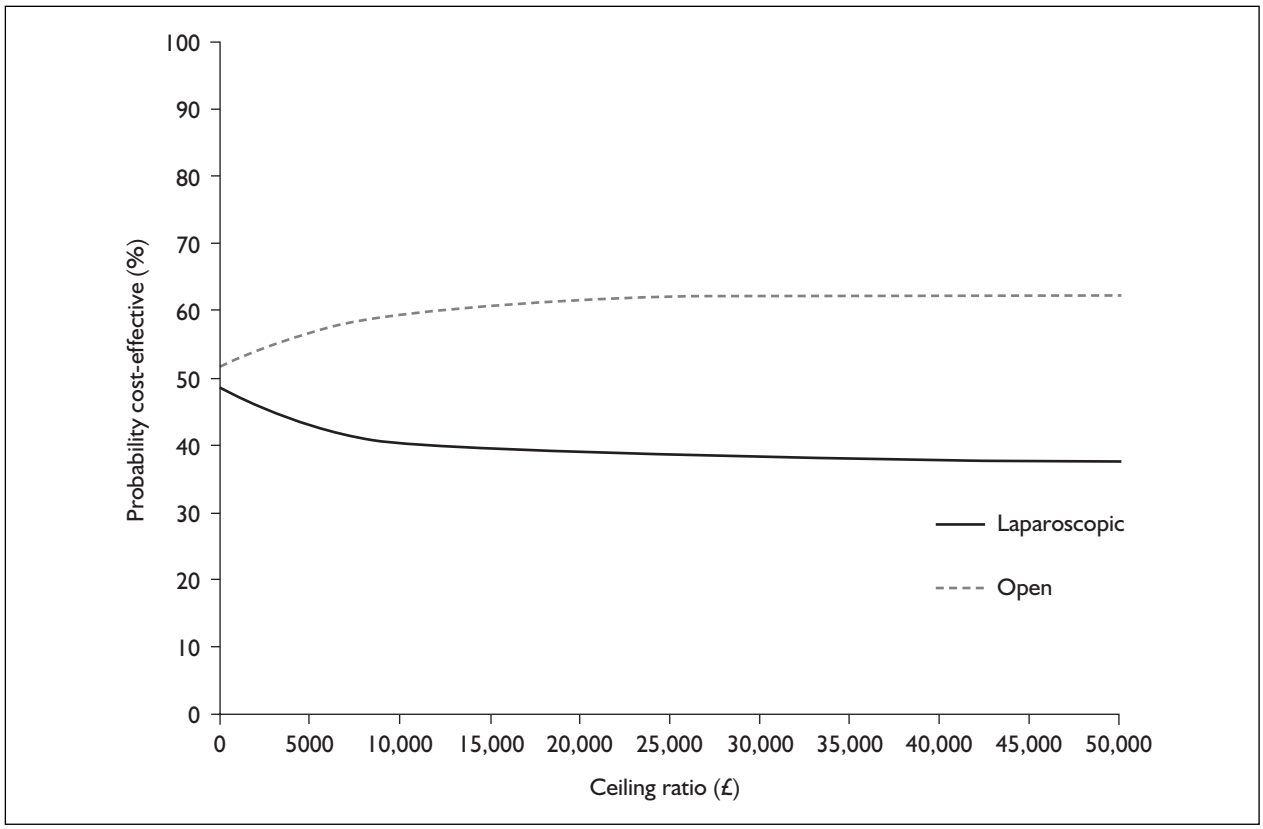

FIGURE 9 *CEACs showing society's willingness to pay for a QALY for the comparison of laparoscopic with open surgery (base-case analysis)*

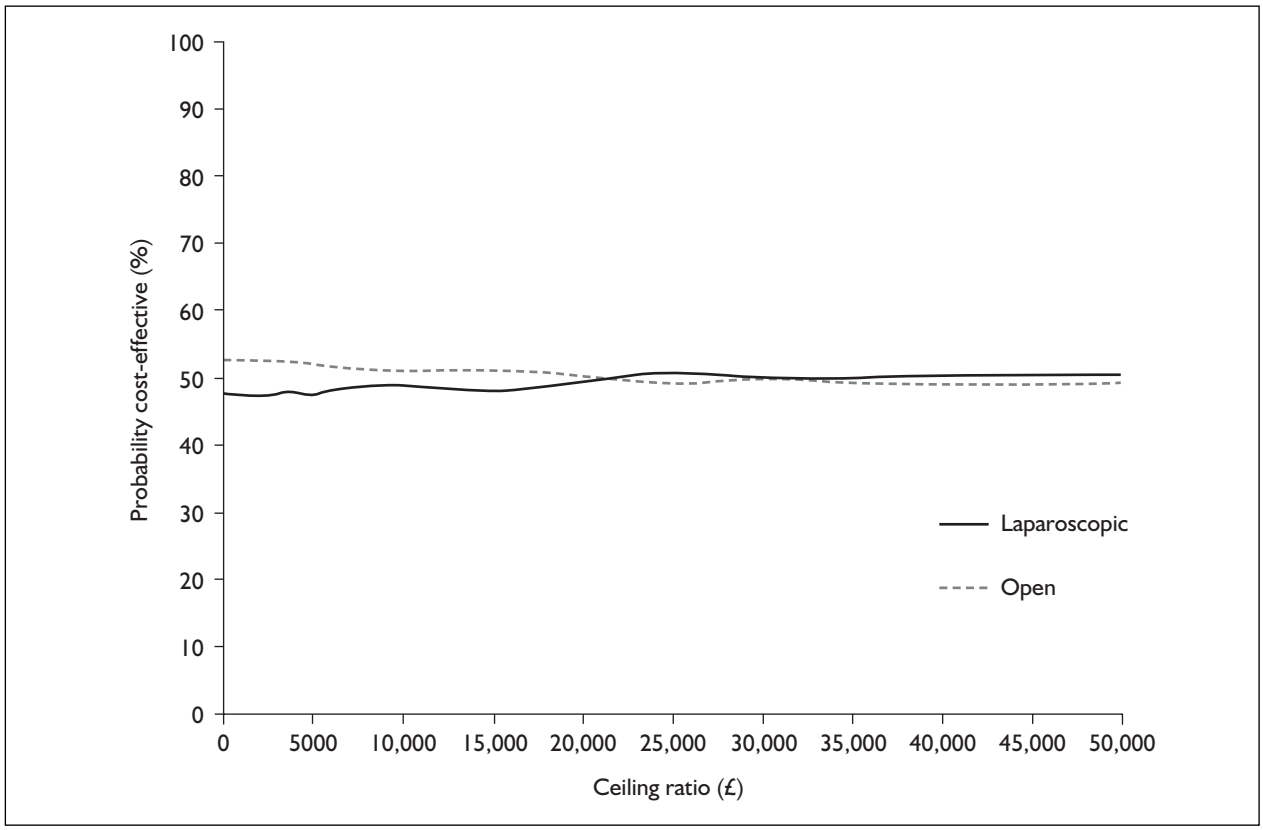

FIGURE 10 *CEACs showing society's willingness to pay for a life-year for the comparison of laparoscopic with open surgery assuming equal survival and disease-free survival*

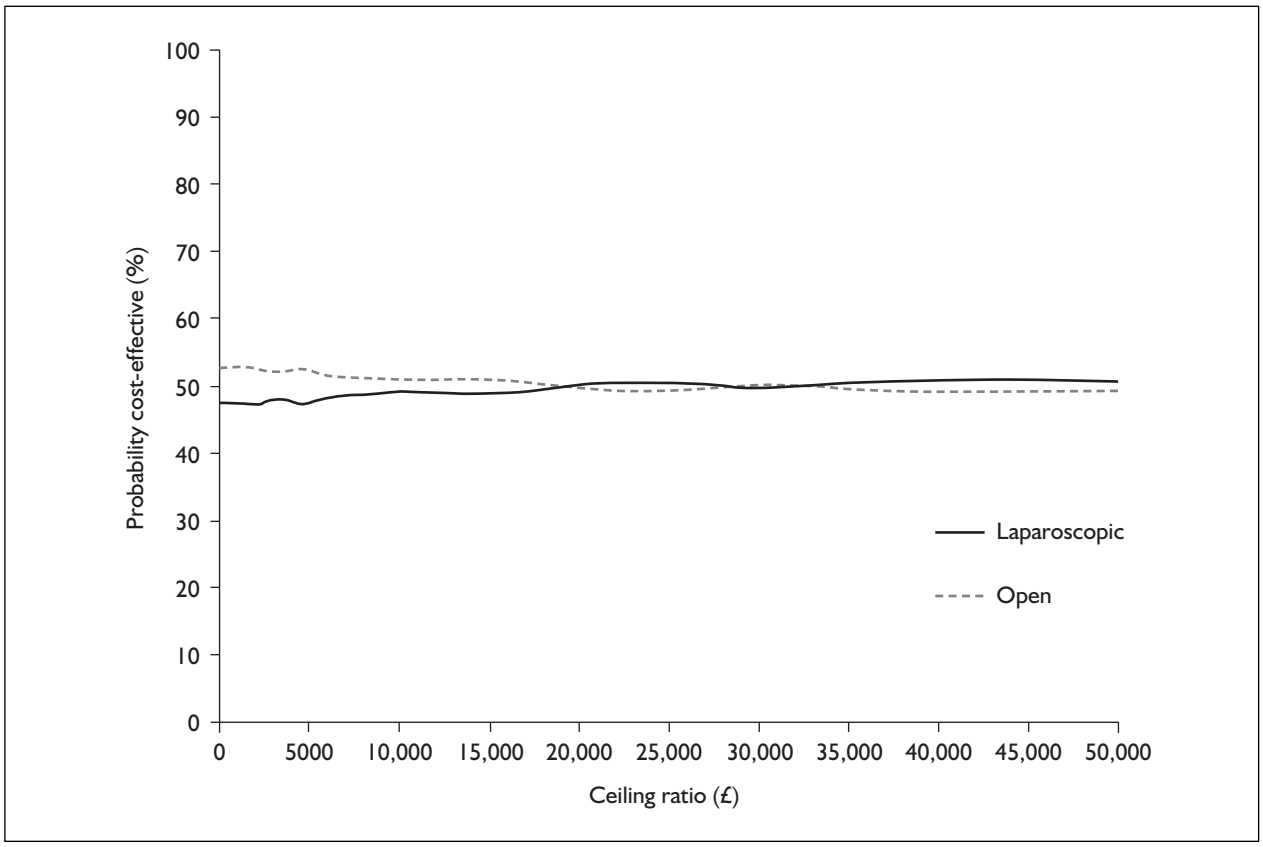

FIGURE 11 *CEACs showing society's willingness to pay for a QALY for the comparison of laparoscopic with open surgery assuming equal survival and disease-free survival*

patients from the CLASICC trial produced interesting results. In the first sensitivity analysis using estimates from Franks and colleagues (Franks PJ, Thames Valley University: personal communication, 2005), cost data for the two interventions were re-estimated using the methods described in the section 'Sensitivity analysis and subgroup analysis' (p. 44). The second sensitivity analysis used the cost estimates for open resection from Franks and colleagues but utilised the difference in length of stay between open and laparoscopic surgery from the review of effectiveness. The results of these sensitivity analyses were based on data supplied as academic-in-confidence and have not been presented in this report.

A cost analysis taking into account the cost for preoperative staging of disease with respect to each intervention was also performed [see the section 'Sensitivity analysis and subgroup analysis' (p. 44)]. 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 (see *Table 43* for life-years and *Table 44* for QALYs). 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).

Changes in the rates of reoperations

Changing the rate at which patients with recurrent cancer receive a further surgical resection had little effect on cost-effectiveness in comparison with the base-case analysis (*Table 45* for life-years and *Table 46* for QALY results). This would be expected given the similarities in mortality and disease-free survival along with the assumption of no difference in reoperation rates between the two surgical approaches. Changing the RR of a reoperation was shown to influence markedly the likelihood that laparoscopic surgery would be cost-effective. For example, adopting an RR 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 reoperation for subsequent

TABLE 43 *Sensitivity analysis around changes in costs and changes in survival and disease-free survival from pooled estimates taken from the systematic review of effectiveness (life years)*[a]

Sensitivity analysis	Procedure	Cost (£)	Life-years	ICER (£)	Probability cost-effective 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 for overall survival and disease-free survival from meta-analysis conducted in systematic review of effectiveness	Open	9613	15.351		25.9	20.4	18.7	17.9
	Laparoscopic	9924	15.541	1641	74.1	79.6	81.3	82.1
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

[a] The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence.

TABLE 44 *Sensitivity analysis around changes in costs and changes in survival and disease-free survival from pooled estimates taken from the systematic review of effectiveness (QALYs)*[a]

Sensitivity analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effective 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
RR for overall survival and disease-free survival from meta-analysis conducted in systematic review of effectiveness	Open	9613	14.679		26.1	20.5	18.8	18.0
	Laparoscopic	9924	14.864	1674	73.9	79.5	81.2	82.0
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

[a] The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence.

TABLE 45 *Sensitivity analysis around changes in the risk of reoperation for recurrent disease (life-years)*

Sensitivity analysis	Procedure	Cost (£)	Life-years	ICER (£)	Probability cost-effective 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	9,613	15.351		60.4	63.0	64.0	64.2
	Laparoscopic	9,876	15.298	Dominated	39.6	37.0	36.0	35.8
Equal survival	Open	9,613	15.351		51.0	50.3	49.9	49.5
	Laparoscopic	9,903	15.351	Dominated	49.0	49.7	50.1	50.5
Reoperation rate 1% (BC = 5)	Open	9,567	15.173		60.1	64.9	66.0	66.2
	Laparoscopic	9,830	15.122	Dominated	39.9	35.1	34.0	33.8
Reoperation rate 10% (BC = 5)	Open	9,671	15.574		60.7	64.5	64.5	64.7
	Laparoscopic	9,933	15.518	Dominated	39.3	35.5	35.5	35.3
RR of 0.5 for reoperation rate (BC = 1)	Open	9,613	15.351		75.0	81.0	81.3	83.2
	Laparoscopic	9,847	15.188	Dominated	25.0	19.0	18.7	16.8
RR of 2 for reoperation rate (BC = 1)	Open	9,613	15.351		28.1	22.6	20.8	19.0
	Laparoscopic	9,933	15.518	1921	71.9	77.4	79.2	81.0
RR of 0.5 for reoperation rate (BC = 1) and 1% rate of reoperation (BC = 5%)	Open	9,567	15.173		64.7	69.1	70.0	71.4
	Laparoscopic	9,825	15.100	Dominated	35.3	30.9	30.0	28.6
RR of 2 for reoperation rate (BC = 1) and 10% rate of reoperation (BC = 5%)	Open	9,671	15.574		9.7	4.4	2.8	1.8
	Laparoscopic	10,047	15.957	980	90.3	95.6	97.2	98.2

BC, base-case,

TABLE 46 *Sensitivity analysis around changes in the risk of re-operation for recurrent disease (QALYs)*

Sensitivity analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	9,613	14.679		59.9	61.2	62.0	62.2
	Laparoscopic	9,876	14.630	Dominated	40.1	38.8	38.0	37.8
Equal survival	Open	9,613	14.679		50.8	49.8	50.2	49.3
	Laparoscopic	9,903	14.679	Dominated	49.2	50.2	49.8	50.7
Reoperation rate 10% (BC = 5%)	Open	9,671	14.912		59.7	63.0	62.6	62.4
	Laparoscopic	9,933	14.860	Dominated	40.3	37.0	37.4	37.6
RR of 0.5 for reoperation rate (BC = 1)	Open	9,613	14.679		75.2	80.9	80.9	82.2
	Laparoscopic	9,847	14.515	Dominated	24.8	19.1	19.1	17.8
RR of 2 for reoperation rate (BC = 1)	Open	9,613	14.679		26.5	20.4	18.4	16.7
	Laparoscopic	9,933	14.860	1761	73.5	79.6	81.6	83.3
RR of 0.5 for reoperation rate (BC = 1) and 1% rate of reoperation (BC = 5%)	Open	9,567	14.492		63.4	67.6	69.1	69.9
	Laparoscopic	9,825	14.423	Dominated	36.6	32.4	30.9	30.1
RR of 2 for reoperation rate (BC = 1) and 10% rate of reoperation (BC=5%)	Open	9,671	14.911		8.6	3.4	1.4	1.1
	Laparoscopic	10,047	15.320	920	91.4	96.6	98.6	98.9

BC, base-case.

disease would, if the operation were successful, have the same mortality and disease-free survival as someone following the initial surgery (*Table 45* for life-years and *Table 46* for QALY results). A further sensitivity analysis was conducted to examine the interaction between the baseline risk of a reoperation and the relative risk of reoperation (*Table 45* for life-years and *Table 46* 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.

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 47* for life-years and *Table 48* 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 any way be influenced by the choice of initial surgery. Combining changes in the baseline level of non-operative mortality and in the RR between laparoscopic and open surgery provided a similar finding to changes in RR alone (*Table 47* for life-years and *Table 48* 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, that is, the incidence and treatment of a hernia had no effect on utility (*Table 49* for life-years and *Table 50* for QALY results).

Alternative utility values

The data available on utilities were very limited but some alternative utility values were available from Petrou and Campbell[121] and also from a recently published NICE appraisal review.[122] As described in the section 'Sensitivity analysis and subgroup analysis (p. 44), 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 Campbell.[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 by open surgery but was associated with a slightly higher probability of being considered cost-effective (*Table 51*). 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 with 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 with 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 patients with Stage III 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 the section 'Sensitivity analysis and subgroup analysis (p. 44). The first sensitivity analysis using utilities from this review used the low rate of 0.24 for the non-operative management state (*Table 51*). This state related to those on palliative chemotherapy from the NICE review. In this analysis, laparoscopic surgery was still dominated by open surgery 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 3 years. The number of QALYs gained in this analysis for both interventions are, however, less than those using data from Petrou and Campbell.[121] This is because the values for the disease-free state and disease-free after a successfully treated recurrence state were assumed to have the same value as that for the initial operation and for recurrence, that is, they were not assumed to be in full health with a utility score equal to one and 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

TABLE 47 *Sensitivity analysis associated with non-operative management for recurrent disease (life-years)*

Sensitivity analysis	Procedure	Cost (£)	Life-years	ICER (£)	Probability cost-effective 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	9,613	15.351		60.4	63.0	64.0	64.2
	Laparoscopic	9,876	15.298	Dominated	39.6	37.0	36.0	35.8
Equal survival	Open	9,613	15.351		51.0	50.3	49.9	49.5
	Laparoscopic	9,903	15.351	Dominated	49.0	49.7	50.1	50.5
High mortality rate of non-OM (0.31). (BC = 0.2)	Open	8,924	14.520		58.3	60.6	61.6	61.9
	Laparoscopic	9,193	14.475	Dominated	41.7	39.4	38.4	39.1
Low mortality rate for non-OM (0.11) (BC = 0.2)	Open	10,961	17.120		66.5	71.5	73.4	73.2
	Laparoscopic	11,211	17.049	Dominated	33.5	28.5	26.6	26.8
RR of 0.5 for mortality for non-OM state (BC = 1)	Open	9,613	15.351		0.0	0.0	0.0	0.0
	Laparoscopic	11,467	17.405	903	100.0	100.0	100.0	100.0
RR of 1.5 for mortality for non-OM state (BC = 1)	Laparoscopic	9,237	14.530		0.8	0.1	0.1	0.1
	Open	9,613	15.350	456	99.2	99.9	99.9	99.9
RR of 0.5 for non-OM mortality (BC = 1) and low (0.11) mortality rate for non-OM state (BC = 0.2)	Open	10,961	17.120		0.0	0.0	0.0	0.0
	Laparoscopic	13,247	20.021	788	100.0	100.0	100.0	100.0
RR of 1.5 for non-OM mortality (BC = 1) and high (0.31) mortality rate for non-OM state (BC = 0.2)	Laparoscopic	8,745	13.961		2.3	0.8	0.5	0.4
	Open	8,924	14.520	321	97.7	99.2	99.5	99.6

BC, base-case; OM, operative management.

TABLE 48 *Sensitivity analysis associated with non-operative management for recurrent disease (QALYs)*

Sensitivity analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effective for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case	Open	9,613	14.679		59.9	61.2	62.0	62.2
	Laparoscopic	9,876	14.630	Dominated	40.1	38.8	38.0	37.8
Equal survival	Open	9,613	14.679		50.8	49.8	50.2	49.3
	Laparoscopic	9,903	14.679	Dominated	49.2	50.2	49.8	50.7
High rate of non-OM mortality (0.31) (BC = 0.2)	Open	8,924	13.989		57.7	60.2	60.5	60.6
	Laparoscopic	9,193	13.947	Dominated	42.3	39.8	39.5	39.4
Low mortality rate for non-OM (0.11) (BC = 0.2)	Open	10,961	16.146		64.1	69.8	70.1	71.1
	Laparoscopic	11,211	16.084	Dominated	35.9	30.2	29.9	28.9
RR of 0.5 for mortality for non-OM state (BC = 1)	Open	9,613	14.680		0.0	0.0	0.0	0.0
	Laparoscopic	11,467	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	9,237	13.989		1.7	0.6	0.3	0.1
	Open	9,613	14.679	546	98.3	99.4	99.7	99.9
RR of 0.5 for non-OM mortality (BC = 1) and low (0.11) mortality rate for non-OM state (BC = 0.2)	Open	10,961	16.146		0.0	0.0	0.0	0.0
	Laparoscopic	13,247	18.551	951	100.0	100.0	100.0	100.0
RR of 1.5 for non-OM mortality (BC = 1) and high (0.31) mortality rate for non-OM state (BC = 0.2)	Laparoscopic	8,745	13.520		3.7	2.0	1.6	1.3
	Open	8,924	13.989	383	96.3	98.0	98.4	98.7

BC, base-case; OM, operative management.

TABLE 49 *Sensitivity analysis around changes in the risk of hernia (life-years)*

Sensitivity analysis	Procedure	Cost (£)	Life-years	ICER (£)	Probability cost-effective 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.

TABLE 50 *Sensitivity analysis around changes in the risk of hernia (QALYs)*

Sensitivity analysis	Procedure	Cost (£)	QALYs	ICER (£)	Probability cost-effective 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
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.

TABLE 51 *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 39*)	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 39*)	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 40*)	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 40*)	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.

TABLE 52 *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 53 *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

for the non-operative management state, which was classified by the NICE review[122] as patients on adjuvant chemotherapy (*Table 51*). Once again, laparoscopic resection 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 with 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.

Results of subgroup analysis

A deterministic analysis was performed to assess the cost-effectiveness for each intervention by stage of cancer (*Table 52* for life-years and *Table 53* 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 J, QE II Health Sciences Centre, Halifax, NS: personal communication, 2005) **[Academic-in-confidence information removed]**. The results are limited and do not reflect the degree of statistical uncertainty which might surround the mortality and recurrence parameters **[Academic-in-confidence information removed]**, although some difference in mean costs and effects between the stage of disease can be seen from the results in *Table 52* for life-years and *Table 53* 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 with open patients, as this was the only instance where neither intervention clearly dominated the other. The results for patients with Stage I disease are broadly consistent with the base-case analysis with a similar cost and quality-of-life difference between the two interventions (*Table 52* for life-years and *Table 53* 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 to be consistent with this assumption. The data used to allow this analysis should be treated with caution 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.

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 £250–300 per patient. Preliminary results from the cost analysis conducted within the CLASICC trial were supplied as academic-in-confidence and have not been presented in this report.

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 was made of equal survival and disease-free survival, then the mean estimates of incremental cost-effectiveness still suggest that laparoscopic surgery is dominated by open surgery 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, few 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 suggests 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 those of the base-case analysis. Further evidence to allow data synthesis with regard to outcomes by stage is required.

Chapter 6

Implications for other parties

Quality of life for the family and carers

The data reported in Chapter 3 and summarised in *Table 35* (p. 39) suggest that laparoscopic resection is associated with some short-term benefit but takes longer to perform. There is no evidence for a difference in long-term outcomes measured by either surrogate endpoints (e.g. lymph node retrieval and resection margins) or final outcomes up to 3 years postoperation (e.g. death, disease-free survival and hernia for 3 years after surgery). Laparoscopic surgery is therefore an approach that offers patients some short-term advantages without appearing to compromise safety or long-term outcomes (at least up to 3 years). 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.

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 an 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]

Chapter 7
Implications for the NHS

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 increasing numbers of training courses and schemes available for surgeons wishing to develop the necessary skills.

The Association of Perioperative Practice has also suggested that in addition to the training of the surgeon, training would also be required for the rest of the perioperative team. This would include nurses and operating department practitioners involved with the laparoscopic technology or assisting the operating surgeons (Association of Perioperative Practice submission to NICE, 2006).

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 for, or complement to laparoscopic surgery.

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.

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 the 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]

Availability of theatre space

The evidence available from the systematic review of effectiveness reported in Chapter 3 indicates that the duration of operation is greater for laparoscopic resection (by approximately 40 minutes). Given the limited availability of theatre space, the increased use of laparoscopic resection may cause problems for theatre managers and others involved in managing theatre capacity.

Budgetary impact on the NHS

The budgetary impact of increasing use of laparoscopic surgery from current level of provision of open surgery is estimated in the section 'Expected costs' (p. 7). 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 that they will not differ between treatments) or differences in the cost of presurgery, which may differ between laparoscopic and open resection. One reason for a difference in presurgery 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, owing to the limited availability of CT, an ultrasound is performed instead. Hence any increase in the use of laparoscopic surgery may lead to increased demand for CT imaging.

An enhanced recovery programme may result in a 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 therefore may not result in reduced overall costs to the NHS.

Chapter 8
Discussion

Main results

As stated in Chapter 1, previous guidance from NICE on the use of laparoscopic surgery for colorectal cancer was that open rather than laparoscopic surgery was the preferred procedure and that laparoscopic surgery should only be undertaken as part of an RCT.[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 3 years after surgery. Furthermore, the data from the individual patient data meta-analysis allowed consideration of the relative time to either death or disease recurrence, whereas only limited data on how outcomes changed over the duration of follow-up were available from the trial reports.

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 £250–300 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. **[Academic-in-confidence information removed.]** 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. With respect to the risk of hernias, a decision was taken to focus on data from studies comparing laparoscopic and open resection. Alternative data on incisional hernia and port-site hernias may have been obtained from studies reporting the outcomes for open and laparoscopic surgery for other conditions. Such data may not, however, be generalisable to this surgery.

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 trade-offs that have to be taken into account when making decisions about which type of surgery to use. Assuming that 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 £250–300 per patient.

The base-case analysis suggests that laparoscopic resection is dominated by open resection 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, **[Academic-in-confidence information removed]**.

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 and 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 3-month follow-up of 0.00583 QALYs (i.e. about two-thirds of 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 those 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 that 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 3–4 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 suggests 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 with 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 4 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.

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 whereas 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, which 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, which 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 J, QE II Health Sciences Center, Halifax, NS: personal communication, 2005). This meta-analysis did not include all the data from all the available RCTs and it had a follow-up of only 3-years. **[Academic-in-confidence information removed.]** Nonetheless, had the data from the other trials been incorporated, it is likely that the precision of the estimates would have been improved. The greatest limitation of this review is that the data available relate to at most a 3-year time horizon. More long-term follow-up data are therefore required before it could be 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 with 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. This 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 and in improving operator expertise might be expected to reduce both of 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 reoperations, 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. A further simplifying assumption was the constant rate of all-cause mortality. Although this assumption is unrealistic, it will have little effect

on the results given the very much higher mortality, but similar mortality for each type of surgery, for colorectal cancer.

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 they had been derived from a small RCT.[40] Alternative cost data from the CLASICC trial were also explored within the economic model, in sensitivity analysis, and produced similar results to the base-case analysis (Franks PJ, Thames Valley University: personal communication, 2005). It should be noted that the data from CLASICC are preliminary and may be subject to change, hence they should be treated with caution. With respect to utilities, data were almost entirely absent and the results presented in terms of incremental cost per QALY 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, such as shorter hospitalisation, earlier return to usual activities and less postoperative pain, are non-existent, 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 3-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 are very few 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, that is, 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 3-year disease-free survival data used within the analysis suggest no difference in rates, although longer term data are needed to substantiate this. A further area in which the data available are limited is the management of patients following a recurrence. The likelihood that a recurrence would occur and the likelihood that a reoperation 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 3 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 suggest a difference in survival, further work to develop this aspect of the model estimates would be warranted.

Chapter 9
Conclusions

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 3 years.
- Laparoscopic surgery costs (approximately £250–300 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 3 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.

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.

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 have 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 RR 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 locations 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.

Acknowledgements

We thank our peer reviewers for critical advice and support and Kirsten Harrild for providing statistical advice. We also thank Bronwyn Davidson for secretarial support. We thank Andy Pring of the South West Cancer Registry and Professor David Brewster of the Scottish Cancer Registry for providing data and also nurse Flora O'Dea of the Hospital Specialist Palliative Care Team at Aberdeen Royal Infirmary for providing clinical advice on patient management. The Health Services Research Unit and the Health Economics Research Unit are both core funded by the Chief Scientist Office of the Scottish Executive Health Department.

Contribution of authors

Alison Murray (Research Fellow) and Tania Lourenco (Research Fellow) completed the review of effectiveness and 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.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA programme. Any errors are the responsibility of the authors.

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Appendix 1

Search strategies

Clinical effectiveness

Search strategies used to identify reports of randomised controlled trials and systematic reviews of laparoscopic surgery for colorectal cancer

MEDLINE (2000–May Week 1, 2005)/EMBASE (2000–Week 19, 2005) (MEDLINE Extra, 11 May 2005)

Ovid Multifile Search URL:
http://gateway.ovid.com/athens

1 exp colorectal neoplasms/su use medf
2 exp colon cancer/su use emef
3 exp rectum cancer/su use emef
4 exp colectomy/
5 exp colon resection/ use emef
6 exp rectum resection/ use emef
7 (colectom$ or hemicolect$ or colotom$).tw.
8 (mesorect$ adj3 excision$).tw.
9 or/1-8
10 exp colorectal neoplasms/ use medf
11 exp colon cancer/ use emef
12 exp rectum cancer/ use emef
13 (cancer adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
14 (carcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
15 (neoplas$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
16 (adenocarcinoma$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
17 (malignan$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
18 or/10-17
19 adenocarcinoma/
20 carcinoma/
21 neoplasms/
22 or/19-21
23 exp colon/
24 rectum/ use medf
25 exp rectum/ use emef
26 or/23-25
27 22 and 26
28 colorectal surgery/
29 Surgical procedures,operative/ use medf
30 surgery/ use emef
31 su.fs.
32 (surgery or surgical or surgeon$).tw.
33 resect$.tw.
34 operat$.tw.
35 or/28-34
36 (18 or 27) and 35
37 9 or 36
38 laparoscopy/
39 laparoscopic surgery/ use emef
40 Surgical procedures,minimally invasive/ use medf
41 Minimally invasive surgery/ use emef
42 (minimal$ adj3 (invasiv$ or access$)).tw.
43 laparoscop$.tw.
44 (key hole or keyhole).tw.
45 hand assist$.tw.
46 robotic$.tw.
47 robotics/
48 or/38-47
49 37 and 48
50 limit 49 to yr=2000-2005
51 animal/ not human/ use medf
52 (animal/ or nonhuman/) not human/ use emef
53 50 not (51 or 52)
54 clinical trial.pt. use medf
55 exp controlled clinical trials/ use medf
56 randomised controlled trial/ use emef
57 clinical trial/ use emef
58 random allocation/ use medf
59 randomization/ use emef
60 random$.tw.
61 or/54-60
62 53 and 61
63 meta analysis.tw.
64 meta analysis.pt. use medf
65 meta analysis/ use emef
66 review.ab.
67 review.pt. use medf
68 systematic review/ use emef
69 or/63-68
70 53 and 69
71 62 or 70
72 remove duplicates from 71

Science Citation Index (2000–27 May 2005)

Web of Knowledge URL: http://wok.mimas.ac.uk/

#1 TS=(colectom* OR hemicolect* OR colotom*)
#2 TS=(mesorect* SAME excision*)
#3 TS=((colon or colorectal) SAME resect*)
#4 #1 OR #2 OR #3
#5 TS=(cancer SAME (colorectal or colon* OR rectal OR rectum OR intestin* OR bowel))

#6 TS=(carcinoma SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#7 TS=(neoplas* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#8 TS=(adenocarcinoma* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#9 TS=(malignan* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#10 #5 OR #6 OR #7 OR #8 OR #9
#11 TS=laparoscop*
#12 TS=(minimal* SAME (invasiv* OR access*))
#13 TS=(key hole or keyhole)
#14 TS=robotic*
#15 TS=hand assist*
#16 #11 OR #12 OR #13 OR #14 OR #15
#17 (#4 OR #10) AND #16
#18 TS=(randomised OR randomized)
#19 TS=random* allocat*
#20 TS=review*
#21 TS=meta analysis
#22 TS= #18 OR #19 OR #20 OR #21
#23 #17 AND #22

BIOSIS (2000–May 2005)
Edina URL: http://edina.ac.uk/biosis/
((al: (random*) or al: (trial*) or al: (control*)) and ((((((al: (minimal* n3 invasiv*) or al: (minimal* n3 access*)) or (al: (hand assist*) or al: (robotic*))) or (al: (laparoscop*) or al: (key hole) or al: (keyhole)))) and ((((((((((al: (rectum n3 surgical) or al: (intestin* n3 surgical) or al: (bowel n3 surgical)) or (al: (colorectal n3 surgical) or al: (colon* n3 surgical) or al: (rectal n3 surgical))) or (al: (rectum n3 surgery) or al: (intestin* n3 surgery) or al: (bowel n3 surgery))) or (al: (colorectal n3 surgery) or al: (colon* n3 surgery) or al: (rectal n3 surgery)))) and (al: (neoplas*) or al: (adenocarcinoma*)))) or (((((((al: (rectum n3 surgical) or al: (intestin* n3 surgical) or al: (bowel n3 surgical)) or (al: (colorectal n3 surgical) or al: (colon* n3 surgical) or al: (rectal n3 surgical))) or (al: (rectum n3 surgery) or al: (intestin* n3 surgery) or al: (bowel n3 surgery))) or (al: (colorectal n3 surgery) or al: (colon* n3 surgery) or al: (rectal n3 surgery)))) and (al: (cancer) or al: (carinoma) or al: (malignan*))))) or (((al: (mesorect* n3 excision*) or al: (colon* n3 resect*)) or (al: (colectom*) or al: (hemicolectom*) or al: (colotom*)))))))))

Cochrane Library (Issue 2, 2005)
URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
#1 MeSH descriptor Colorectal Neoplasms explode all trees with qualifier: SU in MeSH products
#2 MeSH descriptor Colectomy explode all trees in MeSH products
#3 colectom* in All Fields or hemicolect* in All Fields or colotom* in All Fields
#4 (mesorect* NEAR/3 excision*) in All Fields
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Colorectal Neoplasms explode all trees in MeSH prodcuts
#7 (cancer NEAR/3 (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel)) in All Fields
#8 (carcinoma NEAR/3 (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel)) in All Fields
#9 (neoplas* NEAR/3 (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel)) in All Fields
#10 (adenocarcinoma* NEAR/3 (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel)) in All Fields
#11 (malignan* NEAR/3 (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel)) in All Fields
#12 (#6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 MeSH descriptor Adenocarcinoma, this term only in MeSH products
#14 MeSH descriptor Carcinoma, this term only in MeSH products
#15 MeSH descriptor Neoplasms, this term only in MeSH products
#16 (#13 OR #14 OR #15)
#17 MeSH descriptor Colon explode all trees in MeSH products
#18 MeSH descriptor Rectum, this term only in MeSH products
#19 (#17 OR #18)
#20 (#16 AND #19)
#21 MeSH descriptor Colorectal Surgery, this term only in MeSH products
#22 MeSH descriptor Surgical Procedures, Operative, this term only in MeSH products
#23 su.fs in All Fields
#24 (surgery OR surgical OR surgeon*) in All Fields
#25 (resect* OR operation*) in All Fields
#26 (#21 OR #22 OR #23 OR #24 OR #25)
#27 ((#12 OR #20) AND #26)
#28 (#5 OR #27)
#29 MeSH descriptor Laparoscopy, this term only in MeSH products
#30 MeSH descriptor Robotics, this term only in MeSH products
#31 MeSH descriptor Surgical Procedures, Minimally Invasive, this term only in MeSH products
#32 (minimal* NEAR/3 (invasiv* or access*)) in All Fields

#33 laparoscop* OR key hole OR keyhole OR hand assist* OR robotic* in All Fields
#34 (#29 OR #30 OR #31 OR #32 OR #33)
#35 (#28 AND #34), from 2000 to 2005

Journals@Ovid Full Text (21 July 2005)
URL: http://gateway.ovid.com/athens
Journals searched: *Annals of Surgery*; *Archives of Surgery*; *British Journal of Surgery*; *Surgical Laparoscopy*

1 annals of surgery.jn.
2 archives of surgery.jn.
3 british journal of surgery.jn.
4 surgical laparoscopy endoscopy & percutaneous techniques.jn.
5 or/1-4
6 (random$ or control$ or trial?).tw.
7 (colectom$ or hemicolect$ or colotom$).tw.
8 (mesorect$ adj3 excision$).tw.
9 ((colorectal or colon$ or rectal or rectum or intestin$ or bowel) adj3 (cancer or carcinoma or neoplas$ or surg$)).tw.
10 laparoscop$.tw.
11 (minimal$ adj3 (invasiv$ or access$)).tw.
12 (key hole or keyhole).tw.
13 hand assist$.tw.
14 robotic$.tw.
15 or/7-9
16 or/10-14
17 6 and 15 and 16
18 5 and 17
19 limit 18 to yr="2000 - 2005"

National Research Register (Issue 2,2005)
URL: http://www.update-software.com/National/
#1. COLORECTAL NEOPLASMS [su] explode all trees (MeSH)
#2. COLECTOMY single term (MeSH)
#3. colectom* or hemicolect* or colotom*
#4. (#1 or #2 or #3)
#5. COLORECTAL NEOPLASMS explode all trees (MeSH)
#6. (cancer near (colorectal or colon* or rectal or rectum or intestin* or bowel))
#7. (carcinoma near (colorectal or colon* or rectal or rectum or intestin* or bowel))
#8. (neoplasm* near (colorectal or colon* or rectal or rectum or intestin* or bowel))
#9. (adenocarcinom* near (colorectal or colon* or rectal or rectum or intestin* or bowel))
#10. (mailignan* near (colorectal or colon* or rectal or rectum or intestin* or bowel))
#11. (#5 or #6 or #7 or #8 or #9 or #10)
#12. ADENOCARCINOMA single term (MeSH)
#13. CARCINOMA single term (MeSH)
#14. NEOPLASMS single term (MeSH)
#15. (#12 or #13 or #14)
#16. COLON explode all trees (MeSH)
#17. RECTUM single term (MeSH)
#18. #16 or #17
#19. (#15 and #18)
#20. COLORECTAL SURGERY single term (MeSH)
#21. SURGICAL PROCEDURES, OPERATIVE single term (MeSH)
#22. (surgery or surgical or surgeon*)
#23. (resect* or operation*)
#24. (#20 or #21 or #22 or #23)
#25. ((#11 or #19) and #24)
#26. (#4 or #25)
#27. LAPAROSCOPY single term (MeSH)
#28. ROBOTICS single term (MeSH)
#29. SURGICAL PROCEDURES, MINIMALLY INVASIVE single term (MeSH)
#30. (minimal * near (invasiv* OR access*))
#31. (laparoscop* or key hole or keyhole or hand assist* or robotic*)
#32. (#27 or #28 or #29 or #30 or #31)
#33. (#26 and #32) from 2000 to 2005

Clinical Trials (May 2005)
URL: http://clinicaltrials.gov/ct/gui/c/r
Colorectal and laparoscopy

Current Controlled Trials (May 2005)
URL: http://www.controlled-trials.com/
Colorectal and laparoscop%

Cost-effectiveness and economic evaluations

Search strategies used to identify reports of cost-effectiveness and economic evaluations of laparoscopic surgery for colorectal cancer

MEDLINE (2000–May Week 2, 2005)/EMBASE (2000–Week 21, 2005) (MEDLINE Extra, 23 May 2005)
Ovid Multifile Search URL: http://gateway.ovid.com/
1 exp colorectal neoplasms/su use medf
2 exp colon cancer/su use emef
3 exp rectum cancer/su use emef
4 exp colectomy/ (8272)
5 exp colon resection/ use emef
6 exp rectum resection/ use emef
7 (colectom$ or hemicolect$ or colotom$).tw.
8 (mesorect$ adj3 excision$).tw.
9 or/1-8
10 exp colorectal neoplasms/ use medf
11 exp colon cancer/ use emef
12 exp rectum cancer/ use emef

13 (cancer adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
14 (carcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
15 (neoplas$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
16 (adenocarcinoma$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
17 (malignan$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
18 or/10-17
19 adenocarcinoma/
20 carcinoma/
21 neoplasms/
22 or/19-21
23 exp colon/
24 rectum/ use medf
25 exp rectum/ use emef
26 or/23-25
27 22 and 26
28 colorectal surgery/
29 Surgical procedures,operative/ use medf
30 surgery/ use emef
31 su.fs.
32 (surgery or surgical or surgeon$).tw.
33 resect$.tw.
34 operation$.tw.
35 or/28-34
36 (18 or 27) and 35
37 9 or 36
38 laparoscopy/
39 laparoscopic surgery/ use emef
40 Surgical procedures,minimally invasive/ use medf
41 Minimally invasive surgery/ use emef
42 (minimal$ adj3 (invasiv$ or access$)).tw.
43 laparoscop$.tw.
44 (key hole or keyhole).tw.
45 hand assist$.tw.
46 robotic$.tw.
47 robotics/
48 or/38-47
49 37 and 48
50 limit 49 to yr=2000-2005
51 exp "costs and cost analysis"/
52 economics/
53 exp economics,hospital/
54 exp economics,medical/
55 economics,pharmaceutical/
56 exp budgets/
57 exp models, economic/
58 exp decision theory/
59 ec.fs.
60 monte carlo method/
61 markov chains/
62 exp quality of life/
63 "Value of Life"/
64 cost of illness/
65 exp health status indicators/
66 cost$.ti.
67 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
68 economics model$.tw.
69 (economics$ or pharmacoeconomic$ or pharmo-economic$).ti.
70 (price$ or pricing$).tw.
71 (financial or finance or finances or financed).tw.
72 (value adj2 (money or monetary)).tw.
73 quality adjusted life.tw.
74 disability adjusted life.tw.
75 (qaly? or qald? or qale? or qtime? or daly?).tw.
76 (euroqol or euro qol or eq5d or eq 5d).tw.
77 (hql or hqol or h qol or hrqol or hr qol).tw.
78 (hye or hyes).tw.
79 (health adj3 (indicator? or status or utilit?)).tw.
80 markov$.tw.
81 monte carlo.tw. (
82 (decision$ adj2 (tree? or analy$ or model$)).tw.
83 or/51-82
84 50 and 83
85 remove duplicates from 84

Science Citation Index (2000–27 May 2005)
Web of Knowledge URL: http://wok.mimas.ac.uk/

#1 TS=(colectom* OR hemicolect* OR colotom*)
#2 TS=(mesorect* SAME excision*)
#3 TS=((colon OR colorectal) SAME resect*)
#4 #1 OR #2 OR #3
#5 TS=(cancer SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#6 TS=(carcinoma SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#7 TS=(neoplas* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#8 TS=(adenocarcinoma* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#9 TS=(malignan* SAME (colorectal OR colon* OR rectal OR rectum OR intestin* OR bowel))
#10 #5 OR #6 OR #7 OR #8 OR #9
#11 TS=laparoscop*
#12 TS=(minimal* SAME (invasiv* OR access*))
#13 TS=(key hole OR keyhole)
#14 TS=hand assist*
#15 TS=robotic*
#16 #12 OR #13 OR #14 OR #15 OR #16
#17 (#4 OR #10) AND #16
#18 TS=economic*
#19 TS=cost*

#20 TS=(price* OR pricing*)
#21 TS=(financial or finance*)
#22 TS=(decision* SAME (tree* OR analy* or model*))
#23 TS=markov*
#24 TS=monte carlo
#25 TS=(health SAME (indicator* or status or utilit*))
#26 TS=quality of life
#27 TS=quality adjusted life
#28 TS=disability adjusted life
#29 TS=(qaly* or qald* or qale* or qtime* or daly*)
#30 TS=(euroqol* or euro qol* or eq5d or eq 5d)
#31 TS=(hql or hqol or h qol or hrqol or hr qol)
#32 TS=(hye or hyes)
#33 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 #17 AND #30

NHS Economic Evaluation Database (May 2005)
URL: http://www.york.ac.uk/inst/crd/nhsdhp.htm
Colorectal-neoplasms (exploded)
and
laparoscop or surgery or surgical

General searches

Search strategies used to identify reports of clinical or cost-effectiveness of laparoscopic surgery for colorectal cancer

Health Management Information Consortium 2000–May 2005
URL: http://gateway.ovid.com/
1 (colectom$ or hemicolect$ or colotom$).tw.
2 (mesorect$ adj3 excision$).tw.
3 ((colon$ or colrect$) adj3 resect$).tw.
4 1 or 2 or 3
5 (cancer adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
6 (carcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
7 (neoplas$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
8 (adenocarcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
9 (malignan$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
10 or/5-9
11 (surgery or surgical or surgeon$).tw.
12 resect$.tw.
13 operat$.tw.
14 surgery/
15 or/11-14
16 4 or (10 and 15)
17 limit 16 to yr=2000 - 2005

DARE and HTA databases (May 2005)
NHS Centre for Reviews and Dissemination
URL: http://nhscrd.york.ac.uk/welcome.htm
Colorectal-neoplasms (exploded)
and
laparoscop or surgery or surgical

Conference Proceedings Abstracts screened
Association of Coloproctology of Great Britain and Ireland:
Annual Meeting, Manchester, July 2002
Annual Meeting, Edinburgh, July 2003
Annual Meeting, Birmingham, June 2004

European Association of Coloproctology:
Scientific Annual Meeting, Barcelona, September 2003
Scientific Annual Meeting, Geneva, September 2004

Society of American Gastrointestinal and Endoscopic Surgeons:
8th World Congress, New York, March 2002
9th World Congress, Los Angeles, March 2003
10th World Congress, Colorado, March 2004
11th World Congress, Fort Lauderdale, April 2005

European Association for Endoscopic Surgery:
10th International Congress, Lisbon, June 2002
12th International Congress, Barcelona, June 2004
13th International Congress, Venice, June 2005

Association of Endoscopic Surgeons of Great Britain and Ireland (AESGBI):
Annual Meeting, Dublin, April 2002

American Society of Colon and Rectal Surgeons:
Annual Meeting, Chicago, April 2002
Annual Meeting, New Orleans, April 2003
Annual Meeting, Dallas, April 2004
Annual Meeting, Philadelphia, April 2005

Websites searched for other evidence-based reports and background information
American Society for Colon and Rectal Surgeons
URL: http://www.fascrs.org/index.cfm. Accessed July 2005]

Association of Coloproctology of Great Britain and Ireland (ACPGBI)
URL: http://www.acpgbi.org.uk/. Accessed June 2005

Cancer Research UK
URL: http://www.cancerresearchuk.org/. Accessed July 2005

NHS Health and Social Care Cancer Information Services
URL: http://www.icservices.nhs.uk/cancer/pages/dataset/. Accessed July 2005

Society of American Gastrointestinal and Endoscopic Surgeons
URL: http://www.sages.org/index.html. Accessed July 2005

Trip database.
URL: http://www.tripdatabase.com/. Accessed May 2005

Appendix 2

Study eligibility form

Paper number: _____ **Assessor initials:** _____ **Date assessed:** _____

Study identifier
(surname of first author + year of publication)

Type of study
Q1. Is the study a systematic review or meta-analysis of randomised controlled trials, a randomised controlled trial, or a cohort study or UK registry with a minimum of three years follow-up?

(If Yes, please indicate which type of study design)

Yes ⇩ Go to Next question | Unclear ⇩ Go to Next question | No ⇩ **Exclude**

Participants in the study
Q2. Are some or all of the participants in the study adults with colorectal cancer?

Yes ⇩ Go to Next question | Unclear ⇩ Go to Next question | No ⇩ **Exclude**

Interventions in the study
Q3. Did some or all of the participants receive open surgical procedure, laparoscopic, laparoscopic-assisted or hand-assisted laparoscopic surgery?

Yes ⇩ Go to Next question | Unclear ⇩ Go to Next question | No ⇩ **Exclude**

Outcomes in the study
Q4. Does the study report short-term and/or long-term outcome data on the patients that underwent the intervention (s)?

Yes ⇩ **Include**, subject to clarification of 'unclear' points | Unclear ⇩ **Exclude** | No ⇩ **Exclude**

Final decision **Include** **Unclear** **Exclude**

Appendix 3

Data extraction form

Laparoscopic and hand-assisted laparoscopic versus Open surgery for the treatment of colorectal cancer

Reviewer ID: ☐

Study	
Study ID: **Country:** **Funding:** government / private / manufacturer / other (specify)	**RCT** ☐ **Quasi-RCT** ☐ **Cohort study** ☐ **Unclear** ☐

Participants
Recruitment dates: _____ Number of eligible patients: _____ Number of patients randomised: _____
Criteria for Inclusion:
Criteria for Exclusion:

Intervention		
	Surgical technique	**No. of Patients**
Intervention 1		
Intervention 2		
Intervention 3		
Comments: (i.e. operator information, adjuvant therapy, length of incision)		

Patient Characteristics				
Specify	**Intervention 1**	**Intervention 2**	**Intervention 3**	**Overall**
Age (years)				
Sex (M/F)				
Body Weight (kg)				

Follow-up period: _____ Number of patients lost to follow-up: _____

_____

Comments:

Location of cancer				
Specify	**Intervention 1**	**Intervention 2**	**Intervention 3**	**Overall**
Total (No.) **Colon (No.)** • Caecum • Ascending colon • Hepatic flexure • Transverse colon • Splenic flexure • Descending colon • Sigmoid colon • Rectosigmoid junction **Rectum (No.)**				

Stage of cancer				
Specify	**Intervention 1**	**Intervention 2**	**Intervention 3**	**Overall**
TNM or Dukes stage (No.) (***Specify***)				
Comments:				

Short-term Outcomes			
Intra-operative	**Intervention 1**	**Intervention 2**	**Intervention 3**
Duration of operation (min)			
Blood loss			
Anastomotic leakage			
Abdominal wound breakdown			
Lymph node retrieval			
Number of ports used for laparoscopic resection			
Opposite method initiated			
Completeness of resection/margins of tumours clearance			
Conversion			
Post-operative			
Seroma			
Infection • Specify			
Port site hernia			
Vascular injury			
Visceral injury			
30-day mortality			
Length of hospital stay			
Post-operative pain • Specify			
Time to return to usual activities (days)			
Other			

Long-term Outcomes	Intervention 1	Intervention 2	Intervention 3
Survival (years)			
Disease-free survival (years)			
Health-related quality of life			
Tumour recurrence type • Port site metastasis • Wound metastasis			
Time to recurrence (months)			
Incidence of incisional hernia			
Long term pain			
Other			

Additional information/Other comments

Contact with Author

Date: ……/……/……

Signature: ……

Appendix 4

Quality assessment form – systematic reviews

Question	Yes	No	Partially	Unknown
1. Were the search methods used to find evidence (primary studies) on the primary question(s) stated?				
2. Was the search for evidence reasonably comprehensive?				
3. Were the criteria used for deciding which studies to include in the review reported?				
4. Was bias in the selection of articles avoided?				
5. Were the criteria used for assessing the validity of the studies that were reviewed reported?				
6. Was the validity of all of the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?				
7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?				
8. Were the findings of the relevant studies combined appropriately relative to the primary question the review addresses?				
9. Were the conclusions made by the author(s) supported by the data and/or the analysis reported in the review?				

Appendix 5

Quality assessment form – RCTs

Question	Yes	No	Unclear
1. Was a method of randomisation performed? **Adequate approaches to sequence generation** • computer-generated random tables • random number tables **Inadequate approaches to sequence generation** • use of alternation, case record numbers, birth dates or week days			
2. Was the treatment allocation concealed? **Adequate approaches to concealment of randomisation** • centralised or pharmacy-controlled randomisation • serially-numbered identical containers • on-site computer based system with a randomisation sequence that is not readable until allocation • other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients **Inadequate approaches to concealment of randomisation** • use of alternation, case record numbers, birth dates or week days • open random number lists • serially numbered envelopes			
3. Were the groups similar at baseline regarding the most important prognostic indicators?			
4. Were the eligibility criteria specified?			
5. Was the outcome assessor blinded?			
6. Was the care provider blinded?			
7. Was the patient blinded?			
8. Were point estimates and measures of variability presented for the primary outcome measures?			
9. Did the analysis include an intention-to-treat analysis?			

Appendix 6

List of included studies

Araujo, 2003

Primary reference

Araujo SE, da Silva eSousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, *et al*. Conventional approach × 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**:133–40.

Bonjer (unpublished)

Primary reference

The Trans Atlantic Laparoscopically-Assisted versus Open Colectomy Trials Study Group. Laparoscopically assisted versus open colectomy for colon cancer – a meta-analysis.

COLOR, 2005

Primary reference

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**:477–84.

Related references

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**:409–17.

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

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**:1670–4.

COST, 2004

Primary reference

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

Related references

Nelson H. Laparoscopic colectomy for colon cancer – a trial update. *Swiss Surg* 2001;**7**:248–51.

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

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**:636–7.

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**:321–8.

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

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**:637–8.

CLASICC, 2005

Primary reference

Guillou PJ, 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.

Curet, 2000

Primary reference

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**:1062–6.

Hasegawa, 2003

Primary reference

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**:636–40.

Related reference

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.

Hewitt, 1998

Primary reference

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**:901–9.

Kaiser, 2004

Primary reference

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**:329–34.

Kim, 1998

Primary reference

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**:971–8.

King, 2006

King PM,Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, *et al*. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006;**93**:300–8.

Lacy, 2002

Primary reference

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**:2224–9.

Related references

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**:22–6.

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**:638–46.

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

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**:1101–5.

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**:1039–42.

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**:96–8.

Leung, 2004

Primary reference

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**:1187–92.

Related references

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

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**:1305–10.

Milsom, 1998

Primary reference

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**:46–54.

Neudecker, 2003

Primary reference

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**:73–7.

Related reference

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

Schwenk, 1998

Primary reference

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**:49–55.

Related references

Bohm B, Junghans T, Neudecker J, Schwenk W. Hepatic and renal function following laparoscopic and conventional resection of colorectal cancer – results from a prospective randomized trial. *Viszeralchirurgie* 1999;**34**:20–4.

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**:600–8.

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

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

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**:6–12.

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

Stage, 1997

Primary reference

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**:391–6.

Tang, 2001

Primary reference

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**:801–7.

Vignali, 2004

Primary reference

Vignali A, Braga M, Zuliani W, Frasson M, Radaelli G, Di Carlo V. Laparoscopic colorectal

surgery modifies risk factors for postoperative morbidity. *Dis Colon Rectum* 2004;**47**:1686–93.

Related reference

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**:759–66.

Zhou, 2004

Primary reference

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**:1211–15.

Appendix 7

Detailed quality assessment score for each of the included studies

Randomised controlled trials

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Araujo, 2003	Y	U	Y	Y	U	N	U	N	U
CLASICC, 2005	Y	Y	Y	Y	U	N	U	Y	Y
COLOR, 2005	Y	Y	Y	Y	N	N	N	Y[a]	Y
COST, 2004	Y	Y	Y	Y	Y	N	U	Y[a]	Y
Curet, 2000	Y	N	Y	Y	U	N	U	Y[b]	N
Hasegawa, 2003	Y	U	Y	Y	U	N	U	Y[b]	N
Hewitt, 1998	Y	U	N	Y	U	N	U	Y[a]	N
Kaiser, 2004	Y	U	N	Y	U	N	U	Y[b]	N
Kim, 1998	Y	N	N	Y	U	N	U	Y[a]	U
King, 2006	Y	Y	Y	Y	U	N	U	Y	Y
Lacy, 2002	Y	N	Y	Y	U	N	U	Y	U
Leung, 2004	Y	Y	Y	Y	U	N	U	Y	N
Milsom, 1998	Y	U	Y	Y	N	N	N	Y[a]	N
Neudecker, 2003	Y	Y	Y	Y	U	N	N	Y[a]	U
Schwenk, 1998a	Y	U	Y	Y	U	N	U	Y	Y
Stage, 1997	Y	U	N	Y	U	N	U	Y[a]	N
Tang, 2001	Y	N	Y	Y	U	N	U	Y[a]	Y
Vignali, 2004	Y	N	N	Y	U	N	U	Y	Y
Zhou, 2004	U	U	Y	Y	U	N	U	Y	U

N, No; U, Unclear; Y, Yes.
[a] Median (range).
[b] Mean (range).

Systematic reviews and meta-analyses

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Bonjer, 2005	**[Academic-in-confidence information removed]**								

Appendix 8

Characteristics of included studies

Randomised controlled trials published from 2000 onwards

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Araujo, 2003[47] **Study design**: RCT **Location**: Brazil **Mean follow-up**: 47.2 months **Recruitment dates**: September 1997–September 2000 **Funding**: not reported	**Inclusion criteria**: distal rectal adenocarcinoma with preoperative staging favourable to radical resection by abdominoperineal resection **Number of eligible patients**: 28 **Number of patients randomised**: 28	Laparoscopic (n = 13) versus open (n = 15) **Additional information**: 4 trocars were used; all patients underwent chemoradiation before surgery	**Mean age (range)**: 59.1 (31–75) years **Gender (M/F)**: 9/4 **Mean BMI (range)**: 23.5 (21.7–24.6) **Location of cancer**: rectum **Stage of cancer (Aster–Coller)**: A: 4 B_1: 1 B_2: 5 C_1: 2 C_2: 1 D: 0	**Mean age (range)**: 56.4 (24–78) years **Gender (M/F)**: 10/5 **Mean BMI (range)**: 25.6 (17.1–38.5) **Location of cancer**: rectum **Stage of cancer (Aster–Coller)**: A: 1 B_1: 5 B_2: 3 C_1: 2 C_2: 3 D: 0	Duration of operation Lymph node retrieval Conversion Abdominal wound breakdown Length of hospital stay Recurrence
CLASICC, 2005[3] **Study design**: RCT **Location**: UK **Recruitment dates**: July 1996 to July 2002 **Follow-up range**: 1–3 months **Funding**: UK Medical Research Council	**Inclusion criteria**: patients suitable for hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection or abdominoperineal resection **Exclusion criteria**: adenocarcinoma of the colon, contraindications to pneumoperitoneum (chronic cardiac or pulmonary disease), acute intestinal obstruction, malignant disease in the past 5 years, synchronous adenocarcinoma, pregnancy and associated gastrointestinal disease needing surgical intervention **Number of eligible patients**: 794 **Number of patients randomised**: 794	Laparoscopic-assisted (n = 526) versus open (n = 268) **Additional information**: the trial design required that every surgeon had undertaken at least 20 laparoscopic-assisted resections	**Mean age (SD)**: 69 (11) years **Gender (M/F)**: 296/230 **Mean BMI (SD)**: 25 (4) **Location of cancer**: Colon: 273 Rectum: 253 **Stage of cancer (TNM)**: T stage: T0: 4 T1: 26 T2: 68 T3: 261 T4: 70 N stage: N0: 244 N1: 107 N2: 72 M stage: M0: 167 M1: 12	**Mean age (SD)**: 69 (12) years **Gender (M/F)**: 145/123 **Mean BMI (SD)**: 26 (4) **Location of cancer**: Colon: 140 Rectum: 128 **Stage of cancer (TNM)**: T stage: T0: 1 T1: 12 T2: 35 T3: 136 T4: 33 N stage: N0: 129 N1: 52 N2: 38 M stage: M0: 91 M1: 7	Anastomotic leakage Lymph node retrieval Completeness of resection/margins of tumour clearance Conversions Wound infection 30-day mortality Quality of life Postoperative pain

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
COLOR, 2005[4] **Study design**: RCT **Location**: Europe **Recruitment dates**: March 1997–March 2003 **Follow-up**: not reported **Funding**: Ethicon Endo-Surgery (Hamburg, Germany) *Linked reports*: Wu, 2003,[84] 2004[85] Janson, 2004[66]	**Inclusion criteria**: patients with adenocarcinoma localised in the caecum, ascending colon, descending colon or sigmoid colon above the peritoneal deflection who were age 18 years or older and who gave written informed consent **Exclusion criteria**: BMI > 30 kg/m^2; adenocarcinoma of the transverse colon or splenic flexure; metastases in the liver or lungs; acute intestinal obstruction; multiple primary tumours of the colon; scheduled need for synchronous intra-abdominal surgery; preoperative evidence of invasion of adjacent structures, as assessed by CT, magnetic resonance imaging or ultrasonography; previous epsilateral colon surgery; previous malignant disease (except those who had had curative treatment for basocellular carcinoma of the skin or *in situ* carcinoma of the cervix); absolute contraindications to general anaesthesia; and a long-term pneumoperitoneum. After randomisation, patients were excluded if metastasis was detected during surgery, microscopic examination of the resected sample showed no signs of malignant disease, other malignant disease was discovered before or during surgery, patients needing emergency surgery or if patients withdrew consent **Number of eligible patients**: 1248 **Number of patients randomised**: 1248	Laparoscopic (n = 627; 536 analysed) versus open (n = 621; 546 analysed) 153 patients were excluded post-randomisation, 13 had missing data **Additional information**: for laparoscopy, all surgical teams had done at least 20 laparoscopic-assisted colectomies. All open surgeries were done by surgical teams who had at least one staff member with credentials in colon surgery	**Median age (range)**: 71 (27–92) years **Gender (M/F)**: 326/301 **Median BMI (range)**: 24.5 (12.1–37.1) **Location of cancer**: Right colon: 259 Left colon: 57 Sigmoid colon: 199 Other: 21 **Stage of cancer (TNM)**: I: 129 II: 218 III: 181 Data were missing for some patients	**Median age (range)**: 71 (31–95) years **Gender (M/F)**: 336/285 **Median BMI (range)**: 24.9 (14.5–40.5) **Location of cancer**: Right colon: 253 Left colon: 56 Sigmoid colon: 212 Other: 25 **Stage of cancer (TNM)**: I: 125 II: 239 III: 175 Data were missing for some patients	Duration of operation Blood loss Abdominal wound breakdown Lymph node retrieval Conversion Wound infection Urinary tract infection Length of hospital stay

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
COST, 2004[2] **Study design**: RCT **Location**: USA **Recruitment dates**: August 1994–August 2001 **Median Follow-up**: 4.4 years **Funding**: National Cancer Institute *Linked reports*: Nelson, 2001,[73] 2004[74] Stocchi, 2005[81] Weeks, 2002[82] Winslow, 2002[83] Young-Fadok, 2005[86]	**Inclusion criteria**: clinical diagnosis of adenocarcinoma of the colon (histological confirmation was required at surgery), an age of at least 18 years and the absence of prohibitive abdominal adhesions **Exclusion criteria**: advanced local or metastatic disease, rectal or transverse colon cancer, acute bowel obstruction or perforation from cancer and severe medical illness. Inflammatory bowel disease, familial polyposis, pregnancy or concurrent or previous malignant tumour **Number of eligible patients**: 872 **Number of patients randomised**: 872	Laparoscopic-assisted (n = 435) versus open (n = 437; 428 analysed, 9 excluded post-randomisation) **Additional information**: 66 credentialed surgeons at 48 institutions. Each surgeon had performed at least 20 laparoscopic-assisted colorectal operations Length of incisions was 18 (3–35) cm in the open group and 6 (2–35) cm in the laparoscopic-assisted group	**Median age (range)**: 70 (28–96) years **Gender (M/F)**: 223/212 **Location of cancer**: Right colon: 237 Left colon: 32 Sigmoid colon: 166 **Stage of cancer (TNM)**: 0: 20 I: 153 II: 136 III: 112 IV: 10 Unknown: 4	**Median age (range)**: 69 (29–94) years **Gender (M/F)**: 208/220 **Location of cancer**: Right colon: 232 Left colon: 32 Sigmoid colon: 164 **Stage of cancer (TNM)**: 0: 33 I: 112 II: 146 III: 121 IV: 16 Unknown: 0	Duration of operation Lymph node retrieval Conversion 30-day mortality Length of hospital stay Disease-free survival Recurrence Number of ports used for laparoscopic resection Wound infection Incidence of incisional hernia Survival Postoperative pain Quality of life
Curet, 2000[48] **Study design**: RCT **Location**: USA **Recruitment dates**: January 1993–November 1995 **Follow-up range**: 2.5–63 months (mean: 4.9 years) **Funding**: not reported	**Inclusion criteria**: patients with colon cancer Exclusion criteria: individuals undergoing colostomy placement alone or its removal, patients aged <18 years, concurrent pregnancy, complete colon obstruction resulting in significant proximal distention and the presence of malignant fistulisation or fixation in adjacent tissues **Number of eligible patients**: 43 **Number of patients randomised**: 43	Laparoscopic-assisted (n = 25) versus open (n = 18) **Additional information**: all surgery was performed either by attending surgeons or residents under direct supervision. All attending surgeons had performed multiple laparoscopically assisted colectomies for benign disease and palliation before participation in this study. A total of 4 and 5 laparoscopic trocars were used	**Mean age (range)**: 65.6 (45–83); converted: 66.3 (51–76) **Gender (M/F)**: 11/7; converted: 4/3 **Location of cancer (conversion)**: Right colon: 6 (4) Left colon: 1 (1) Sigmoid colon: 7 (1) Low anterior resection: 4 (1) **Stage of cancer (Dukes) (conversion)**: A: 1 (0) B: 10 (2) C: 7 (3) D: 0 (2)	**Mean age (range)**: 69.2 (49–82) years **Gender (M/F)**: 14/4 **Location of cancer**: Right colon: 5 Left colon: 5 Sigmoid colon: 3 Low anterior resection: 5 **Stage of cancer (Dukes)**: A: 0 B: 2 C: 3 D: 2	Duration of operation Blood loss Lymph node retrieval Conversion Infection Length of hospital stay Recurrence Late mortality

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Hasegawa, 2003[49] **Study design**: RCT **Location**: Japan **Recruitment dates**: June 1998–October 2000 **Follow-up**: not reported **Funding**: not reported *Linked report*: Hasegawa, 2001[65]	**Inclusion criteria**: patients with preoperative diagnosis of T_2 or T_3 colorectal cancer (N_0) who underwent curative surgery **Exclusion criteria**: patients with T_2 and T_1 tumours. Patients with T_3 tumours in the upper and lower rectum. Patients with T_3 tumours in the transverse colon **Number of eligible patients**: 97 **Number of patients randomised**: 59	Laparoscopic (n = 29; 24 analysed) versus open (n = 30; 26 analysed) **Additional information**: length of incision was 5.9 (3–12) cm in the laparoscopic group compared with 17.8 (12–23) cm in the open group; 5-port technique in the laparoscopic group and bowel was delivered through a small wound and divided extra-corporeally	**Mean age (range)**: 61 (33–75) years **Gender (M/F)**: 14/10 **Location of cancer**: Caecum: 1 Ascending colon: 7 Descending colon: 1 Sigmoid colon: 13 Rectosigmoid junction: 2 **Stage of cancer (Dukes)**: A: 2 B: 14 C: 8 D: 0	**Mean age (range)**: 61 (37–78) years **Gender (M/F)**: 18/8 **Location of cancer**: Caecum: 8 Ascending colon: 4 Descending colon: 0 Sigmoid colon: 12 Rectosigmoid junction: 2 **Stage of cancer (Dukes)**: A: 1 B: 16 C: 9 D: 0	Duration of operation Blood loss Anastomotic leakage Lymph node retrieval Conversion Wound infection Length of hospital stay Recurrence
Kaiser, 2004[51] **Study design**: RCT **Location**: USA **Recruitment dates**: January 1995–February 2001 **Follow-up range**: 3–69 months (median: 35 months) **Funding**: not reported	**Inclusion criteria**: patients diagnosed with colon cancer and scheduled for an elective colon resection, elective surgery in curative intent, primary right, left or sigmoid colon adenocarcinoma, age >18 years, ability to participate in follow-up evaluation, American Society of Anaesthesiology class I–III **Exclusion criteria**: emergency or urgent surgery (acutely obstructed or perforated colon cancer), tumour Stage IV, rectal or transverse colon cancer, known prohibitive adhesions from previous abdominal surgery, ASA class IV, V, associated gastrointestinal disease (Crohn's disease, chronic ulcerative colitis, FAP), pregnancy **Number of eligible patients**: 49 **Number of patients randomised**: 49	Laparoscopic-assisted (n = 28; 13 were converted) versus open (n = 20) **Additional information**: surgical teams headed by two surgeons who had previously demonstrated experience in laparoscopic-assisted colon surgery for either benign or malignant disease before participation in this study	**Mean age (range)**: 59.0 (4–83); converted: 60.5 (48–68) years **Gender (M/F)**: 7/8; converted: 5/8 **Location of cancer; conversion**: Caecum: 3; 3 Ascending colon: 6; 4 Sigmoid colon: 6; 6 **Stage of cancer; conversion**: I: 2; 2 II: 10; 5 III: 3; 2 IV: 0; 4	**Mean age (range)**: 60.5 (42–80) years **Gender (M/F)**: 9/11 **Location of cancer**: Caecum: 6 Ascending colon: 6 Sigmoid colon: 8 **Stage of cancer**: I: 7 II: 3 III: 10 IV: 0 **Additional information**: patients in this group had significantly more advanced disease than the intervention group	Duration of operation Blood loss Lymph node retrieval Conversion Infection Length of hospital stay Recurrence Survival

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
King, 2006[40] **Study design**: RCT **Location**: UK **Recruitment dates**: January 2002–March 2004 **Follow-up**: not reported **Funding**: NHS Developments in the Organisation of Care Project Grant	**Inclusion criteria**: patients diagnosed with adenocarcinoma of the colon or rectum. Patients with transverse colon carcinomas and those who had had another cancer within the preceding 5 years **Exclusion criteria**: any non-elective admission, those with preoperative evidence of haematogenous metastases, patients less than 18 years old, those who were pregnant and patients who did not consent to randomisation. Patients not able to have epidural anaesthetic **Number of eligible patients**: 94 **Number of patients randomised**: 62	Laparoscopic-assisted (n = 43; 41 analysed) versus open (n = 19) **Additional information**: Laparoscopic-assisted and open surgeries are both embedded in an enhanced recovery programme	**Mean age (SD)**: 72.3 (11) years **Gender (M/F)**: 23/18 **Body weight (SD)**: 26.1 (3.8) kg **Location of cancer**: Colon: 27 Rectum: 14 **Stage of cancer (Dukes)**: A: 9 B: 19 C_1: 11 C_2: 2	**Mean age (SD)**: 70.4 (10.5) years **Gender (M/F)**: 8/11 **Body weight (SD)**: 27.2 (4.6) kg **Location of cancer**: Colon: 14 Rectum: 5 **Stage of cancer (Dukes)**: A: 1 B: 11 C_1: 6 C_2: 1	Duration of operation Blood loss Abdominal wound breakdown Anastomotic leakage Conversion Wound infection Length of hospital stay Quality of life
Lacy, 2005[22] **Study design**: RCT **Location**: Spain **Recruitment dates**: November 1993–July 1998 **Follow-up range**: 27–85 months (median: 43 months) **Funding**: Fonde de Investigaciones Sanitarias, Ministerio de Ciencia y Tecnologia and Agencia d'Avaluacio de Tecnologia Medica of the Generalitat de Catalunya *Linked reports*: Delgado, 2000,[63] 2001[64] Lacy, 1995,[68] 1998,[69] 2001,[67] 2002[70]	**Inclusion criteria**: adenocarcinoma of the colon, 15 cm above the anal verge **Exclusion criteria**: cancer located at the transverse colon, distant metastasis, adjacent organ invasion, intestinal obstruction, past colonic surgery and no consent to participate in the study **Number of eligible patients**: 442 **Number of patients randomised**: 219	Laparoscopic-assisted (n = 111) versus open (n = 108) **Additional information**: both laparoscopic-assisted and open colectomies were done by a single gastrointestinal surgical team with wide experience in laparoscopic procedures After surgery, 68 (61%) of the laparoscopic assisted group received adjuvant chemotherapy according to the established protocol	**Mean age (SD)**: 68 (12) years **Gender (M/F)**: 56/55 **Location of cancer**: Caecum: 32 Ascending colon: 7 Hepatic flexure: 10 Descending colon: 8 Sigmoid colon: 54 **Stage of cancer (TNM)**: I: 27 II: 42 II: 37 IV: 5	**Mean age (SD)**: 71 (11) years **Gender (M/F)**: 50/58 **Location of cancer**: Caecum: 21 Ascending colon: 17 Hepatic flexure: 11 Descending colon: 11 Sigmoid colon: 48 **Stage of cancer (TNM)**: I: 18 II: 48 III: 36 IV: 6	Duration of operation Blood loss Anastomotic leakage Infection Length of hospital stay Recurrence Port-site metastasis Time to recurrence Survival Disease-free survival Opposite method initiated

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Leung, 2004[53] **Study design**: RCT **Location**: Hong Kong **Recruitment dates**: September 1993–October 2002 **Follow-up: median (IQR)**: Laparoscopic group 52.7 (38.9) months Open group 49.2 (35.4) months **Funding**: not reported *Linked reports*: Leung, 2000,[71] 2003[72]	**Inclusion criteria**: patients diagnosed to have rectosigmoid carcinoma seen in Prince of Wales Hospital, Hong Kong. From July 1995 onwards, patients from United Christian Hospital, Hong Kong, were included **Exclusion criteria**: patients with distal tumour requiring anastomosis within 5 cm of the dentate line, patients with tumours larger than 6 cm or with tumour infiltration to the adjacent organs on sonography or CT, patients with previous abdominal operations near the field of the colorectal operation, patients who did not give consent to the procedure and patients with intestinal obstruction or perforation **Number of eligible patients**: 825 **Number of patients randomised**: 403	Laparoscopic (n = 203) versus open (n = 200) **Additional information**: the operations were performed by surgeons experienced in both laparoscopic and colorectal surgery	**Mean age (SD)**: 67.1 (11.7) years **Gender (M/F)**: 104/99 **Location of cancer**: rectosigmoid junction **Stage of cancer (TNM)**: I: 31 II: 72 III: 64 IV: 36	**Mean age (SD)**: 66.5 (12.3) years **Gender (M/F)**: 114/86 **Location of cancer**: rectosigmoid junction **Stage of cancer (TNM)**: I: 28 II: 73 III: 69 IV: 30	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 Postoperative pain Survival Disease-free survival Recurrence
Neudecker, 2003[55] **Study design**: RCT **Location**: Germany **Recruitment dates**: April 1999–August 2000 **Follow-up**: not reported **Funding**: Deutsche Forschunsgemeinschaft *Linked report*: Neudecker, 2002[75]	**Inclusion criteria**: patients scheduled to elective colorectal cancer resection. Only sigmoidectomies, anterior rectal resections and right hemicolectomies **Exclusion criteria**: emergency surgery, operative risk greater than ASA class III; coagulopathy, trombopathy, or history of thromboembolic complications; tumour size >8 cm in preoperative CT scan, BMI > 30 kg/m^2; intraabdominal abscess or sepsis **Number of eligible patients**: 30 **Number of patients randomised**: 30	Laparoscopic (n = 14) versus open (n = 16)	**Median age (range)**: 62 (46–76) years **Gender (M/F)**: 7/7 **BMI (range)**: 25.7 (21.3–28.5) **Location of cancer**: Right colon: 3 Sigmoid colon: 11	**Median age (range)**: 64 (52–82) years **Gender (M/F)**: 10/6 **BMI (range)**: 26.2 (22.7–29.6) **Location of cancer**: Right colon: 4 Sigmoid colon: 12	Duration of operation

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Tang, 2001[58] **Study design**: RCT **Location**: Singapore **Recruitment dates**: March 1997–August 1999 **Follow-up**: not reported **Funding**: National Medical Research Council	**Inclusion criteria**: patients with clinical diagnosis of colorectal cancer based on colonoscopy or barium enema following histological confirmation. At least 18 years old and suitable for elective surgical resection or abdominoperineal resection **Exclusion criteria**: adenocarcinoma of the transverse colon, any contraindications to pneumoperitoneum, acute intestinal obstruction, any malignancy within the previous 5 years, synchronous multiple adenocarcinomas and pregnancy **Number of eligible patients**: 236 **Number of patients randomised**: 236	Laparoscopic (n = 118) versus open (n = 118) **Additional information**: incision length was 9 (1–40) cm for the laparoscopic group and 15 (5–40) cm for the open group	**Median age (range)**: 64 (33–87) years **Gender (M/F)**: 61/57 **Location of cancer**: colon **Stage of cancer (Dukes)**: A: 9 B: 45 C: 42 D: 14 Histopathological examination not performed in some patients	**Median age (range)**: 62 (31–89) years **Gender (M/F)**: 70/48 **Location of cancer**: colon **Stage of cancer (Dukes)**: A: 8 B: 50 C: 43 D: 11 Histopathological examination not performed in some patients	Duration of operation Anastomotic leakage Conversion Wound infection Urinary tract infection
Vignali, 2004[59] **Study design**: RCT **Location**: Italy **Recruitment dates**: from February 2001 **Funding**: not reported *Linked report*: Braga, 2002[62]	**Inclusion criteria**: age at least 18 years and suitability for elective surgery **Exclusion criteria**: cancer infiltrating adjacent organs as assessed by CT or magnetic resonance imaging, cardiovascular dysfunction (New York Heart Association class >3), respiratory dysfunction (arterial PO_2 < 70 mmHg), hepatic dysfunction (Child–Pugh class C), ongoing infection and plasma neutrophil level less than 2.0×10^9/l **Number of eligible patients**: 384 **Number of patients randomised**: 384	Laparoscopic (n = 190 including 144 with cancer) versus open (n = 194 including 145 with cancer)	**Location of cancer**: Right colon: 48 Transverse colon: 2 Descending colon: 27 Sigmoid colon: 21 Rectum: 48 **Stage of cancer (TNM)**: I: 34 II: 38 III: 57 IV: 15	**Location of cancer**: Right colon: 44 Transverse colon: 2 Descending colon: 25 Sigmoid colon: 23 Rectum: 49 **Stage of cancer (TNM)**: I: 32 II: 35 III: 64 IV: 14	Lymph node retrieval

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Zhou, 2004[60] **Study design**: RCT **Location**: China **Recruitment dates**: June 2001–September 2002 **Follow-up range**: 1–16 months **Funding**: National Outstanding Youth Foundation of China	**Inclusion criteria**: patients diagnosed with rectal carcinoma, with the lowest margin of tumour located under the peritoneal reflection and 1.5 cm above the dentate line. Obese patients and those with a history of inferior abdominal surgery, hypertension (blood pressure well controlled), chronic cholecystitis or/and cholecystolithiasis, pediculotorsion of ovarian cysts and multiple primary rectal cancer **Exclusion criteria**: patients diagnosed with low rectal cancer of other pathological type (e.g. lymphoma), those with the lowest margin of tumour within 1.5 cm above the dentate line, those in emergency situations (e.g. acute obstruction during enema, haemorrhage, and perforation), those in Dukes' stage D with local infiltration affecting adjacent organs and those unwilling to take part in the study **Number of eligible patients**: 171 **Number of patients randomised**: 171	Laparoscopic (n = 82) versus open (n = 89) **Additional information**: all 171 patients underwent total mesorectal excision and anal sphincter preservation. Both laparoscopic and open procedures were performed by 4 colon and rectal surgeons	**Mean age (range)**: 44 (26–85) years **Gender (M/F)**: 46/36 **Stage of cancer (Dukes)**: A: 5 B: 10 C_1: 33 C_2: 30 D: 4	**Mean age (range)**: 45 (30–81) years **Gender (M/F)**: 43/46 **Stage of cancer (Dukes)**: A: 6 B: 8 C_1: 35 C_2: 33 D: 7	Duration of operation Blood loss Anastomotic leakage Infection Length of hospital stay Recurrence

Randomised controlled trials published before 2000

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Hewitt, 1998[50] **Study design**: RCT **Location**: Hong Kong **Recruitment dates**: not reported **Follow-up**: not reported **Funding**: Chinese University of Hong Kong	**Exclusion criteria**: Age older than 80 years, previous abdominal surgery, a rectal tumour less than 10 cm from the anal verge, advanced local disease, evidence of metastatic disease, concurrent debilitating disease or infection, administration of any immune-modulating drugs, blood or blood products within 6 months of surgery **Number of eligible patients**: 25 **Number of patients randomised**: 16	Laparoscopic-assisted (n = 8) versus open (n = 8) **Additional information**: all operations were performed by surgeons who had significant experience with both laparoscopic and open techniques	**Median age (range)**: 54 (40–72) years **Gender (M/F)**: 4/4 **Location of cancer**: Transverse colon: 1 Sigmoid colon: 4 Anterior resection : 3 **Stage of cancer (Dukes)**: A: 1 B_1: 1 B_2: 2 C_1: 1 C_2: 3	**Median age (range)**: 70 (38–77) years **Gender (M/F)**: 3/5 **Location of cancer**: Sigmoid colon: 4 Anterior resection: 3 Left hemicolectomy: 1 **Stage of cancer (Dukes)**: A: 1 B_1: 2 B_2: 1 C_1: 1 C_2: 3	Duration of operation Length of hospital stay
Kim, 1998[52] **Study design**: RCT **Location**: USA **Recruitment dates**: June 1996–May 1997 **Follow-up range**: 1–12 months **Funding**: Minimally Invasive Surgery Center, The Cleveland Clinic Foundation	**Inclusion criteria**: patients diagnosed with colorectal cancer **Exclusion criteria**: patients who had a lesion in the lower or middle rectum that required a sphincter-saving operation or a lesion located at the splenic flexure. If diagnostic laparoscopy revealed a direct invasion of cancer to adjacent organs (*en bloc* resection is not suitable using a laparoscopic technique), distant metastasis or peritoneal carcinomatosis, the patient was excluded **Number of eligible patients**: 38 **Number of patients randomised**: 38	Laparoscopic (n = 19) versus open (n = 19)	**Median age (range)**: 70 (43–84) years **Gender (M/F)**: 8/11 **Location of cancer**: Right colectomy: 9 Extended right colectomy: 2 Left colectomy: 0 Proctosigmoidectomy: 8 **Stage of cancer (TNM)**: I: 7 II: 3 III: 9	**Median age (range)**: 65 (40–81) years **Gender (M/F)**: 8/10 **Location of cancer**: Right colectomy: 7 Extended right colectomy: 1 Left colectomy: 1 Proctosigmoidectomy: 9 **Stage of cancer**: I: 9 II: 3 III: 6	Tumour recurrence

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Milsom, 1998[54] **Study design**: RCT **Location**: USA **Recruitment dates**: October 1993–July 1997 **Follow-up range**: 1.5–48 months (median in the laparoscopic group: 1.5 years; median in the open group: 1.7 years) **Funding**: US Surgical Corporation and the Minimally Invasive Surgery Center of The Cleveland Clinical Foundation	**Inclusion criteria**: curative elective surgery, primary right or sigmoid colon cancer or polyps, upper or lower primary rectal cancers or polyps, American Society of Anaesthesiology class I–III, aged >18 years **Exclusion criteria**: emergency or urgent surgery, evidence for dissemination disease or adjacent organ invasion, primary tumour size >8 cm in cancer or polyps, BMI >32 kg/m^2 **Number of eligible patients**: 109 **Number of patients randomised**: 109	Laparoscopic (n = 55, including 42 with cancer) versus open (n = 54, including 38 with cancer) **Additional information**: incision length in the intervention group was 15 ± 1.5 versus 22 ± 5 cm in the comparator group	**Median age (range)**: 69 (41–89) years **Gender (M/F)**: 26/29 **Stage of cancer (TNM)**: I: 10 II: 13 II: 16 IV: 3	**Median age (range)**: 69 (44–86) years **Gender (M/F)**: 36/18 **Stage of cancer (TNM)**: I: 9 II: 11 III: 14 IV: 4	Duration of operation Blood loss Lymph node retrieval[a] Completeness of resection[a] Conversion Length of hospital stay 30-day mortality Recurrence[a] [a] Cancer patients only

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Schwenk, 1998a[56] **Study design**: RCT **Location**: Germany **Recruitment dates**: May 1995–November 1996 **Follow-up**: not reported **Funding**: not reported *Linked reports*: Bohm, 1999[61] Ordemann, 2001[76] Schwenk, 1998b,[77] 1998c,[78] 1999,[79] 2000[80]	**Inclusion criteria**: colorectal tumour, elective resection by right colectomy, sigmoid resection, anterior rectum resection or abdominoperineal rectum extirpation **Exclusion criteria**: rectum carcinoma within 12 cm of the anus, scheduled for sphincter-preserving anterior rectum resection with total mesorectal excision, tumour of the transverse colon or flexures scheduled for extended colectomy, tumour infiltration of adjacent organs, anaesthesia risk >ASA III, scheduled for abdominoperineal rectum extirpation with dynamic gracilis plasty, excessive obesity with BMI >32 kg/m^2, pronounced peritoneal adhesions from previous interventions, synchronous second tumour in extracolonic location, coagulopathy not responding to treatment; intestinal obstruction, transverse tumour diameter >8 cm on CT, immunopathy, pregnancy **Number of eligible patients**: 60 **Number of patients randomised**: 60	Laparoscopic (n = 30) versus open (n = 30)	**Mean age ± SD**: 63.3 ± 12.2 years **Gender (M/F)**: 14/16 **Location of cancer**: Right colectomy: 4 Sigmoid resection: 15 Abdominal peritoneal extirpation: 4 Rectum: 7 **Stage of cancer (TNM)**: 0: 1 I: 9 II: 12 III: 6 IV: 2	**Mean age ± SD**: 64.8 ± 14.7 years **Gender (M/F)**: 16/14 **Location of cancer**: Right colectomy: 3 Sigmoid resection: 17 Abdominal peritoneal extirpation: 3 Rectum: 7 **Stage of cancer (TNM)**: 0: 3 I: 8 II: 5 III: 8 IV: 6	Duration of operation Infection Length of hospital stay Postoperative pain Quality of life

continued

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Stage, 1997[57] **Study design**: RCT **Location**: Denmark **Recruitment dates**: not reported **Follow-up range**: 7–19 months (median: 14 months) **Funding**: not reported	**Exclusion criteria**: patients with preoperative signs of extensive local tumour growth, as judged from these investigations, and patients scheduled for low anterior resection and abdominoperineal resection, patients randomised to laparoscopic surgery in whom the operation was converted to open surgery **Number of eligible patients**: 34 **Number of patients randomised**: 29	Laparoscopic (n = 15) versus open (n = 14) **Additional information**: incision for tumour removal 3–5 cm	**Median age (range)**: 72 (61–93) years **Gender (M/F)**: 8/7 **Location of cancer**: Right side colon: 7 Left side colon: 2 Sigmoid resection: 6 **Stage of cancer (Dukes)**: A: 3 B: 8 C: 2 D: 2	**Median age (range)**: 73 (48–87) years **Gender (M/F)**: 5/9 **Location of cancer**: Right side colon: 7 Left side colon: 3 Sigmoid resection: 4 **Stage of cancer (Dukes)**: A: 4 B: 4 C: 2 D: 4	Duration of operation Conversion Blood loss Lymph node retrieval Number of ports used Completeness of resection Length of hospital stay Postoperative pain Recurrence

Individual patient data meta-analysis

Study details	Participant characteristics	Intervention/comparator	Intervention population characteristics	Comparator population characteristics	Outcomes
Bonjer, 2005 (unpublished) **Study design**: individual patient data meta-analysis **Location**: multicenter **Recruitment dates**: before April 2000 **Follow-up**: **[Academic-in-confidence information removed.]** **Funding**: not reported	**Inclusion criteria**: randomised clinical trials comparing laparoscopic and open surgery for colonic cancer. Only trials which accrued more than 150 patients with colonic cancer were included: Barcelona, CLASICC, COST and COLOR trials	**[Academic-in-confidence information removed.]** **Additional information**: the different trials contributed to the meta-analysis as follows: **[Academic-in-confidence information removed.]**	**[Academic-in-confidence information removed.]**	**[Academic-in-confidence information removed.]**	**[Academic-in-confidence information removed.]**

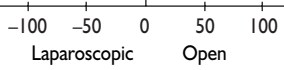
Appendix 9

Results of meta-analysis: laparoscopic resection versus conventional open resection

Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 01 Duration of operation

Study or subcategory	Laparoscopic N	Laparoscopic Mean (SD)	Open N	Open Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Lacy, 2002	111	142.00 (52.00)	108	118.00 (45.00)		38.78	24.00 (11.13 to 36.87)
Leung, 2004	203	189.90 (55.40)	200	144.20 (57.80)		52.54	45.70 (34.64 to 56.76)
Schwenk 1998	30	219.00 (64.00)	30	146.00 (41.00)		8.68	73.00 (45.80 to 100.20)
Total (95% CI)	344		338			100.00	39.65 (31.64 to 47.67)

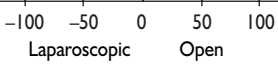
Test for heterogeneity: $\chi^2 = 12.61$, df = 2 ($p = 0.002$), $I^2 = 84.1\%$
Test for overall effect: $z = 9.70$ ($p < 0.00001$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair (random effects model)
Outcome: 01 Duration of operation

Study or subcategory	Laparoscopic N	Laparoscopic Mean (SD)	Open N	Open Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Lacy, 2002	111	142.00 (52.00)	108	118.00 (45.00)		36.53	24.00 (11.13 to 36.87)
Leung, 2004	203	189.90 (55.40)	200	144.20 (57.80)		37.73	45.70 (34.64 to 56.76)
Schwenk 1998	30	219.00 (64.00)	30	146.00 (41.00)		25.74	73.00 (45.80 to 100.20)
Total (95% CI)	344		338			100.00	44.80 (22.43 to 67.16)

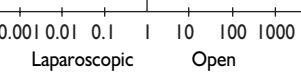
Test for heterogeneity: $\chi^2 = 12.61$, df = 2 ($p = 0.002$), $I^2 = 84.1\%$
Test for overall effect: $z = 3.93$ ($p < 0.0001$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 02 Anastomotic leakage

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
CLASICC, 2005	35/526	13/268		44.23	1.37 (0.74 to 2.55)
COLOR	15/535	10/545		25.44	1.53 (0.69 to3.37)
Hasegawa, 2003	0/24	0/26			Not estimable
King, 2006	1/41	1/19		3.51	0.46 (0.03 to 7.02)
Lacy, 2002	0/111	2/108		6.51	0.19 (0.01 to 4.01)
Leung, 2004	1/203	4/200		10.35	0.25 (0.03 to 2.18)
Tang, 2001	2/118	1/118		2.57	2.00 (0.18 to 21.76)
Zhou, 2004	1/82	3/89		7.39	0.36 (0.04 to 3.41)
Total (95% CI)	1640	1373		100.00	1.13 (0.74 to 1.73)

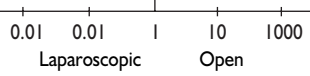
Total events: 55 (Laparoscopic), 34 (Open)
Test for heterogeneity: $\chi^2 = 5.73$, df = 6 ($p = 0.45$), $I^2 = 0\%$
Test for overall effect: $z = 0.55$ ($p = 0.58$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 03 Abdominal wound breakdown

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
Araujo, 2003	4/13	3/15		25.12	1.54 (0.42 to 5.64)
COLOR	2/534	7/544		62.55	0.29 (0.06 to 1.39)
King, 2006	1/41	1/19		12.33	0.46 (0.03 to 7.02)
Total (95% CI)	588	578		100.00	0.63 (0.26, 1.52)

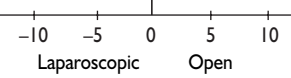
Total events: 7 (Laparoscopic), 11 (Open)
Test for heterogeneity: $\chi^2 = 2.80$, df = 2 ($p = 0.25$), $I^2 = 28.7\%$
Test for overall effect: $z = 1.03$ ($p = 0.30$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 04 Lymph node retrieval

Study or subcategory	Laparoscopic N	Laparoscopic Mean (SD)	Open N	Open Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Lacy, 2002	111	11.10 (7.90)	108	11.10 (7.40)		24.57	0.00 (–2.03 to 2.03)
Leung, 2004	203	11.10 (7.90)	200	12.10 (7.10)		46.95	–1.00 (–2.47 to 0.47)
Vignali, 2004	144	15.20 (8.60)	145	15.00 (7.70)		28.48	0.20 (–1.68 to 2.08)
Total (95% CI)	458		453			100.00	–0.41 (–1.42 to 0.59)

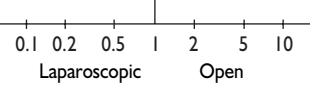
Test for heterogeneity: $\chi^2 = 1.18$, df = 2 ($p = 0.55$), $I^2 = 0\%$
Test for overall effect: $z = 0.80$ ($p = 0.42$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 05 Completeness of resection – positive resection margins

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
CLASICC, 2005	46/439	20/228		72.70	1.19 (0.72 to 1.97)
COLOR	10/526	10/538		27.30	1.02 (0.43 to 2.44)
Milsom, 1998	0/42	0/42			Not estimable
Zhou, 2004	0/82	0/89			Not estimable
Total (95% CI)	1089	897		100.00	1.15 (0.74 to 1.77)

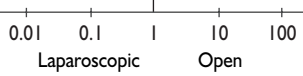
Total events: 56 (Laparoscopic), 30 (Open)
Test for heterogeneity: $\chi^2 = 0.09$, df = 1 ($p = 0.76$), $I^2 = 0\%$
Test for overall effect: $z = 0.62$ ($p = 0.53$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 06 Wound infection

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
CLASICC, 2005	47/526	22/268		31.02	1.09 (0.67 to 1.77)
COLOR	20/535	16/545		16.87	1.27 (0.67 to 2.43)
Curet, 2000	2/25	1/18		1.24	1.44 (0.14 to 14.69)
Hasegawa, 2003	1/24	3/26		3.07	0.36 (0.04 to 3.24)
King, 2006	1/41	3/19		4.36	0.15 (0.02 to 1.39)
Lacy, 2002	8/111	18/108		19.42	0.43 (0.20 to 0.95)
Leung, 2004	9/203	15/200		16.08	0.59 (0.26 to 1.32)
Tang, 2001	3/118	3/118		3.19	1.00 (0.21 to 4.85)
Winslow, 2002 (COST)	5/37	5/46		4.74	1.24 (0.39 to 3.97)
Total (95% CI)	1620	1348		100.00	0.86 (0.64 to 1.14)

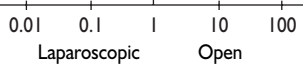
Total events: 96 (Laparoscopic), 86 (Open)
Test for heterogeneity: $\chi^2 = 9.64$, df = 8 ($p = 0.29$), $I^2 = 17.0\%$
Test for overall effect: $z = 1.05$ ($p = 0.29$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 07 Urinary tract infections

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
COLOR	12/535	13/545		54.58	0.94 (0.43 to 2.04)
Curet, 2000	1/25	0/18		2.45	2.19 (0.09 to 50.93)
Kaiser, 2004	1/28	0/19		2.46	2.17 (0.09 to 50.74)
Lacy, 2002	1/111	0/108		2.15	2.92 (0.12 to 70.89)
Leung, 2004	8/203	7/200		29.89	1.13 (0.42 to 3.05)
Schwenk, 1998	2/30	0/30		2.12	5.00 (0.25 to 99.95)
Tang, 2001	0/118	1/118		6.36	0.33 (0.01 to 8.10)
Total (95% CI)	1050	1039		100.00	1.15 (0.66, 1.98)

Total events: 25 (Laparoscopic), 21 (Open)
Test for heterogeneity: $\chi^2 = 2.41$, df = 6 ($p = 0.88$), $I^2 = 0\%$
Test for overall effect: $z = 0.49$ ($p = 0.62$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 08 Operative mortality

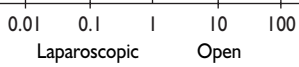
Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
Curet, 2000	0/25	0/18			Not estimable
Lacy, 2002	1/111	3/108		43.01	0.32 (0.03 to 3.07)
Leung, 2004	5/203	4/200		56.99	1.23 (0.34 to 4.52)
Total (95% CI)	339	326		100.00	0.84 (0.29 to 2.47)

Total events: 6 (Laparoscopic), 7 (Open)
Test for heterogeneity: $\chi^2 = 1.02$, df = 1 ($p = 0.31$), $I^2 = 2.0\%$
Test for overall effect: $z = 0.31$ ($p = 0.75$)

Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 08 30-day mortality

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
COLOR	6/535	10/545		64.73	0.61 (0.22 to 1.67)
COST	2/435	4/428		26.34	0.49 (0.09 to 2.67)
King, 2006	1/41	1/19		8.93	0.46 (0.03 to 7.02)
Total (95% CI)	1011	992		100.00	0.57 (0.25 to 1.29)

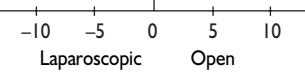
Total events: 9 (Laparoscopic), 15 (Open)
Test for heterogeneity: $\chi^2 = 0.07$, df = 2 ($p = 0.97$), $I^2 = 0\%$
Test for overall effect: $z = 1.35$ ($p = 0.18$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 09 Length of hospital stay

Study or subcategory	Laparoscopic N	Laparoscopic Mean (SD)	Open N	Open Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
COLOR	536	8.20 (6.60)	546	9.30 (7.30)		43.30	–1.10 (–1.93 to –0.27)
Lacy, 2002	111	5.20 (5.10)	108	7.90 (9.30)		7.48	–2.70 (–4.69 to –0.71)
Schwenk, 1998	30	10.10 (3.00)	30	11.60 (2.00)		17.87	–1.50 (–2.79 to –0.21)
Zhou, 2004	82	8.10 (3.10)	89	13.30 (3.40)		31.35	–5.20 (–6.17 to –4.23)
Total (95% CI)	759		773			100.00	–2.58 (–3.12 to –2.03)

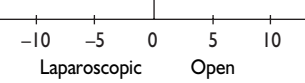
Test for heterogeneity: $\chi^2 = 42.73$, df = 3 ($p < 0.00001$), $I^2 = 93.0\%$
Test for overall effect: $z = 9.26$ ($p < 0.00001$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair (random effects model)
Outcome: 09 Length of hospital stay

Study or subcategory	Laparoscopic N	Laparoscopic Mean (SD)	Open N	Open Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) (95% CI)
COLOR	536	8.20 (6.60)	546	9.30 (7.30)		26.45	–1.10 (–1.93 to –0.27)
Lacy, 2002	111	5.20 (5.10)	108	7.90 (9.30)		22.39	–2.70 (–4.69 to –0.71)
Schwenk, 1998	30	10.10 (3.00)	30	11.60 (2.00)		25.09	–1.50 (–2.79 to –0.21)
Zhou, 2004	82	8.10 (3.10)	89	13.30 (3.40)		26.07	–5.20 (–6.17 to –4.23)
Total (95% CI)	759		773			100.00	–2.63 (–4.82 to –0.44)

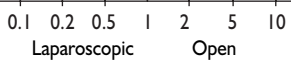
Test for heterogeneity: $\chi^2 = 42.73$, df = 3 ($p < 0.00001$), $I^2 = 93.0\%$
Test for overall effect: $z = 2.35$ ($p = 0.02$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 10 Overall survival

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
COST	344/435	333/428		58.46	1.02 (0.95 to 1.09)
Curet, 2000	19/25	12/18		2.43	1.14 (0.77 to 1.69)
Kaiser, 2004	25/28	19/20		3.86	0.94 (0.80 to 1.11)
Lacy, 2002	87/106	78/102		13.84	1.07 (0.93 to 1.23)
Leung, 2004	127/167	124/170		21.40	1.04 (0.92 to 1.18)
Zhou, 2004	82/82	89/89			Not estimable
Total (95% CI)	843	827		100.00	1.03 (0.98 to 1.09)

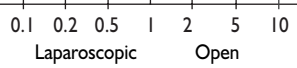
Total events: 684 (Laparoscopic), 655 (Open)
Test for heterogeneity: $\chi^2 = 1.98$, df = 4 ($p = 0.74$), $I^2 = 0\%$
Test for overall effect: $z = 1.07$ ($p = 0.28$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 11 Disease-free survival

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
COST	317/435	311/428		62.45	1.00 (0.92 to 1.09)
Kaiser, 2004	22/28	18/20		4.18	0.87 (0.69 to 1.11)
Lacy, 2002	48/53	34/48		7.11	1.28 (1.05 to 1.56)
Leung, 2004	126/167	133/170		26.26	0.96 (0.86 to 1.08)
Total (95% CI)	683	666		100.00	1.01 (0.95 to 1.07)

Total events: 513 (Laparoscopic), 496 (Open)
Test for heterogeneity: $\chi^2 = 7.27$, df = 3 ($p = 0.06$), $I^2 = 58.7\%$
Test for overall effect: $z = 0.22$ ($p = 0.83$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 12 Tumour recurrence – total

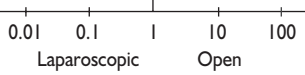
Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
Araujo, 2003	0/13	0/13			Not estimable
COST	76/435	84/428		58.29	0.89 (0.67 to 1.18)
Curet, 2000	1/25	1/18		0.80	0.72 (0.05 to 10.76)
Kaiser, 2004	3/28	1/20		0.80	2.14 (0.24 to 19.13)
Lacy, 2002	18/106	28/102		19.64	0.62 (0.37 to 1.05)
Leung, 2004	37/167	30/170		20.47	1.26 (0.82 to 1.93)
Stage, 1997	0/15	0/14			Not estimable
Total (95% CI)	789	765		100.00	0.92 (0.74 to 1.14)

Total events: 135 (Laparoscopic), 144 (Open)
Test for heterogeneity: $\chi^2 = 4.84$, df = 4 ($p = 0.30$), $I^2 = 17.3\%$
Test for overall effect: $z = 0.77$ ($p = 0.44$)

Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 13 Tumour recurrence – wound

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
COST	2/435	1/428		100.00	1.97 (0.18 to 21.62)
Kaiser, 2004	0/28	0/20			Not estimable
Kim, 1998	0/19	0/19			Not estimable
Leung, 2004	0/167	0/170			Not estimable
Total (95% CI)	649	637		100.00	1.97 (0.18 to 21.62)

Total events: 2 (Laparoscopic), 1 (Open)
Test for heterogeneity: not applicable
Test for overall effect: $z = 0.55$ ($p = 0.58$)



Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 14 Incisional hernia

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
Leung, 2004	8/203	4/200		33.43	1.97 (0.60 to 6.44)
Winslow, 2002 (COST)	9/37	9/46		66.57	1.24 (0.55 to 2.81)
Total (95% CI)	240	246		100.00	1.49 (0.76 to 2.92)

Total events: 17 (Laparoscopic), 13 (Open)
Test for heterogeneity: $\chi^2 = 0.40$, df = 1 ($p = 0.53$), $I^2 = 0\%$
Test for overall effect: $z = 1.15$ ($p = 0.25$)

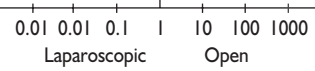
Review: Colorectal cancer
Comparison: 01 Laparoscopic repair vs Conventional open repair
Outcome: 15 Anastomotic leakage

Study or subcategory	Laparoscopic N/n	Open N/n	RR (fixed) 95% CI	Weight %	RR (fixed) (95% CI)
01 Colon					
CLASICC, 2005	9/273	4/140		15.76	1.15 (0.36 to 3.68)
COLOR	15/535	10/545		29.52	1.53 (0.69 to 3.37)
Lacy, 2002	0/111	2/108		7.55	0.19 (0.01 to 4.01)
Tang, 2001	2/118	1/118		2.98	2.00 (0.18 to 21.76)
Subtotal (95% CI)	1037	911		55.81	1.27 (0.70 to 2.31)
02 Rectum					
CLASICC, 2005	26/253	9/128		35.62	1.46 (0.71 to 3.03)
Zhou, 2004	1/82	3/89		8.57	0.36 (0.04 to 3.41)
Subtotal (95% CI)	335	217		44.19	1.25 (0.63 to 2.46)
Total (95% CI)	1372	1128		100.00	1.26 (0.80 to 1.97)

Total events: 26 (Laparoscopic), 17 (Open)
Test for heterogeneity: $\chi^2 = 1.85$, df = 3 ($p = 0.60$), $I^2 = 0\%$
Test for overall effect: $z = 0.77$ ($p = 0.44$)

Total events: 27 (Laparoscopic), 12 (Open)
Test for heterogeneity: $\chi^2 = 1.35$, df = 1 ($p = 0.25$), $I^2 = 26.0\%$
Test for overall effect: $z = 0.64$ ($p = 0.52$)

Total events: 53 (Laparoscopic), 29 (Open)
Test for heterogeneity: $\chi^2 = 3.21$, df = 5 ($p = 0.67$), $I^2 = 0\%$
Test for overall effect: $z = 1.00$ ($p = 0.32$)



Appendix 10

Summary of outcomes reported in converted patients

Study ID	Laparoscopic		Open		Converted		*p*-Value	Comments
	n	Value	*n*	Value	*n*	Value		
Duration of operation (minutes)								
Curet, 2000[48]	18	210 (128–275)	18	138 (95–240)	7	194 (105–485)	<0.05[a]	
CLASICC, 2005[3]	345	180 (140–220)	276	135 (100–175)	143	180 (135–223)		Median (IQR)
Kaiser, 2004[51]	15	125 (70–155)	20	65 (45–125)	13	125 (80–270)	<0.05[b]	Mean (range)
Blood loss (ml)								
Curet, 2000[48]	18	284 (100–700)	18	407 (100–1000)	7	683 (100–12000)	<0.05[a]	
Kaiser, 2004[51]	15	100 (100–300)	20	100 (100–800)	13	200 (100–1000)		Mean (range)
Anastomotic leakage								
CLASICC, 2005[3]	345	20	276	15	143	13		
Lymph node retrieval								
Curet, 2000[48]	18	11 (2–23)	18	10 (1–21)	7	12 (1–29)		
Kaiser, 2004[51]	15	11 (4–26)	20	14 (3–27)	13	16 (1–32)		Mean (range)
Wound infection								
Curet, 2000[48]	18	1	18	1	7	1		
CLASICC, 2005[3]	345	24	276	23	143	21		
Urinary tract infection								
Curet, 2000[48]	18	0	18	0	7	1		
Kaiser, 2004[51]	15	1	20	0	13	0		
Length of hospital stay (days)								
Curet, 2000[48]	18	5.2	18	7.3	7	8	<0.05[a]	
CLASICC, 2005[3]	345	9 (7–13)	276	11 (8–15)	143	12 (9–16)		Median (IQR)
Kaiser, 2004[51]	15	5 (3–8)	20	6 (5–9)	13	7 (5–13)	<0.05[a]	Mean (range)
Overall survival								
Curet, 2000[48]	18	14	18	12	7	6		Follow-up: 2.5–6.3 years, mean 4.9 years
Kaiser, 2004[51]	15	14	20	19	13	11		Follow-up: 3–69 months, median 35 months
Disease-free survival								
Kaiser, 2004[51]	15	14	20	18	13	8		Follow-up: 3–69 months, median 35 months
Recurrence								
Curet, 2000[48]	18	0	18	1	7	1		Follow-up: 2.5–6.3 years, mean 4.9 years
Kaiser, 2004[51]	15	0	20	1	13	3		Follow-up: 3–69 months, median 35 months

[a] Laparoscopic compared with open procedure.
[b] Open compared with laparoscopic procedure.

Appendix 11

Summary of included economic evaluations

Study identification: Franks, 2005 (Franks PJ, Thames Valley University: personal communication, 2005)	**Authors and year**	**Franks et *al*., 2005**
	Interventions studied/ comparators	Laparoscopic resection compared with open resection in the treatment of colorectal cancer
	Hypothesis/question	Total cost to society of laparoscopic resection would be similar to or less than those of open resection within 3 months of operation. The authors reported that the societal perspective was adopted for the analysis
Key elements of the study	Type of study	A preliminary cost analysis based on an RCT (CLASICC trial)
	Target population/study sample	A subset of the patients recruited to the CLASICC trial. Included patients were those who agreed to participate in the quality of life/health economics component or for whom details of the operative procedure were missing at the time of the analysis (n = 682 in economic analysis, n = 794 in trial). Details of inclusion/exclusion criteria not described in this paper but are described elsewhere (see descriptions of the CLASICC trial reported earlier)
	Setting	Secondary care. 27 centres and 32 surgeons, UK
	Dates to which data relate	Patients recruited to the trial from 1996
	Source of effectiveness data	The effectiveness data were derived from the whole sample (n = 794) of the CLASICC RCT
	Modelling	NA
	Link between effectiveness and cost data	Costs are derived from a subgroup of the patients included in the CLASICC trial. Approximately 86% of the whole sample from CLASICC was included in the economic study. It is assumed (although not stated) that the costs of those recruited into the economic study are applicable to the patients included in the whole study (which provides evidence on effectiveness)
Details about clinical evidence: study design and main outcomes	Eligibility/patient group/study sample	Details of the eligibility and study sample were not reported but are provided elsewhere. For details, see the summary of the CLASSICC trial provided earlier. The data from the CLASICC trial were stratified by surgeon, site of operation, presence of liver metastases and preoperative radiotherapy. Subgroup analysis was conducted by colon and rectum cancer
	Study design	A multicentre RCT with 27 centres and 32 surgeons contributing data
	Analysis of effectiveness	The analysis was done on an intention-to-treat basis. The primary end-points were resection margins, Dukes' C tumours and in-hospital mortality. Secondary outcomes were complication rates, transfusion requirements and quality of life up to 3 months after surgery
	Effectiveness results/outcome measures	Details of primary and secondary end-points were not reported. The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence
	Clinical conclusions	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence

continued

Economic analysis	Measure of health benefits used in the economic analysis	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence. A cost-analysis was performed
	Direct costs	The 682 patients who consented to be part of the economic study and for whom operative data were available. In CLASICC, patients were randomised in a 2:1 ratio to either laparoscopic or open resection and costs were based on 452 patients allocated to laparoscopic resection and 230 to open resection. The costing was undertaken prospectively on a subset of the whole trial population. Detailed theatre resource use was based on a subgroup of patients (10 laparoscopic and 10 open patients for each recruiting surgeon). These data were used to impute values for the rest of the sample. Hospital stay was from date of operation to discharge (or death) plus one day for a preoperative admission. Stay was divided into intensive, high-dependency and surgical ward care. Postoperative complications were obtained for each patient. For complications resulting in surgery, costs were based on detailed descriptions of the operation, which included anaesthetic time, length of hospitalisation (including stay in ICU and HDU). Other complications were costed according to national figures. Post-discharge resource use was based on patient-completed questionnaires. Unit costs were based on national figures or study specific estimates based on data from manufacturers. The same unit costs were used for all patients
	Indirect costs	Cost of productivity loss was based on the time taken for individuals to return to employment and costed using average salary costs for full or part-time workers based on the Department of Work and Pensions
	Currency	Pounds sterling. Year not stated but between 2002 and 2004
	Statistical analysis of quantities/ costs	Non-parametric bootstrap method was used to provide CIs around each difference in cost for area or resource use and the difference in total cost
	Sensitivity analysis	One-way sensitivity analysis on the perioperative costs, equipment costs, recovery costs, ICU costs and hospital costs (ward, ICU and HDU). Costs were varied by either +20% or –20% of base-case values. Subgroup analysis was conducted by site of the cancer (colon or rectum)
Results	Estimated benefits used in the economic evaluation	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence
	Costs results	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence
	Synthesis of costs and benefits	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence
	Authors' conclusions	The results from Franks and colleagues have been removed from this table as they were supplied as academic-in-confidence

continued

Study identification: Janson, 2004[66]	**Authors and year**	**Janson *et al.*, 2004**
	Interventions studied/ comparators	Laparoscopic colonic resection (LCR) compared with open colonic resection (OCR) in the treatment of colonic cancer
	Hypothesis/question	1. Total cost to society of LCR would be less than those of OCR within 12 weeks of operation. 2. Higher operating room costs of LCR would be compensated for by a faster recovery, shorter duration of hospital stay and reduction in use of outpatient healthcare resources. The authors reported that the societal perspective was adopted for the analysis
Key elements of the study	Type of study	A CCA based on an RCT (COLOR trial)
	Target population/study sample	A subset of the Swedish contribution to the COLOR trial. The inclusion criteria focus on selection of patients admitted for elective surgery with potentially curable colonic cancer best treated by right or left hemicolectomy or sigmoid resection. Exclusion criteria: cancer in the transverse colon or rectum, synchronous colonic cancers, distant metastases, BMI >30, previously treated malignant disease, pregnancy and preoperative signs of a fixed tumour or acute intestinal obstruction
	Setting	Secondary care. 10 centres in Sweden
	Dates to which data relate	January 1999–May 2002
	Source of effectiveness data	The effectiveness data were derived from this subgroup of the COLOR trial (RCT)
	Modelling	NA
	Link between effectiveness and cost data	The costing was undertaken prospectively on the same sample as that used for the effectiveness study. Allocations for all inpatient services costs were retrieved from one centre, which contributed with 33% of the patients to the cost analysis. This centre has a well-developed cost per patient accounting system
Details about clinical evidence: study design and main outcomes	Eligibility/patient group/study sample	12 Swedish centres that contributed to the COLOR trial were invited to participate, and 10 agreed. These centres contributed with 263 patients to the trial and 234 entered into the cost analysis (111 LCR, 123 OCR). Of these 234 patients, 24 were excluded from the primary cost analysis (13 LCR, 11 OCR); then, 98 patients were included in the cost analysis for the LCR group and 112 for the OCR group
	Study design	A multicentre RCT. 10 centres agreed to participate. Randomisation was performed in the original trial. Follow-up was 3 years
	Analysis of effectiveness	The analysis was done on an intention-to-treat basis. The primary end-point was cancer-free 3-year survival. Other outcomes were number of complications and reoperations and deaths. Complications include anastomotic leak, bowel perforation, wound rupture, ileus, postoperative bleeding, incarcerated abdominal hernia, endoscopic dilatation, closure loop ileostomy
	Effectiveness results/outcome measures	Primary end-point results were not reported. During the first admission, 21 patients had complications in the LCR group and 18 in the OCR group. 8 patients had reoperations in the LCR group and 4 in the OCR group (anastomotic leak 4 LCR, 1 OCR; bowel perforation 1 LCR, 0 OCR; wound rupture 1 LCR, 3 OCR; ileus 1 LCR, 0 OCR; postoperative bleeding 1 LCR, 0 OCR). After discharge, 12 patients had complications in the LCR group and 8 in the OCR group. There was 1 death in the LCR group and 0 in the OCR

continued

		group. 6 patients had reoperations in the LCR group and 3 in the OCR group (anastomotic leak 1 LCR, 1 OCR; wound rupture 1 LCR, 0 OCR; ileus 1 LCR, 1 OCR; incarcerated abdominal hernia 1 LCR, 0 OCR; endoscopic dilatation 1 LCR, 1 OCR; closure loop ileostomy 1 LCR, 1 OCR)
	Clinical conclusions	The results from the present cohort of patients showed significant but clinically modest differences in HRQoL 2 and 4 weeks after operation (data not shown)
Economic analysis	Measure of health benefits used in the economic analysis	No summary of health benefit was used in the economic analysis. Clinical outcomes were left disaggregated. A cost–consequences analysis was performed
	Direct costs	Data related to perioperative period and postoperative follow-up were retrieved by use of case record forms, which were completed by the relevant surgical departments. Data on costs after discharge were registered by the patient in a diary. Direct costs included staff, drugs, physicians, laboratory testing, overheads and maintenance, operating room resources, anaestegiology and recovery room services. Capital costs of expensive equipment were calculated after estimating the yearly use of these items at Huddings University Hospital (HUH). Mean cost per item of disposable material between centres was used in the analysis. Cost of medical services, including radiological and endoscopic investigations, blood products and bacteriological testing, were allocated using the internal price list of services at HUH. Costs of outpatient care services were retrieved from the internal reinbursements system in the county of Stockholm, Sweden. Discounting was performed at a 5% rate. This was relevant as the follow-up period was over 2 years
	Indirect costs	Costs of productivity loss were calculated from official Swedish statistics. Average income rates were converted to a daily cost of productivity loss. Whether a patient was retired or not was taken into account when considering number of days off work. No commuting costs were considered as they were not relevant. Discounting was performed at a 5% rate
	Currency	Euros, 2001 prices
	Statistical analysis of quantities/ costs	Non-parametric bootstrap method was used for checking the robustness of results from standard parametric approaches. Other statistical tests used were *t*-test, χ^2 and Fisher's exact test. $p < 0.05$ was considered statistically significant
	Sensitivity analysis	One-way sensitivity analyses on the cost per minute for the operating room, anaesthesia and recovery room time were explored (–50 to +100% range from original mean values)
Results	Estimated benefits used in the economic evaluation	No health benefit summary measure for economic analysis was used. A cost–consequences analysis was performed. However, the authors stated that the results from the present cohort of patients showed significant but clinically modest differences in HRQoL at 2 and 4 weeks after operation
	Costs results	Total costs, including productivity loss, were not significantly different between LCR and OCR groups (€11,660 vs €9814; $p = 0.104$). Total costs, excluding productivity loss, that is, cost to the healthcare system, were significantly higher for LCR (€9474 vs €7235; $p = 0.018$), as were costs related to the first admission (€6931 vs €5375; $p = 0.015$)

continued

		and costs of primary surgery (€3493 vs €2322, $p = 0.001$). The secondary cost analysis, which included 24 patients who were excluded in the primary analysis after randomisation, yielded similar data; figures calculated in a secondary analysis were within a range of €–35 to +316, and the statistical significance of the results remained unchanged
	Synthesis of costs and benefits	The cost of extra resources consumed during the first admission and resources used after discharge, because of readmissions and reoperations, appeared to be higher in the LCR group. Although there was no difference in complication rates, reoperations were more frequent in the LCR group during the first admission and after discharge. However, this difference was not tested for statistical significance owing to the small number of observations. The mean total costs, excluding productivity loss, for reoperated patients were €19,376 (range €5543–49,835) for LCR and €13,637 (range €6080–29,305) for OCR
	Authors' conclusions	Within 12 weeks of surgery for colonic cancer, there was no difference in total costs to society incurred by LCR and OCR. The LCR procedure, however, was more costly to the healthcare system
Study identification: King, 2006[40]	**Author and year**	**King, 2006**
	Interventions studied/ comparators	Laparoscopic resection versus open resection for colorectal cancer with enhanced recovery programme
	Hypothesis/question	This study examined the null hypothesis that there is no difference in short-term outcomes after laparoscopic or open resection for colorectal cancer when both are embedded within an enhanced recovery programme
Key elements of the study	Type of study	CCA based on an RCT
	Target population/study sample	Adult patients diagnosed with colorectal cancer. Exclusion criteria: any non-elective admission, those patients with preoperative evidence of haematogenous metastases, patients less than 18 years old, those who were pregnant and patients who did not consent to randomisation. A protocol amendment to exclude patients not able to have epidural anaesthesia was made after 1 year
	Setting	Secondary care. Yeovil District Hospital, Yeovil, UK
	Dates to which data relate	January 2002–March 2004
	Source of effectiveness data	The evidence for effectiveness data was derived from a single study
	Modelling	NA
	Link between effectiveness and cost data	Costing was undertaken on the same sample as used for the effectiveness study. Cost outcomes were collected prospectively
Details about clinical evidence: study design and main outcomes	Eligibility/patient group/study sample	During the study period, 94 patients were assessed for entry into the trial. 21 did not meet the inclusion criteria, 5 were excluded as they were not suitable for laparoscopic surgery and 6 were excluded for other reasons. 62 patients with adenocarcinoma of the colon or rectum were randomised (2:1) to receive either laparoscopic ($n = 43$) or open surgery ($n = 19$) and were entered into an enhanced recovery programme. Sample size was determined by a calculation performed for a parallel study involving the same patients, comparing enhanced recovery with a historical cohort of patients receiving conventional care

continued

	Study design	A single-centre RCT. Maximum follow-up was 3 months. 3 patients were lost to follow-up in the laparoscopic arm (1 benign histology, 1 unsuitable for epidural, 1 death) and 1 patient was lost to follow-up in the open arm (death)
	Analysis of effectiveness	The analysis of effectiveness data was based on intention-to-treat. Hospital stay was calculated as from the date of operation to the date of discharge. Hospital stay including convalescent stay and readmission stay was a secondary outcome. Other clinical end-points included mortality, requirement of opioid analgesia and antiemetic administration. Major morbidity was defined as haemorrhage (requiring transfusion), reoperation, readmission, anastomotic leak, wound dehiscence and sepsis requiring at least high-dependency support. Patient-based outcomes included quality of life (measure by EORTC QLQ-C30 and QLQ-CR38 colorectal module). A series of performance tests to assess balance, gait and lower extremity strength and endurance were taken before and after surgery. Sleep and oxygen saturation were also monitored
	Effectiveness results/outcome measures	Patients undergoing laparoscopic surgery had a 32% (95% CI 7 to 51, $p = 0.018$) shorter hospital stay than those in open surgery. Geometric mean for postoperative stay 5.2 days (95% CI 4.2 to 6.5) for laparoscopic group and 7.4 (95% CI 6.0 to 9.2) for open group. Hospital + convalescent stay 5.4 (95% CI 4.2 to 6.8) for laparoscopic group and 7.4 (95% CI 6.0 to 9.2) for open group; ratio laparoscopic to open 0.69 (95% CI 0.49 to 0.78), $p = 0.036$. Hospital + convalescent + readmission stays were also significantly shorter after laparoscopic surgery: 5.5 (95% CI 4.3 to 7.0) for laparoscopic group and 8.3 (95% CI 6.3 to 10.8) for open group; ratio laparoscopic to open 0.63 (95% CI 0.44 to 0.90), $p = 0.012$. There were 11 cases (27%) of blood loss >100 ml in the laparoscopic group and 18 (95%) cases in the open group, $p < 0.001$. Statistically significant differences were reported also for epidural insufficiency requiring opioid supplements: 9 (22%) laparoscopic group and 14 (74%) open group, $p < 0.001$; duration of surgery in minutes (geometric mean): 187 for laparoscopic group (95% CI 168 to 207), open group 140 (95% CI 121 to 163), $p = 0.00$
	Clinical conclusions	Laparoscopic resection for colorectal cancer within an enhanced recovery programme is likely to provide the best short-term clinical outcomes for patients with resectable colorectal cancer
Economic analysis	Measure of health benefits used in the economic analysis	No summary of health benefit is used in the economic analyses and clinical outcomes are left disaggregated; a cost–consequences analysis was performed
	Direct costs	Cost analysis was undertaken from the NHS perspective. The follow-up was 3 months postoperatively. Information on cost of theatre equipment was provided from hospital invoices. Detailed records were taken of staffing including surgical/anaesthetic and nursing grades present at each operation. Disposable equipment was routinely recorded and was considered to be additional to standard theatre costs. One day preoperative was included for hospital stay analysis purposes. Patients were sent questionnaires about their use of health resources at both 2 weeks and 3 months after operation (inpatient days, outpatient visits, GP visits, use of district (community) and stoma nursing services. Staffing costs were estimated as a mid-point in the scale

continued

		given in the UK literature. Cost of theatre equipment specific to procedures undertaken was provided from the manufacturers' invoices. Post-discharge health resource unit costs were estimated from national published figures. Discounting was not performed
	Indirect costs	Indirect costs were assessed by determining the number of days patients in paid work (full- or part-time) took off for their condition and multiplying by the average daily pay
	Currency	sterling Pounds, 2002
	Statistical analysis of quantities/ costs	Costs data were treated stochastically. The authors used bootstrap estimates (10,000 iterations) to derive values for mean and CIs
	Sensitivity analysis	The base-case analysis indicated the there were two areas where costs were likely to vary between groups, namely the duration of inpatient stay and the consumption of community resources after hospital discharge. The costs of these resources were challenged using a sensitivity analysis, with each varying by ±20% of the base case
Results	Estimated benefits used in the economic evaluation	A cost–consequences analysis was developed, then the reader is referred to the effectiveness results reported previously
	Costs results	As expected, the theatre costs were higher in patients randomised to laparoscopic surgery (£2885 versus £1964, difference £921.6, 95% CI –1250.6 to –586.0), partly reflecting the increased duration of these procedures, but also the increased use of disposable equipment in theatre. These costs were more than offset by lower postoperative costs such as reoperations (£287 for laparoscopic group and £1039 for open group, difference £752, 95% CI –278.5 to 2466.6), and indirect costs (£448 for laparoscopic group and £721 for open group, difference £274.2, 95% CI –386.2 to 983.2). Total cost for laparoscopic group was £6433.4 and for open group £6789.8 (difference £353.4, 95% CI –2167.1 to 2991.5). Sensitivity analysis had little effect on this overall mean difference, with variations in perioperative and inpatient costs affecting the difference by less than £100 in either direction
	Synthesis of costs and benefits	Not combined
	Authors' conclusions	Laparoscopic resection of colorectal cancer within the enhanced recovery programme is likely to provide the best short-term clinical outcomes for patients with resectable colorectal cancer. Despite applying enhanced recovery techniques to open surgery for colorectal cancer, short-term outcomes are better with laparoscopic-assisted surgery. There is no deterioration in quality of life or increased cost associated with laparoscopic surgery compared with the open approach
Study identification: Leung, 2004[53]	**Authors and year**	**Leung *et al.*, 2004**
	Interventions studied/ comparators	Laparoscopic-assisted or conventional open resection for rectosigmoid carcinoma
	Hypothesis/question	The authors aimed to test the null hypothesis that there was no difference in survival after laparoscopic and open resection for rectosigmoid cancer
Key elements of the study	Type of study	CCA based on an RCT
	Target population/study sample	The study involved adult patients with rectosigmoid carcinoma

continued

	Setting	Secondary care; 2 institutions (Prince of Wales Hospital and United Christian Hospital) in Hong Kong
	Dates to which data relate	21 September 1993–21 October 2002
	Source of effectiveness data	The effectiveness data were derived from a single study
	Modelling	NA
	Link between effectiveness and cost data	Costing was undertaken on the same sample as used in the effectiveness study. Cost outcomes were collected prospectively
Details about clinical evidence: study design and main outcomes	Eligibility/patient group/study sample	The authors considered the study sample in a planning phase: to show a difference of 15% in 5-year survival (from 60 to 70%) with an 80% probability ($\beta = 0.2$) and a 5% significance threshold ($\alpha = 0.05$), 150 patients were needed in each group). Patients diagnosed to have rectosigmoid carcinoma seen in the participating institutions were randomly allocated to laparoscopic-assisted or conventional open sigmoid colectomy or anterior resection. There were 825 eligible patients and 422 were excluded as they did not fulfil the inclusion criteria. 203 patients were allocated to the laparoscopic group and 200 to the open group. Exclusion criteria: distal tumour needing anastomosis within 5 cm of the dentate line; tumour larger than 6 cm or with tumour infiltration to adjacent organs on sonography with or without CT scan; patients with previous abdominal operations near the region of the colorectal operation; individuals who did not consent to randomisation; and patients with intestinal obstruction or perforation
	Study design	The patients were recruited from two hospitals. Patients were randomly allocated to laparoscopic-assisted or conventional open sigmoid colectomy or anterior resection by a computer-generated random sequence kept concealed by an independent operating theatre coordinator. The follow-up time of living patients (months) was 52.7 (SD 38.9) for the laparoscopic group and 49.2 (SD 35.4) for the open group. Patients were followed up regularly at 3-monthly intervals in the first 2 years, then 6-monthly thereafter for clinical examination and carcinoembryonic antigen testing. One patient was lost to follow-up in the laparoscopic group and 3 in the open group
	Analysis of effectiveness	Survival and disease-free interval were the main outcomes. Other outcomes were 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, postoperative pain, recurrence. Operation time and hospital length of stay data were also collected. The analysis was based on intention-to-treat. The two groups of patients had similar baseline demographic data
	Effectiveness results/outcome measures	No statistically significant differences were reported for overall mortality 38 (22.8%) for laparoscopic group and 40 (23.5%) for open group, $p = 0.97$; probability of survival at 5 years 76.1% (3.7%) for laparoscopic group and 72.9% (4.0%) for open group, $p = 0.61$, recurrence 37 (22.2%) for laparoscopic group and 30 (17.6%) for open group, $p = 0.37$ and probability of disease free at 5 years 75.3% (3.7%) for laparoscopic group and 78.3% (3.7%) for open group, $p = 0.45$. Operation time was statistically significantly higher in the laparoscopic group 189.9 minutes (SD 55.4) and 144.2 minutes (SD 57.2) for the open group. Hospital stay was also statistically significantly higher in the

continued

		laparoscopic group 8.2 days (range 2–99) and 8.7 days (range 3–39) in the open group. 40 complications were reported for the laparoscopic group and 45 for the open group (anastomotic bleeding 2 laparoscopic, 3 open; anastomotic leak 1 laparoscopic, 4 open; wound infection 9 laparoscopic, 15 open; strangulated incisional hernia 2 laparoscopic, 0 open; reoperation 6 laparoscopic, 5 open; operative death 5 laparoscopic, 4 open; others: 15 laparoscopic, 17 open)
	Clinical conclusions	Laparoscopic resection did not worsen survival and disease control for patient with rectosigmoid cancer compared with open resection and its benefits in reducing pain and allowing earlier postoperative recovery were confirmed. The justification for preferential use of the laparoscopic technique would depend on the perceived value of its effectiveness in improving short-term postoperative outcomes
Economic analysis	Measure of health benefits used in the economic analysis	No summary of health benefit is used in the economic analyses and clinical outcomes are left disaggregated; a cost–consequences analysis was performed
	Direct costs	Direct cost of operation was estimated by market value of theatre time, the disposable instrument and hospital inpatient service. Operation time and hospital length of stay were reported for the two groups but no further details on disposable instruments or unit costs were reported. No adjustments for inflation or discounting were reported and no details on unit price dates were presented. Average costs for each arm were reported
	Indirect costs	No indirect costs were reported
	Currency	US dollars
	Statistical analysis of quantities/ costs	*t*-Tests were used to test significance of operational time, hospital stay and direct cost differences
	Sensitivity analysis	The authors explored the cost implications of the subgroups with local invasion
Results	Estimated benefits used in the economic evaluation	A cost–consequences analysis was developed, then the reader is referred to the effectiveness results reported previously
	Costs results	Direct cost of operation for the laparoscopic group was \$9297 (SD 2091) and \$7148 (SD 2164) for the open group, $p < 0.001$. The direct cost of operation for the local invasion subgroups were \$9729 (SD 2854) for the laparoscopic subgroup and \$9850 (SD 2955) for the open subgroup
	Synthesis of costs and benefits	Not combined
	Authors' conclusions	Laparoscopic resection of rectosigmoid carcinoma does not jeopardise survival and disease control of patients. The justification for adoption of the laparoscopic technique would depend on the perceived value of its effectiveness in improving short-term postoperative outcomes
Study identification: Zheng, 2005[109]	**Authors and year**	**Zheng *et al.*, 2005**
	Interventions studied/ comparators	Laparoscopic versus open right hemicolectomy for colon carcinoma
	Hypothesis/question	This study was designed to compare the outcomes of laparoscopic right hemicolectomy (LRH) with open right hemicolectomy (ORH) in the treatment of colon carcinoma. The authors did not state the perspective of the analysis but a hospital perspective seems to have been adopted

continued

Key elements of the study	Type of study	CCA based on a matched cohort study
	Target population/study sample	Patient with colon carcinoma
	Setting	Secondary care, 1 institution (Ruijin Hospital) in Shanghai, China
	Dates to which data relate	September 2000–February 2003
	Source of effectiveness data	The evidence for effectiveness data was derived from a single study
	Modelling	NA
	Link between effectiveness and cost data	Costing was undertaken on the same sample as used in the effectiveness study. Cost outcomes were collected prospectively
Details about clinical evidence: study design and main outcomes	Eligibility/patient group/study sample	30 patients with colon carcinoma underwent LHR in the setting hospital and there were 34 patients for the comparative ORH group. Exclusion criteria: patients with tumours larger than 6 cm in diameter, or with tumours infiltrating the adjacent organs as detected by ultrasonography and/or CT, patients who did not consent to the procedure, patients with intestinal obstruction or perforation and patients whose oncological staging was Dukes' D
	Study design	A matched cohort study. Patients for the ORH control group matched in gender, age, Dukes' staging, tumour site, previous abdominal operation and extent of resection were randomly selected from 87 patients who underwent ORH during the same period. The mean duration of follow-up time was 27.15 months (range 12–40 months) for the LRH group and 26.19 months (range 13–40 months) for the ORH group. No patients were lost to follow-up. No blinding methods were reported
	Analysis of effectiveness	The analysis of effectiveness data was based on intention-to-treat. The following parameters were measured prospectively: operation time, blood loss, analgesic requirements, time to flatus passage, time to resume normal diet and duration of hospitalisation, morbidity and mortality, specimen length and lymph node yield, pathological staging (Dukes' staging), local recurrence rate and metachronous metastasis rate and cumulative survival probability. Major complications included massive haemorrhage, anastomotic leak, pulmonary infection, urinary tract infection, wound infection and ileus. There was no significant difference in age, gender, Dukes' staging, previous abdominal operation and tumour site between the LRH and ORH groups
	Effectiveness results/outcome measures	Statistically significant differences were found in blood loss 112.94 ml (SD 96.36 ml) for the LRH group and 274.5 ml (SD 235.43 ml) for the ORH group ($p = 0.009$), analgesia required postoperatively by 14 patients in the LRH group and 26 in the ORH group. Time to flatus passage, hospital stay and time to resume early activity in the LRH group were 2.24 days (SD 0.56 days), 13.94 days (SD 6.5 days) and 3.94 days (SD 1.64 days), respectively, which were significantly shorter than those in the ORH group (3.25 days, SD 1.29 days; 18.25 days, SD 5.96 days; and 5.45 days, SD 1.82 days, respectively), $p < 0.05$ for all differences. Five patients in the LRH group experienced postoperative complications (2 pulmonary infection, 2 wound infection, 1 ileus) and 10 patients in the ORH group (1 massive haemorrhage, 1 anastomotic leak, 3 pulmonary infection, 1 urinary tract infection, 4 wound infection) (16.7 vs 29.4%, respectively, $p = 0.23$)

continued

	Clinical conclusions	LRH in patients with colon cancer has statistically significant advantages over ORH. Hence LRH can be regarded as a safe and effective procedure
Economic analysis	Measure of health benefits used in the economic analysis	No summary of health benefit is used in the economic analysis and clinical outcomes are left disaggregated; a cost–consequences analysis was performed
	Direct costs	Total cost for operation, cost for drugs and total cost (sum of these two) were presented. No details of how these figures were calculated were reported
	Indirect costs	No indirect costs were reported
	Currency	Chinese renminbi (yuan, Y)
	Statistical analysis of quantities/costs	*t*-Tests were used to test the significance of cost differences between groups
	Sensitivity analysis	No sensitivity analysis was reported
Results	Estimated benefits used in the economic evaluation	A cost–consequences analysis was developed, then the reader is referred to the effectiveness results reported previously
	Costs results	The cost of operation in the LRH group was Y7810.7 (SD Y1719.07), which was significantly higher than that in the ORH group, Y5018.92 (SD Y845.62), $p < 0.01$. The cost of drugs in the LRH group (Y3687.85, SD Y1977.42) was significantly less than that in the ORH group (Y5209.42, SD Y2212.37), $p < 0.05$. No significant difference was observed in the total cost of operation and drugs between the two groups: Y11,498.54, SD Y2618.86 vs Y10,228.34, SD Y2372.57, $p = 0.131$
	Synthesis of costs and benefits	Not combined
	Authors' conclusions	LRH for right-sided colon cancer has the same oncological clearance, surgical safety, cost-effectiveness and patient survival as ORH. In addition, patients can benefit from the quicker postoperative recovery of laparoscopic surgery

HDU, high-dependency unit; HRQoL, health-related quality of life; ICU, intensive care unit; LCR, laparoscopic colonic resection; LRH, laparoscopic right hemicolectomy; NA, not applicable; OCR, open colonic resection; ORH, open right haemicolectomy.

Appendix 12

Estimation of parameter estimates used in the economic model

Derivation of the risk of hernia per cycle

The table below outlines the data available on the risk of hernia in the open arms of the identified studies.

Studies providing data to enable the risk of hernia per cycle to be estimated

Study ID	Events	Sample	Cumulative rate (%)	Follow-up (months)	Events per cycle	Risk per cycle
Winslow (COST), 2002[83]	9	46	19.6	30.1	1.8	0.039
Leung, 2004[53]	4	200	2.0	43	0.6	0.003
Patankar, 2003[127] (NR)	2	172	1.2	59	0.2	0.001
Champault, 2002[128] (NR)	3	83	3.6	60	0.3	0.004
Median						**0.003**[a]

NR, non-randomised study.
[a] Estimated 25 and 75 percentile observations 0.002 and 0.012.

Ideally, data on the time to event would have been used to estimate the risk of hernia. However, owing to the limited data available, it has been assumed that the risk per cycle is constant. The number of events per cycle (i.e. per 6-month period) is the observed number of events divided by the follow-up in months. The product of this is multiplied by the cycle length in months. The risk per cycle is the product of the number of events per cycle divided by the sample size. The value used in the model is the median of the values provided by the included studies. From these data, the 25 and 75 percentiles were calculated using the percentiles command in Microsoft Excel and a triangular distribution assumed using these and the median rates.

Derivation of the risk of emergency reoperation

The table below reports the data on risk of anastomic leakages reported in the open arms of the RCTs included in the systematic review of effectiveness. As described in the section 'Estimation of model parameters' (p. 40), the risk of an anastomic leakage has been assumed to be the same as the risk of an emergency reoperation to treat a postoperative complication.

Studies providing data to enable the risk of emergency operation to be estimated[a]

Study ID	Events	Sample	%
COLOR, 2005[4]	10	545	0.018
King, 2006[40]	1	19	0.053
Leung, 2004[53]	4	200	0.020
Zhou, 2004[60]	3	89	0.034
Hasegawa, 2003[49]	0	26	0.000
Lacy, 2002[22]	2	108	0.019
Tang, 2001[58]	1	118	0.008
Median			**0.019**

[a] Estimated IQR, 0.008–0.034.

The value used in the model is the median of the values provided by the included studies (1.9%). From these data, the IQR was estimated and a triangular distribution assumed using these and the median rates.

Estimation of the costs of non-operable management

The table below describes the drugs used for the management of non-operable recurrent disease. The description of resource use was provided by a Macmillan Nurse (O'Dea F, Hospital Specialist Palliative Care Team, Grampian University Hospital NHS Trust: personal communication, 2005). The cost of these drugs was obtained from the BNF.[129]

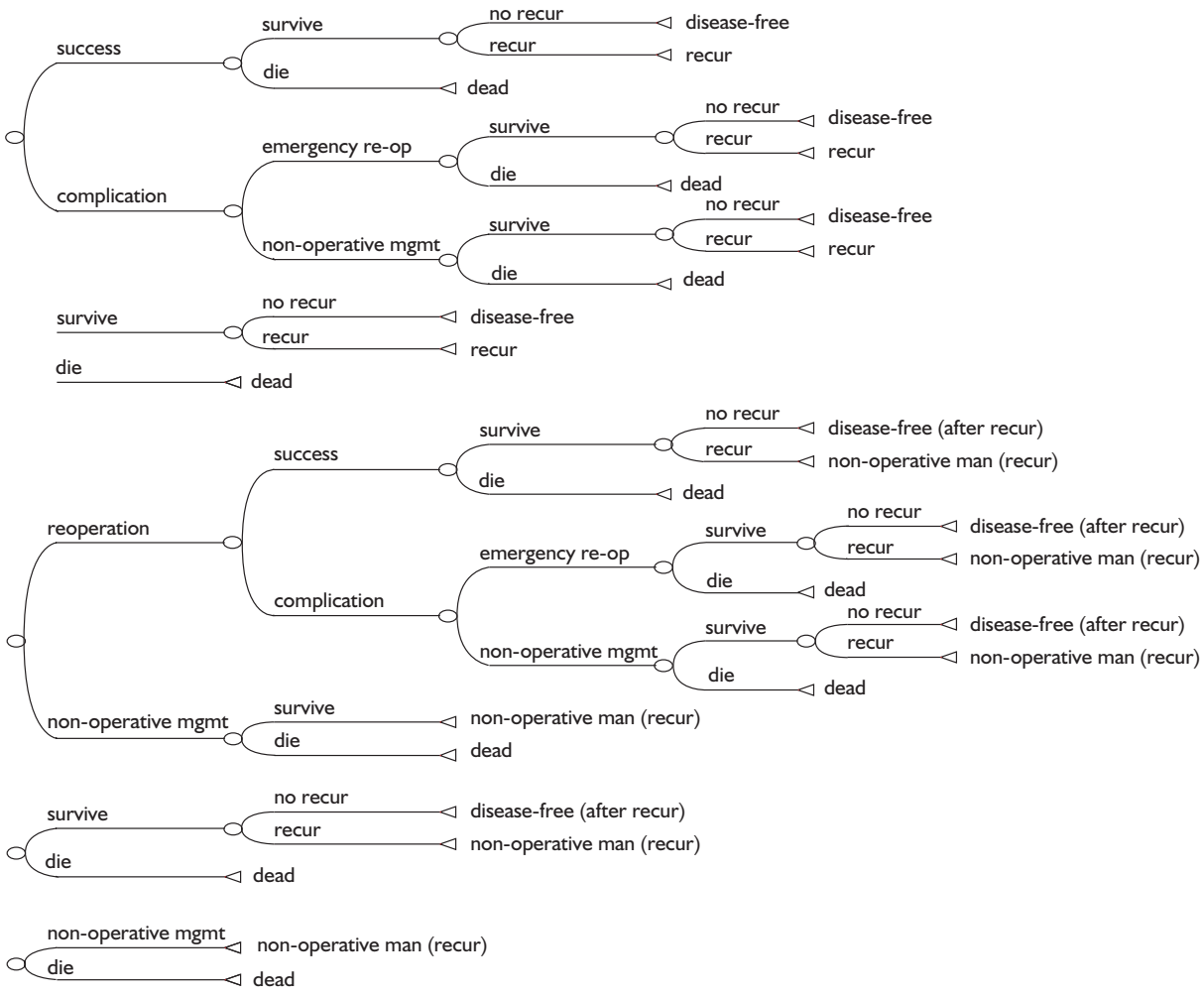
Drug costs used for model for typical patients being treated for non-operable disease

Drug	Dose per day	Cost per cycle (£)
Paracetamol	1 g, 4 × day	10.95
Diclofenac	50 mg, 3 × day	21.05
Oxycodone (oxycontin)	40 mg, 2 × day	633.67
Oxynorms	20 mg, 2 × day	289.07
Co-danthramer	10 mg, 2 × day	31.29
Docusate (dioctyl)	200 mg, 2 × day	58.40
Metaclopramide	10 mg, 4 × day	22.68
Omeprazole	10 mg, 2 × day	148.61
Total		**1215.72**

Appendix 13

Markov model for the management of colorectal cancer

The diagram below displays the unpopulated model for the laparoscopic arm. The tree structures for the open and laparoscopic arms are identical.



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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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ISSN 1366-5278