

A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer

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Executive summary

Background

Colorectal cancer is the second most common malignancy in the western world. There are over 34,000 new cases and around 18,000 deaths each year in the United Kingdom. The only curative treatment is surgical resection. Traditionally, this has involved open surgery. In recent years, laparoscopic surgery has been pioneered for colorectal pathologies because it is perceived to have lower post-operative morbidity than open surgery. The technique has been adopted for a range of colorectal conditions but widespread uptake for colorectal cancer has been limited because of concern about its long-term effectiveness. Specifically, there are fears that the laparoscopic technique may increase the risk of spreading metastases when resecting the tumour, or that resection may be incomplete.

Objectives

We performed a systematic review of the available literature in order to evaluate the effectiveness and cost-effectiveness of laparoscopic versus open surgery for colorectal cancer. We compared laparoscopic and open surgery with respect to a range of short-term and long-term outcome measures, resource use and cost. We also estimated the frequency of outcomes for patients undergoing laparoscopic surgery from case series.

Methods

Data sources

Comprehensive electronic search strategies were developed and used to search a range of databases: Medline, EMBASE, Science Citation Index (SCI), Cochrane Database of Systematic Review (CDSR), Cochrane Controlled Trials Register (CENTRAL/CCTR), NHS Centre for Reviews and Dissemination, DARE, NHS EED and HTA and OHE HEED. Date and language restrictions were not used. PubMed was searched to identify recent studies not yet indexed on Medline. Current research registers such as National Research Register (NRR), MRC Clinical Trials Register, and the US National Institutes of Health (NIH) Clinical Trials Register were also searched to identify current studies.

Study selection

Duplicate citations from different sources, publications deemed to be ineligible from their title and review articles were rejected without reading the abstracts. Remaining abstracts, where available, were read in full by two reviewers. Only randomised controlled trials and prospective cohort studies were eligible for the review of short-term outcomes. All study

designs, including case series, were eligible for the review of long-term outcomes but case series of less than 10 patients were ineligible. Studies which included a mixed population of patients with either benign or malignant pathologies were eligible for the review of short-term, but not long-term, outcomes. A total of 69 papers contributed data, 22 on short-term outcomes, 57 on long-term outcomes, including 10 on both. Eight papers containing relevant economic data were identified, one of which contributed data on long and short-term outcomes.

Data extraction

All eligible papers were double-read to extract data describing each study, e.g. publication date, author, study type, study duration, and short and long-term outcomes. Short-term outcomes included: conversion rate, complications, length of hospital stay, duration of operation, blood loss, time to restart diet, time to bowel movement and the number of lymph nodes harvested. Long-term outcomes included: survival, disease free survival, cancer related deaths, local recurrences, distant metastases, port site metastases. The quality of all included studies was assessed using different instruments for studies reporting short and long-term outcomes.

Data synthesis

Two kinds of synthesis were carried out. Meta-analyses of all studies that reported results for both laparoscopic and open groups were conducted for both short and long-term outcomes and for binary and continuous data. We also derived pooled estimates of outcome frequency for laparoscopic patients for conversions, port-site metastases and long-term outcomes, e.g. cancer related deaths, local recurrence and distant metastases rates. Where data for converted laparoscopic cases were presented separately, we recalculated numerators and denominators or means for the laparoscopic group to include these cases. For both kinds of synthesis, we explored heterogeneity between studies with respect to study quality and other covariates, e.g. date when a study was carried out.

Results

All short-term outcomes were reduced for laparoscopic surgery, i.e. indicating benefit, except for duration of operation, which was significantly longer, and number of lymph nodes excised, which showed no difference. The overall conversion rate was 13% across all studies, but about 8% for studies that included only colorectal cancer patients. Most studies found that laparoscopic surgery reduced complications but three trials found a non-significant increase in major complications. There were no significant differences in long-term outcomes between groups. We estimated that about 10% of laparoscopic patients died of cancer with 26 months, and that the incidence of port site metastasis was about 1%.

The net cost of laparoscopic surgery compared to open surgery was estimated to be £227 per admission, which mainly reflects the extra cost of theatre consumables since the increase in theatre time is approximately balanced by a reduction in the length of stay compared to open patients. The net increase in the cost is sensitive to changes in operating time and length of stay and, from experience with other technologies, would be expected to disappear within the next 5 years.

Conclusions

There is no evidence of long-term harms or benefits from laparoscopic compared to open surgery but the existing evidence cannot exclude the possibility of clinically important benefits *or* harms. There is a need for higher quality evidence about long-term outcomes with adequate precision to detect clinically important differences. Two large, high quality trials are in place, which will report in 4-5 years. There is no action that can be taken at present to provide high quality evidence about long-term outcomes sooner.

There is a need for quantification of the health related 'quality of life' gains for patients during the peri-operative and recuperation periods. Care would need to be taken in the design of such a study to avoid bias arising from patients' preconceptions about the potential advantages of minimally invasive surgery.

Laparoscopic surgery for colorectal cancer currently costs more than open surgery, although the difference is relatively small in relation to the imprecision of the estimate and would be expected to disappear as expertise and uptake of the technology increases.

List of Abbreviations

CRC	Colorectal cancer
RCT	randomised controlled trial
PCS	prospective cohort study
WMD	weighted mean difference
D & L	DerSimonian and Laird
OR	odds ratio
DOP	duration of operation
SD	standard deviation
CI	confidence interval
BDL	blood loss
TRD	time to restart diet
TBM	time to bowel movement
NLN	number of lymph nodes harvested
DARE	Database of Abstracts of Reviews of Effectiveness
NHS EED	National Health Service Economic Evaluation Database
OHE HEED	Office of Health Economics Health Economic Evaluation Database
NICE	National Institute for Clinical Excellence
MRC	Medical Research Council
TNM	tumour, nodes, metastases
UICC	Union International Contre le Cancer
SCI	Science Citation Index
CCCCRG	Cochrane Colorectal Cancer Collaborative Review Group
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systemic Review
NRR	National Research Register
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
HTA	Health Technology Assessment
HRG	Health Resources Group

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1 Background

Colorectal cancer (CRC) is second only to lung cancer as the most common malignancy in the western world. The incidence of colorectal cancer in the UK is 48/100,000 population per year, rising sharply with age, to 300/100,000 per year among those aged 75 and over ⁽¹⁾.

There are around 18,000 CRC deaths in the U.K annually. There has been only a modest improvement in survival over the last 30 years, despite improvements in adjuvant treatment, with an overall five-year survival of approximately 50% ⁽²⁾.

The only curative treatment in CRC is surgical resection. Traditionally, this has involved open resection using a laparotomy to enable both resection of the primary tumour with sufficient excision margins and an adequate, systematic lymphadenectomy. Additionally, for rectal cancer, a total mesorectal excision is performed to reduce the probability of local recurrence ⁽³⁾.

Excision of the tumour is the primary treatment for new CRC cases with potential for cure (80%). In the remaining 20%, the disease is too far advanced at presentation for any curative intervention. These patients also frequently undergo surgery for palliation, where optimising quality of life is the main objective of treatment.

The introduction of laparoscopic surgery, however, has led to conventional resection techniques being questioned because of the associated morbidity of the open approach. The successful adoption and benefits demonstrated for laparoscopic surgery soon led to its use in colorectal conditions. Initially this was for benign disease. The commonest indication for a resection, however, is malignancy, but the introduction of this new technique for CRC has been questioned because of controversy regarding its oncological safety. At present many clinicians advocate its use only in the setting of a randomised controlled trial until more data is available concerning its ability to fulfil established criteria for cancer surgery. Few centres in the UK, outside the MRC-CLASICC trial ⁽⁴⁾, currently use laparoscopic techniques for curative excision of CRC.

Stages of colorectal malignancy are well described, (see Appendix A) and is based on prognostic features described by Duke in 1932 ⁽⁵⁾. Firstly, the depth of the invasion of the

cancer is assessed and secondly, whether or not the cancer has spread to regional lymph nodes. Stage of disease is highly prognostic of survival.

1.1 Principles of Laparoscopic Surgery

The first laparoscopic appendicectomy was performed in 1983 ⁽⁶⁾. However, it was the performance of the first laparoscopic cholecystectomy by Mouret in 1987 that led to an explosion of interest ⁽⁷⁾ and to the acceptance of this as a standard procedure even before the introduction of formalised trials demonstrating the benefit. By the early 1990s, first reports of laparoscopic colorectal surgery entered the literature.

Laparoscopic-assisted right hemi-colectomy was first performed in 1990 ⁽⁸⁾ and a left sided colonic laparoscopic resection was reported later that year ⁽⁹⁾. The initial hope was that the immediate benefits observed after laparoscopic cholecystectomy, in terms of rapid recovery and reduction in post-operative morbidity would also be seen after laparoscopic colectomy. The development of laparoscopic techniques and their comparison with open surgery, particularly for cholecystectomy, has made the morbidity associated with traditional methods more evident. It has revolutionised the surgical management of many conditions, mainly benign, but it has also been advocated in the palliation of malignant disease principally because it allows the surgeon to reach areas previously only accessible through large abdominal incisions.

Inherent reduction in wound size with laparoscopic surgery has led to more rapid recovery with decreased pain and morbidity for certain procedures including resectional operations, for example, cholecystectomy and appendicectomy, as well as repairs such as herniorrhaphy or fundoplication ⁽¹⁰⁻¹²⁾. Widely recognised advantages (earlier return of bowel function, reduction in pain, shorter hospital stay and better cosmesis) have been demonstrated for pelvic floor disorders, diverticular disease and inflammatory bowel disease ⁽¹³⁾⁽¹⁴⁾⁽¹⁵⁾, even if the changes are of a lesser magnitude than those seen with laparoscopic cholecystectomy ⁽¹⁶⁾.

In addition to patient benefits, laparoscopic techniques also offer advantages to the surgeon. For example, the greatly magnified view is especially useful for operating in the pelvis since it facilitates dissection of the mesorectum when resecting rectal tumours ⁽¹⁷⁾.

However, there are drawbacks to laparoscopic techniques. These include a loss of depth perception and tactile feedback, and a reduced ability to control bleeding. The loss of direct manual palpation prevents the surgeon examining the liver for evidence of metastases, and thus staging of the primary tumour may be less accurate. In addition, identification of vital structures may be complicated by inadequate retraction thus increasing the risk of intra-operative damage.

1.2 Present Standards in Open surgery for colorectal cancer

For comparative purposes it is important to determine the currently accepted long-term outcomes for patients undergoing traditional open surgery for CRC. Overall survival at five years is reported as around 50%. Stage-specific survivals at two years are between 85-100% for Dukes A, 82-92% for Dukes B, 55-65% for Dukes C and around 20% for Dukes D, although, survival rates following open resection vary between different centres ⁽¹⁸⁻²⁰⁾.

1.3 Current guidance about the use of laparoscopic surgery for colorectal disease

Guidelines on the use of laparoscopic surgery for colorectal cancer have been published, and recommend that surgeons undertaking these minimally invasive techniques should be appropriately trained and experienced, in both open and laparoscopic colorectal surgery, and their results carefully audited ^(2;21;22). The use of laparoscopic surgery for benign colorectal disease is already well established ⁽²¹⁾.

1.4 Objectives

In the light of this debate, we performed a systematic review of the available literature in order to evaluate the effectiveness and cost-effectiveness of laparoscopic versus open surgery for CRC. More specifically we set out to compare these two surgical methods with respect to:

1. Short-term measures of effectiveness, e.g. complications, analgesia use, time to mobilisation and oral diet, length of stay.
2. Long-term measures of effectiveness, i.e. local recurrence, metastasis at a local or distant site and patient survival.
3. Cost-effectiveness taking account of both short and long-term measures of effectiveness.

2 Methods

2.1 Search Strategy

Our aim was to identify all papers relating to laparoscopic surgery for CRC. Comprehensive search strategies were developed based on the terminology and indexing terms found in articles retrieved in preliminary searches. Terms relating to CRC were also identified from strategies devised for reviews undertaken by the Cochrane Colorectal Cancer Collaborative Review Group. Keyword strategies for all databases are available, that for Medline is shown in Appendix B.

The following databases were used: Medline, EMBASE, Science Citation Index (SCI), Cochrane Database of Systematic Reviews (CDSR), Cochrane Controlled Trials Register (CENTRAL/CCTR), NHS Centre for Reviews and Dissemination, DARE, NHS EED and HTA and OHE HEED. Date and language restrictions were not used. PubMed entries for the last 180 days were searched to identify possible recent studies not yet indexed on the full Medline database.

The searches were not limited by study design or publication types for the review of clinical effectiveness. They were re-run with additional terms relating to economic evaluation of laparoscopic surgery in order to retrieve a subset of references for the review of cost-effectiveness (Appendix C).

We also looked at current research registers such as National Research Register (NRR), MRC Clinical Trials Register, and the US National Institutes of Health (NIH) Clinical Trials Register. The publication lists and research registers of health technology assessment (HTA) organisations, guideline development agencies and relevant professional bodies were consulted. The Cochrane Colorectal Cancer Collaborative Review Group (CCCCRG) was contacted to check the progress of two relevant review titles registered with the Group. The CCCCCRG undertook a search of the Group's trials register to identify studies possibly not listed on CENTRAL/CCTR.

We obtained a copy of a review recently published by the Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP) and cross-checked references against those identified in our review. Reference lists of included studies were hand-searched and, at

the final stage of the review, citation searches of the included studies, using the citation search facility of the Science Citation Index, were undertaken. The manufacturers' submissions to NICE were reviewed and handsearched.

2.2 Selection of eligible papers

A total of 2345 citations from 12 sources were considered for this review. Of these, 1906 citations were identified using similar searches in the electronic databases Medline, Embase and the Science Citation and a further 439 from nine other sources (see Table 1). Citations from electronic databases were considered first. A number of citations were identified from two or more of the electronic databases and so duplications were identified and systematically deleted. This first round of deletions removed 744 duplicated citations. Due to the broad nature of the search strategies used, 872 citations were deemed to be ineligible from their titles alone. These citations described irrelevant operation types, procedures or outcomes and were also deleted. Abstracts, where available, for the remaining 290 citations were read in full by two members of the review team. Of these 290 citations, only 69 contained data suitable for this review. Abstracts for the further 439 citations were read in the same way, but no additional papers that were considered potentially relevant were found.

For the remit of this review, we wished to use published primary data to construct two databases for analysis, one containing data on short-term outcomes following laparoscopic resection of colorectal cancer, the other describing long-term outcomes.

A total of 69 publications contributed data to these two databases. Ten of these publications described both long and short-term data and were included in both databases. Eight papers containing relevant economic data for the cost-effectiveness part of this review were identified, one of which also contributed data to both short and long-term databases.

2.3 Inclusion and Exclusion criteria

Papers were considered eligible for the review:

- They reported outcome data for patients who had undergone surgery for colorectal cancer using laparoscopic or laparoscopically-assisted operative techniques;
- They included data on any of the short- or long-term outcomes of interest (see 2.4 and 2.5);
- They used an appropriate study design, in the case of short-term outcomes (see 2.4)

Papers were excluded from the review if:

- They did not include primary data, relevant to the review
- They were written in Dutch, Swedish, Norwegian, Danish, Portuguese and Russian and did not have an English abstract
- They reported case-series and included less than 10 patients

Papers written in the languages above were excluded because translators could not be found for these papers in the time-frame for this review. Case-series of less than 10 patients were excluded because they were considered likely to contain selected and hence unrepresentative patients.

2.4 Short-term outcomes of laparoscopic and open surgery

Randomised controlled trials and prospective cohort studies with concurrent controls were chosen for the review if relevant short-term outcomes were presented. Other study designs were excluded because a) we anticipated there would be a reasonable number of these high-quality designs and b) data from poorer quality designs are less likely to be valid.

Publications describing data on benign patients were included, if they could not be separated from data on malignant cases, since it was considered unlikely that the type of colorectal disease would significantly affect the difference between laparoscopic and open groups in these outcomes.

A number of short-term 'time-to recovery' outcomes were considered relevant to the remit of this review. During the piloting of the data-extraction proforma, it was decided only to include outcomes that were consistently and well reported in the literature. We collected the following short-term data:

- length of stay
- operating time
- analgesia use
- operative blood loss
- time to mobilisation
- time to oral intake
- time to bowel opening

The number of post-operative complications for both laparoscopic and open surgery was also collected. These were scored as ‘major’ or ‘minor’ according to clinical relevance (see Appendix E). Finally, we collected data on the number of lymph nodes excised, a proxy variable for ‘extent of resection’. We note that ‘operating times’, as reported in the literature, can refer to a wide range of procedures for colorectal surgery, from simple stoma creation to complex total colectomies.

Most centres reported the need to ‘convert’ a number of surgical cases from a laparoscopic procedure to an open one. A ‘conversion’ is the requirement to make an unplanned extended incision in order to facilitate the operation because of surgical difficulty encountered after the operation has begun. Reasons for conversion include: bleeding, adhesions, technical difficulties (with equipment), size of tumour, invasion of tumour into surrounding tissue, injury, dissection difficulties (including failure to progress) and unclear anatomy/exposure. We recorded the number and reasons for conversions and, when not specified, classed them as ‘other’.

2.5 Long-term outcomes of laparoscopic and open surgery

The short-term post-operative benefits assume only secondary importance in malignant disease where the primary concerns are long-term survival and recurrence rates. The oncological safety of laparoscopic surgery for colorectal cancer is as yet unproven; indeed some advocate its role only in the palliation of colorectal cancer⁽²³⁾.

While it is important to establish the feasibility of the procedure and the short-term post-operative benefits of the laparoscopic technique, of greater consequences are the disease recurrence and/or cancer-related death rate following laparoscopic resection.

The long-term outcomes of interest to our review were:

- disease recurrence (local and distant)
- incidence of port-site metastases
- overall and disease-free survival

Evidence was collected from publications describing all study types. Most papers described laparoscopic case-series data without controls. We collected length of follow-up data that was given as a mean/median or as a maximum/minimum number of months. Kaplan Meier survival curves were presented for a minority of papers.

For the long-term dataset, we extracted information on malignant cases only as the chosen outcomes do not apply to patients with benign disease. Data were entered onto Excel spreadsheets and imported into STATA (a statistical software package) for analyses.

2.6 Data Collection

All 69 eligible papers describing short- and long-term data were double-read to extract outcomes data according to a proforma devised by the review team, with clinical advice. The proforma was piloted to identify appropriate and inappropriate use and classification of original variables. Any problems were discussed and amendments were made as appropriate. A copy of the final form can be seen in Appendix D. Units for all variables were converted to the lowest common denominator for comparability.

Descriptive data were abstracted in the same manner for both the long and short-term databases, e.g. publication date, author, study type, study duration, although key details were often incomplete.

To allow analysis of data by ‘intention to treat’, in studies which described converted cases, we coded papers according to whether these cases were presented with the laparoscopic group (intention to treat), the open surgery group or presented separately.

2.7 Quality assessment

In order to appraise the relative quality of each paper with regard to reporting of data, two proformas were created addressing issues relevant to the particular study types. Twenty-two questions were developed for assessment of the short-term papers (15 prospective cohort studies, five randomised controlled trials) published in the English language. The proforma was divided into four sections, pertaining to reporting quality, generalisability (external validity), bias and confounding (internal validity), based on a similar tool used by MacLehose et al ⁽²⁴⁾. The questions used in this proforma included questions on the dimensions scored by both Jadad and Schulz ⁽²⁵⁾.

Seven questions were asked for each of the 47 long-term papers, published in the English language, 30 of which were case series. This instrument has been used previously by Vardulaki et al ⁽²⁶⁾ for the assessment of quality of case-series. There are no established criteria for the assessment of case-series data. Both proformas can be seen in Appendices G and H.

2.8 Inter-observer reliability

A reliability study was carried out to assess the degree of inter-observer reliability for the quality assessment. Ten papers from both long and short-term datasets were chosen at random and the quality scores independently assessed by a different member of the review team. Kappa statistics, non-parametric measures of inter-rater agreement, were calculated for each question and are shown in Appendix I. Measure of agreement is scaled from zero to one, zero when the amount of agreement is what would be expected by chance and one suggesting perfect agreement. Kappa values appear inconsistent with ‘agreement’ in some cases because of the uniformity of the responses across evaluations for some criteria. When responses are relatively uniform, it is very difficult to obtain a high Kappa score because ‘expected’ agreement is also high.

2.9 Review of cost-effectiveness

Economic literature was identified using relevant bibliographic ‘filters’ for economic evaluations. Any economic evaluation of laparoscopic surgery for CRC was eligible. As in the case of the review of clinical effectiveness, literature reporting relevant economic data for laparoscopic and laparoscopically-assisted techniques was included in the review.

Relevant resource and cost information was extracted from all eligible papers as reported previously ^(27;28). The quality of eligible papers was assessed in accordance with published guidelines ⁽²⁹⁻³¹⁾.

Estimates of UK costs for key resources were identified from the available literature. These were combined with estimates of effectiveness and confidence intervals in a simple model. This model only considered short-term cost and resource use because (a) there were no published measures of short-term benefits and (b) there were no high quality comparative data on the relative long-term effectiveness of laparoscopic and open surgical procedures (see Results 3.3).

2.10 Methods of Analysis

2.10.1 Comparisons of outcome between laparoscopic and open groups

Three kinds of meta-analyses were carried out when studies reported outcome data for both laparoscopic and open groups:

- meta-analyses of binary data, e.g. major and minor complications, cancer-related deaths (STATA v.6 command: **metan**);
- meta-analyses of continuous data, e.g. length of stay, duration of operation, blood loss (STATA v.6 command: **metan**);
- meta-analysis of 'p' values for use of analgesia, where studies measured use of analgesia in different units (STATA v.6 command: **metap**).

Binary outcome data

Binary data meta-analyses were carried out both on the data 'as reported' and after recalculation of numerators and denominators for 3 studies, which reported conversions separately. No assumptions were required to 'correct' the data for these studies to reflect intention-to-treat analyses, so only the latter results are reported here. It should be noted that, for some other studies, authors did not report clearly how the data for converted patients had been treated.

Both fixed effects (Peto method) and random effects (DerSimonian and Laird (D&L) method) methods were applied, although only the results of random effects models are reported here. This decision was taken because:

- for theoretical reasons, a random effects model may be preferred for a non-standardised intervention such as surgery;
- the quality of studies varied considerably, which could contribute to heterogeneity;
- the random effects model produces wider confidence intervals, which we preferred because of general concerns about the quality of data extracted from papers.

With respect to heterogeneity, we always investigated the effect of study quality and explored the importance of other covariates when there appeared to be substantial heterogeneity between studies. Covariates investigated included: (a) the time of data collection (before 1994 / 1994 and after), (b) the average age of patients (≤ 65 years / > 65 years), (c) the use of laparoscopically assisted techniques or not, (d) the inclusion of cases with benign pathology

(only in the analyses of complications). Time of data collection was based on a 'mid-point date' for each study, calculated from the reported date when data collection started and the duration of the study.

Continuous outcome data

Because of the diverse ways in which data were reported, meta-analyses of continuous data required us to make certain assumptions. From studies that reported medians and ranges, it was apparent that the distributions of most continuous outcomes were positively skewed. The **metan** command (and Cochrane RevMan software) requires the user to supply the sample size, mean and SD for each group and, ideally, we would have inputted the mean and SD of outcome variables after log transformation. We simply used the reported means and SDs, assuming that the sampling variances of the means for groups would still be relatively normal, since group sample sizes were rarely less than 20. As mentioned, some authors reported medians rather than means; for these studies, we assumed that the difference between medians was the approximately the same as the difference between means since the distributions for the laparoscopic and open groups were likely to be similar. (This assumption will tend to underestimate the difference between means for positively skewed distributions.)

Three sets of analyses were carried out for each outcome. The first analysis only used studies that reported either means or medians *and* the SD for each group. The second analysis adjusted the estimates of the mean for the laparoscopic group to take account of data for conversions, reported separately by 3 studies; this adjustment assumed that the SD for the converted cases was the same as for the non-converted cases. The third analysis interpolated SDs when they were not reported by authors, based on the SDs reported by other studies. Because the SD appeared to increase as the mean of the outcome increased, interpolated values were calculated from the results of a weighted regression of the average value on the SD; when there was no relationship, the interpolated value was simply the weighted average of the reported SDs. Summary results for all three methods are reported but detailed results are only given for the second method, because of concern about the validity of interpolating SDs.

Again, both fixed effects (Peto method) and random effects (D&L method) were applied. Only the results of random effects models are reported here for the reasons given above. As

for binary meta-analyses, we always investigated the effect of study quality and explored the importance of other covariates when there appeared to be substantial heterogeneity between studies.

2.10.2 Descriptive estimates of outcome frequency for laparoscopic patients

We attempted to derive pooled estimates of outcome frequency for laparoscopic patients in two circumstances:

- for some outcomes, e.g. conversion rate and port-site metastasis, which were only applicable to laparoscopic patients;
- for other long-term outcomes, e.g. cancer-related deaths, local recurrence and distant metastasis rates, which were reported mainly in the context of case series.

Datasets containing summary information from papers were ‘expanded’ so that datasets contained a record for every patient. Characteristics of studies, including variables aggregated across all participants in a group, e.g. mean age was replicated in the records for each patient. Pooled estimates were calculated using logistic regression modelling (STATA v.6: **logistic**), using a ‘robust’ method to calculate confidence intervals; this method takes account of clustering of patients within case series and the replication of variables characterising the study for individual participants.

In addition to estimating pooled outcome frequencies, we also explored the extent to which other attributes of case series (covariates) were associated with the outcomes, namely (a) the time of data collection, (b) the average age of the patients recruited, (c) the use of laparoscopically assisted techniques, (d) the inclusion of cases with benign pathology (in the case of conversions only), (e) proportion of patients with tumours of different stages, (f) duration of follow-up and (g) the quality criteria assessed by reviewers.

3 Results

3.1 Literature available

The total numbers of citations considered for this review can be seen in Table 1. Of the 2345 citations, 2055 were duplicates or irrelevant studies. Of the 290 papers considered in detail only 76 were eligible for inclusion in this review; 214 papers were excluded from the review in the hierarchical order seen in Table 1. Firstly, irrelevant papers were excluded, then review articles, etc. No additional citations were found through Internet searching. Two additional citations were found in the Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP-S)⁽³²⁾, neither of which were included, as they did not meet our eligibility criteria. A list of the publications included in this review can be seen in Appendix F.

Table 1: Number of citations identified

Citations identified from different sources	
Total number considered	2345
Medline	668
Embase	612
Science Citation Index	626
Pub Med	146
Cochrane Controlled Trials Register	72
OHE HEED	5
CDSR	7
Cochrane Colorectal Cancer CRG Trials Register	46
Science Citation Index citation search	151
NHS EED, DARE and HTA	12
Number of papers considered in detail	290
Papers irrelevant to the review	50
Review articles with no primary data	65
Letters, editorials, comments	13
Foreign papers	14
Duplicated abstracts or data published in more than one journal	19
Case-series papers with no long-term data	43
Case-series less than 10	6
Cohort studies with historical controls	4
Number of papers analysed	76
Papers containing short-term outcome data only	12
Papers containing long-term outcome data only	47
Papers containing short- and long-term outcome data	10
Papers containing data for economic review only	7

3.2 Short-term outcomes

A total of 22 studies reported short-term data, 17 of which were prospective cohort studies (PCSs) and five of which were randomised controlled trials (RCTs). One study contributed two lines of data to the analyses as it stratified outcomes by age so, in effect, a total of 18 PCSs are described. Summary characteristics of the studies are summarised in Table 2. The number of cohort studies and trials, respectively, that reported different short-term outcomes are summarised in Table 3.

Table 2: Characteristics of randomised controlled trials and prospective cohort studies

	RCTs: n=5	PCSs: n=18
Publication dates	1998 (1995 to 1999)	1998 (1993 to 2000)
Mid point date (years: median & range)	1993 (1993 to 1995)	1993 (1990 to 1997)
Study duration (months: median & range)	19 (12 to 46)	46 (12 to 75)
Non- English language	1	3
Sample size (median & range) ^a	60 (32 to 109)	84 (25 to 415)
Mixed benign and malignant cases	4	12
Laparoscopic technique:		
Laparoscopic only	3	4
Laparoscopically-assisted	2	11
Either laparoscopic or assisted	0	13
‘Average’ age of laparoscopic group (median & range) ^b	69.0 (63.3 to 72.2)	64.9 (54.8 to 84.0)
‘Average’ of open group (median & range) ^b	69.0 (64.8 to 73.0)	65.9 (59.0 to 84.0)
Intention-to-treat analyses reported	2	5

^a Sample size was calculated as the sum of laparoscopic and open cases unless the paper clearly identified and reported converted cases separately, when the number of converted cases were included in the total.

^b Average age was sometimes reported as a mean and sometimes as a median.

Table 3: Numbers of RCTs and PCSs reporting different short-term outcome data

	RCTs: n=5	PCSs: n=18
Conversions	4	16
Major complications	3	15
Minor complications	3	15
Length of hospital stay (days)	3	14
Duration of operation (minutes)	5	14
Blood loss (mls)	4	8
Time to restart diet	2	8
Time to bowel movement	2	6
Number of lymph nodes harvested	1	13

3.2.1 Conversions

Four RCTs and 16 PCSs reported sufficient data to allow calculation of conversion rates, although the denominator was uncertain for the two RCTs and four PCSs which failed to report clearly how conversions were analysed, i.e. whether or not conversions were included in the total number of laparoscopic cases. In these instances, the reported total number of laparoscopic cases was used.

A total of 974 patients undergoing laparoscopic or laparoscopically-assisted surgery were included in these 20 studies, 130 in the 4 RCTs and 844 in the 16 PCSs. Using robust weighted regression, conversion rates were derived for RCTs (9.2%, 95% CI 4.8% to 16.9%) and PCSs (13.6%, 95% CI 7.7% to 22.9%). These rates did not differ significantly (odds ratio (OR) for RCTs = 0.64, 95% CI 0.25 to 1.65, $p = 0.36$). The overall conversion rate, pooled across study designs, was 13.0% (95% CI 7.8% to 21.0%).

Variation in conversion rates between studies was investigated by modelling the effects of four covariates (other than study design): (a) average age of sample of laparoscopic patients (65 years or less *vs.* greater than 65 years), (b) mid-point date of the study (1994 or earlier *vs.* later than 1994), (c) inclusion of patients with benign lesions or not and (d) the proportion of patients with Duke's stage 4 tumours or equivalent (in whom surgery is non-curative). The inclusion of patients with benign lesions (OR = 3.30, 95% CI 1.80 to 6.07, $p < 0.001$) and the average age of the laparoscopic patients (OR = 0.55, 95% CI 0.32 to 0.97, $p = 0.04$) both appeared to influence the conversion rate (see Table 4).

Table 4: Conversion rates in randomised controlled trials and prospective cohort studies

	Rate %	95% CI
Randomised controlled trials only (n=4)	9.2%	4.8% to 16.9%
Prospective cohort studies only (n=16)	13.6%	7.7% to 22.9%
All studies (n=20)	13.0%	7.8% to 21.0%
average age \leq 65 years, benign lesions included	27.1%	22.4% to 32.3%
average age \leq 65 years, malignant lesions only	10.1%	5.9% to 16.6%
average age $>$ 65 years, benign lesions included	17.1%	10.1% to 25.7%
average age $>$ 65 years, malignant lesions only	5.9%	3.1% to 10.7%

3.2.2 Major and minor complications

Complications were classified as major or minor on the basis of expert clinical advice (see Appendix E). Complications were usually described in a table in papers, listing the frequencies of each. However, since some authors did not describe at the outset (i.e. in the Methods section of a paper) the complications that they proposed to document, we cannot be certain that these complications did not occur if their frequencies were not reported. It was also often not clear from the tables of complications whether or not more than one complication was reported per patient. The results reported in Table 5 are based on the assumption that each complication occurred in a different patient and the complication rates may therefore be inflated. However, since authors almost certainly used the same method for reporting complications for both laparoscopic and open groups, this assumption will not necessarily have biased the comparison between groups.

Three RCTs and 15 PCSs reported data on complications; all studies gave sufficient detail to distinguish major and minor complications. As for conversions, laparoscopic complication rates were calculated as a proportion of the reported number of laparoscopic cases, except where data for converted cases were reported separately. In the latter studies, the complication data for the converted cases was pooled with non-converted laparoscopic cases. Major complication rates for laparoscopic patients ranged from 6% to 11% in RCTs and from 0% to 27% in PCSs; major complication rates for open patients ranged from 0% to 7% in RCTs and from 0% to 40% in PCSs. Minor complication rates for laparoscopic patients ranged from 4% to 8% in RCTs and from 4% to 72% in PCSs; minor complication rates for open patients ranged from 0% to 31% in RCTs and from 2% to 97% in PCSs.

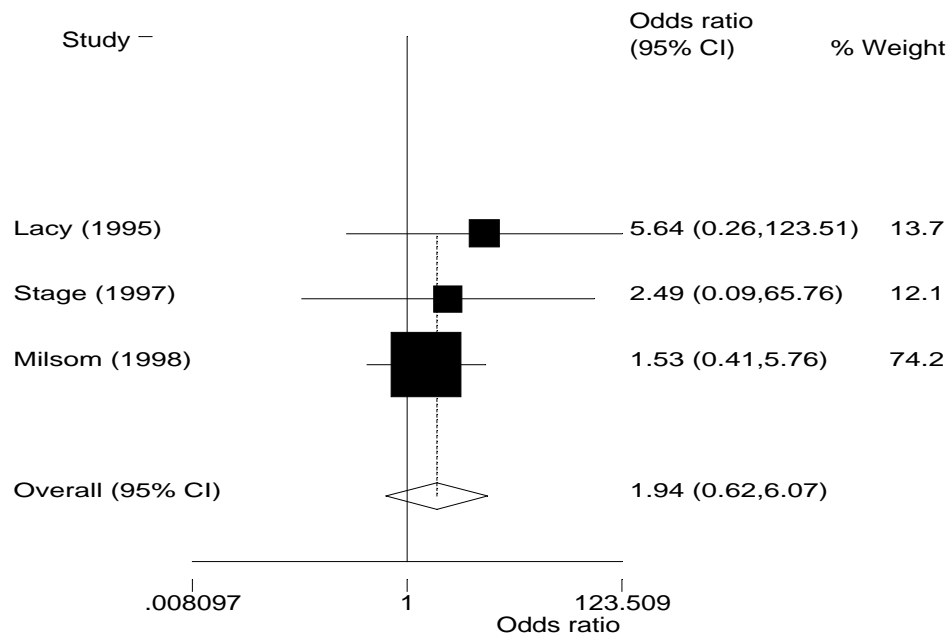
Table 5: Minor and major complication rates for laparoscopic and open groups

Paper	Study type	Laparoscopic groups			Open groups		
		n	Major	Minor	n	Major	Minor
Senagore et al., 1993	PCS	26	0.05	0.13	102	0.02	0.30
Goh et al., 1997	PCS	20	0.00	0.05	20	0.10	0.05
Begos et al., 1996	PCS	33	0.08	0.06	34	0.15	0.09
Leung et al., 2000	PCS	25	0.16	0.72	34	0.18	0.97
Delgado et al., 2000^α	PCS	59	0.04	0.07	67	0.08	0.12
Delgado et al., 2000^α	PCS	59	0.03	0.07	67	0.15	0.16
Ramos et al., 1997	PCS	20	0.20	0.35	18	0.11	0.89
Buchmann et al., 1998	PCS	85	0.09	0.13	67	0.19	0.15
Schwander et al., 1999	PCS	34	0.12	0.18	32	0.22	0.09
Franklin et al., 1996	PCS	191	0.13	0.04	224	0.14	0.08
Stewart et al., 1999	PCS	42	0.11	0.05	35	0.40	0.17
Tate et al., 1993	PCS	11	0.09	0.36	14	0.21	0.07
Bohm et al., 1997	PCS	26	0.27	0.04	85	0.11	0.02
Santoro et al., 1999	PCS	50	0.04	0.10	50	0.00	0.14
Stocchi et al., 2000	PCS	42	0.05	0.10	42	0.05	0.29
Lacy et al., 1995	RCT	25	0.08	0.08	26	0.00	0.31
Stage et al., 1997	RCT	18	0.06	0.06	14	0.00	0.00
Milsom et al., 1998	RCT	55	0.11	0.04	54	0.07	0.04

^α 2 lines of data were created from this paper as all outcomes were given for two age groups, patients aged<70 and patients aged>70.

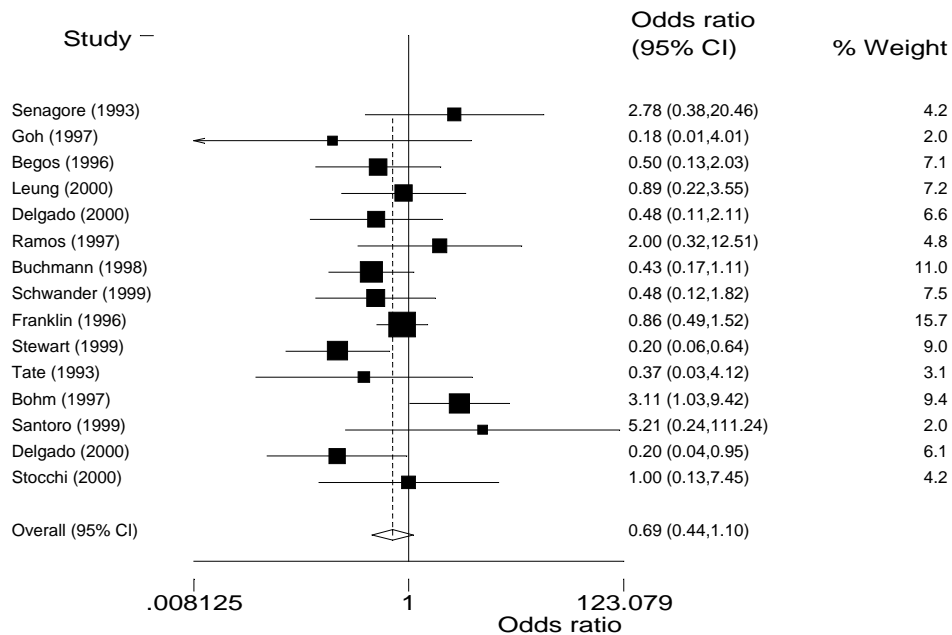
Random effects meta-analyses were carried out for major and minor complications and for RCTs and PCSs separately. In RCTs, laparoscopic surgery was associated with a non-significant increase in the risk of major complications (OR = 1.94, 95% CI 0.62 to 6.07, p = 0.26; see Figure 1). However, in PCSs laparoscopic surgery was associated with a non-significant *decrease* in the risk of major complications (OR = 0.69, 95% CI 0.44 to 1.10, p = 0.12; see Figure 2).

Figure 1: Random effects meta-analysis of major complications, RCTs only



Heterogeneity chi-squared = 0.61 (d.f. = 2) p = 0.737
 Test of OR = 1 : z = 1.14 p = 0.255

Figure 2: Random effects meta-analysis of major complications, PCSs only



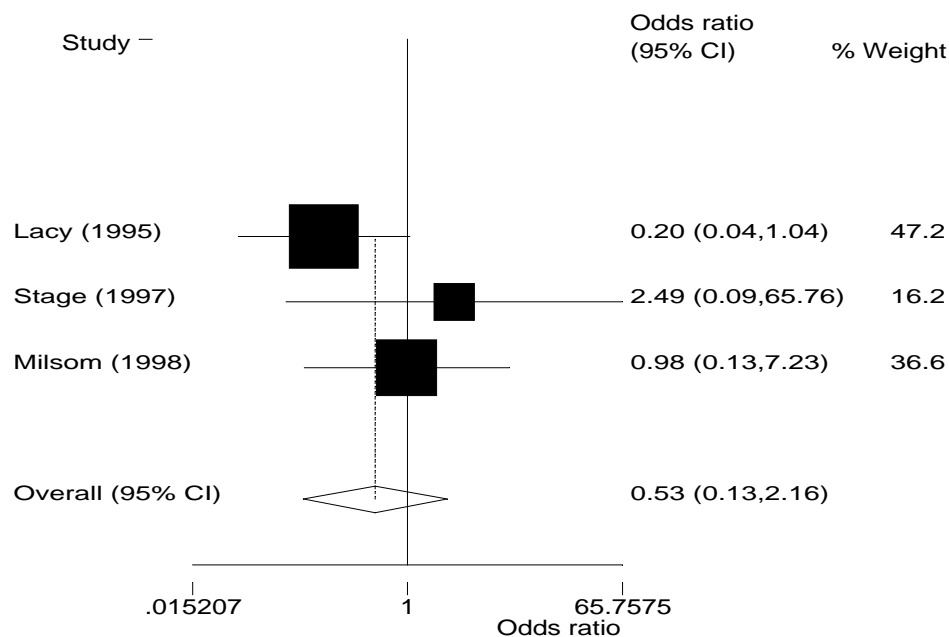
Heterogeneity chi-squared = 22.17 (d.f. = 14) p = 0.075
 Test of OR = 1 : z = 1.56 p = 0.118

Heterogeneity between PCSs reporting major complications was of borderline significance (p=0.08) and this was explored by carrying out further meta-analyses for the following five

covariates: (a) average age of sample of laparoscopic patients (65 years or less vs greater than 65 years), (b) mid-point date of the study (1994 or earlier vs later than 1994), (c) inclusion of patients with benign lesions or not, (d) laparoscopic only vs laparoscopically assisted (any patients) and (e) high quality vs low quality (cut-off score >16). High quality studies yielded a pooled OR closer to unity (n = 4, OR = 1.15) than low quality studies (n = 7, OR = 0.53), and there was no significant heterogeneity between PCSs in each sub-group of studies. ORs closer to unity were also found for studies that (a) included only patients with malignancies (n = 10, OR = 0.83 vs n = 5, OR = 0.50), (b) recruited younger patients (n = 9, OR = 0.98 vs. n = 6, OR = 0.47), (c) were carried out earlier (n = 4, OR = 0.92 vs n = 8, OR = 0.67) and (d) which did not use laparoscopically assisted techniques (n = 3, OR = 0.98 vs n = 12, OR = 0.59). (The number of studies for some contrasts do not sum to 15 because quality was not assessed for non-English papers, and the start date or duration of studies was sometimes not reported).

In RCTs, laparoscopic surgery was associated with a non-significant decrease in the risk of minor complications (OR = 0.53, 95% CI 0.13 to 2.16, p = 0.38; see Figure 3). In PCSs, laparoscopic surgery was associated with a highly significant decrease in the risk of minor complications (OR = 0.50, 95% CI 0.32 to 0.79, p = 0.003; see Figure 4).

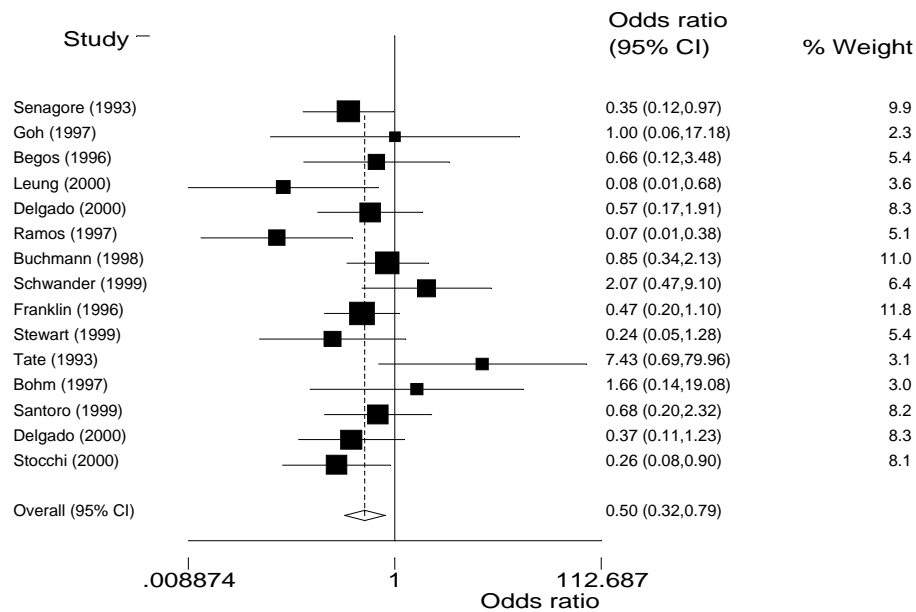
Figure 3: Random effects meta-analysis of minor complications, RCTs only



Heterogeneity chi-squared = 2.57 (d.f. = 2) p = 0.276

Test of OR = 1 : z = 0.88 p = 0.378

Figure 4: Random effects meta-analysis of minor complications, PCSs only



Heterogeneity chi-squared = 21.80 (d.f. = 14) p = 0.083
 Test of OR = 1 : z = 2.96 p = 0.003

Heterogeneity between PCSs reporting minor complications was of borderline significance (p=0.08) and was explored as for major complications. The same covariates did not result in wide separation of pooled ORs for sub-groups of studies, with pooled ORs for all sub-groups being <0.60.

In summary, the evidence on the relative frequency of major and minor complications was not consistent. The balance of the evidence suggests that laparoscopic surgery reduces the frequency of complications, although all three RCTs that reported major complication data found more complications with laparoscopic surgery. When interpreting the meta-analyses, it is also important to remember that the quality of the data is uncertain, for example with respect to multiple complications in the same patient and the frequency of complications that were not described or itemised.

3.2.3 Length of stay

Three RCTs and 14 PCSs reported the average length of stay (mean or median) for laparoscopic and open groups, but only one RCT and seven PCSs reported standard deviations (SDs). Pooled differences in length of stay (LOS) using the three different

methods described in the Methods (see 2.10) are summarised in Table 6 separately for RCTs and PCSs.

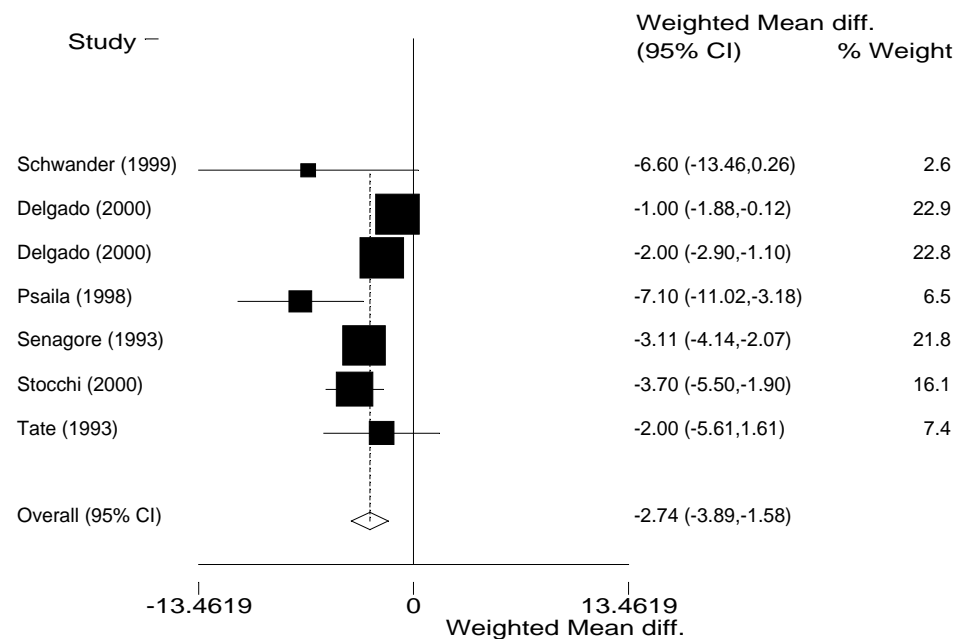
Table 6: Random effects meta-analyses for length of stay (LOS)

Length of stay (days)	Randomised controlled trials			Prospective cohort studies		
	Method ^a	n	difference	95% CI	n	difference
(a)	1	-2.90	-4.43 to -1.37	7	-2.98	-4.30 to -1.67
(b)	1	-2.90	-4.43 to -1.37	7	-2.74	-3.89 to -1.58
(c)	3	-2.14	-3.59 to -0.68	14	-3.24	-4.28 to -2.21

^a Methods (see 2.10): (a) random effects using published estimates of average LOS and SD of LOS; (b) random effects using estimates of average LOS, combining conversion data for average LOS with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average LOS on SD(LOS).

Because of the uncertainties around interpolation of SDs for studies in which these were not reported, we focus on the results for method (b). Weighted mean differences and confidence intervals for this method for PCSs are shown in the ‘forest plot’ in Figure 5. For both RCTs and PCSs, the pooled estimates indicated a highly significant reduction in length of stay of 2.5 to 3 days ($p < 0.001$) when laparoscopic techniques were used.

Figure 5: Random effects meta-analysis of length of stay (method (b)), PCSs only



Heterogeneity chi-squared = 20.53 (d.f. = 6) $p = 0.002$
 Test of WMD = 0 : $z = 4.64$ $p < 0.001$

There was significant heterogeneity between PCSs, which was explored by carrying out further meta-analyses for the following five covariates: (a) average age of sample of laparoscopic patients (65 years or less *vs.* greater than 65 years), (b) mid-point date of the study (1994 or earlier *vs.* later than 1994), (c) inclusion of patients with benign lesions or not, (d) laparoscopic only *vs.* laparoscopically-assisted (any patients) and (e) high quality *vs.* low quality (cut-off score >16). High quality studies yielded a larger estimate of the weighted mean difference (WMD) between groups (n = 4, WMD = -4.49) than low quality studies (n = 2, WMD = -2.32), although there was still significant heterogeneity between PCSs in each sub-group of studies. When patients with benign lesions were included in the studies, the WMD between groups was larger (n = 2, WMD = -3.26) than when only patients with malignant tumours were included (n = 5, WMD = -2.39), although there was still significant heterogeneity between PCSs in the latter sub-group. In studies of older patients, the WMD between groups was larger (n = 5, WMD = -3.37) than in studies of younger patients (n = 2, WMD = -2.52), although there was still significant heterogeneity between PCSs in both sub-groups. Early and recent studies yielded similar estimates of the WMD (n = 1, WMD = -3.11 *vs.* n = 5, WMD = -2.84 respectively) and there was still significant heterogeneity between both these sub-groups.

In summary, length of stay was consistently shorter for laparoscopic surgery. Estimates of the WMD varied from 2.1 to 3.2 days, for different study designs and meta-analyses. It is difficult to choose a 'best' estimate, because there was only one RCT that reported both LOS estimates and SDs and significant heterogeneity between PCSs that could not be explained by the covariates that were investigated. Nevertheless, the estimates are reasonably consistent, except after interpolation of SDs, and we conclude that the reduction in length of stay using laparoscopic surgery is 2.5 to 3 days.

3.2.4 Operating time

Five RCTs and 14 PCSs reported the average duration of operation (mean or median) for laparoscopic and open groups, but only three RCT and 10 PCSs reported standard deviations (SDs). Pooled differences in duration of operation (DOP) using the three different methods described in the Methods (see 2.10) are summarised in Table 7 separately for RCTs and PCSs.

Table 7: Random effects meta-analyses for duration of operation (DOP)

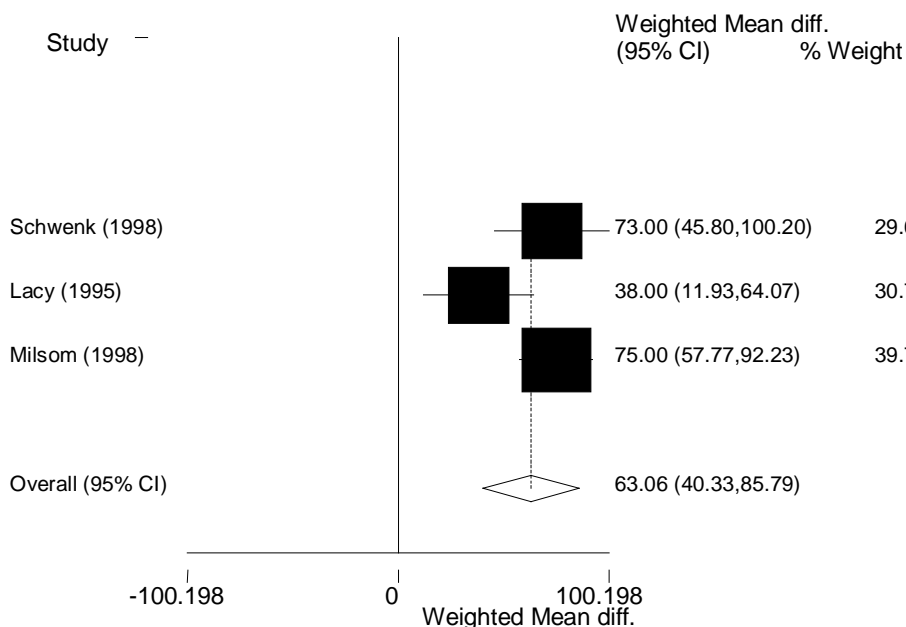
Length of stay (days)	Randomised controlled trials			Prospective cohort studies			
	Method ^a	n	difference	95% CI	n	difference	95% CI
(a)		3	63.1	40.3 to 85.8	10	47.0	32.3 to 61.7
(b)		3	63.1	40.3 to 85.8	10	48.8	35.1 to 62.5
(c)		5	65.0	49.7 to 80.3	14	46.9	32.1 to 61.6

^a Methods (see 2.10): (a) random effects using published estimates of average OPT and SD of OPT; (b) random effects using estimates of average OPT, combining conversion data for average OPT with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average OPT on SD(OPT).

As for LOS, we focus on the results for method (b). Weighted mean differences and confidence intervals for this method for RCTs and PCSs are shown in the ‘forest plot’ in Figure 6. For both RCTs and PCSs, the pooled estimates indicated a highly significant increase in duration of operation of 45 to 65 minutes ($p < 0.001$) when laparoscopic techniques were used.

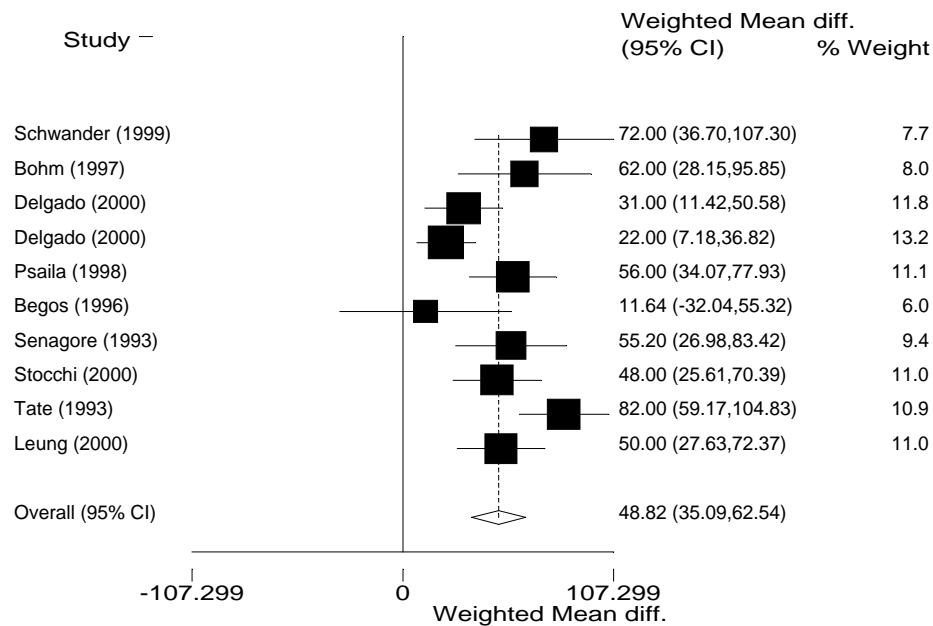
Figure 6: Random effects meta-analysis of duration of operation

(a) RCTs only



Heterogeneity chi-squared = 5.73 (d.f. = 2) $p = 0.057$
 Test of WMD = 0 : $z = 5.44$ $p < 0.001$

(b) PCSs only



Heterogeneity chi-squared = 28.49 (d.f. = 9) p = 0.001

Test of WMD = 0 : z = 6.97 p < 0.001

There was significant heterogeneity between PCSs ($p = 0.001$), which was explored as for LOS. High quality studies yielded a larger estimate of the WMD between groups ($n = 3$, $WMD = 62.5$) than low quality studies ($n = 4$, $WMD = 36.2$), with no significant heterogeneity between PCSs in either sub-group of studies; the estimate for high quality studies was very similar to the pooled estimate for RCTs. When patients with benign lesions were included in the studies, the WMD between groups was smaller ($n = 3$, $WMD = 44.0$) than when only patients with malignant tumours were included ($n = 7$, $WMD = 51.6$), although there was still significant heterogeneity between PCSs in the latter sub-group. In studies of older patients, the WMD between groups was larger ($n = 5$, $WMD = 56.4$) than in studies of younger patients ($n = 5$, $WMD = 40.3$), although there was still significant heterogeneity between PCSs in both sub-groups. Early studies yielded a larger WMD ($n = 4$, $WMD = 56.9$) than for recent studies ($n = 6$, $WMD = 43.4$), with significant heterogeneity remaining between PCSs in both sub-groups. The test of heterogeneity for RCTs was also of borderline significance ($p = 0.06$). However, no attempt was made to explore the source of heterogeneity because only three RCTs contributed to the meta-analysis.

In summary, the duration of operation was consistently longer for laparoscopic surgery. Estimates of the WMD varied from 47 to 65 minutes, for different study designs and meta-

analyses. Considering the varying estimate for high and low quality PCSs, and the greater confidence one has in RCT evidence, we conclude that the difference in duration of operation is about one hour.

3.2.5 Blood loss

Four RCTs and eight PCSs reported the average blood loss (BDL: mean or median) for laparoscopic and open groups, but only two RCT and five PCSs reported standard deviations (SDs). Pooled differences in BDL using the three different methods described in the Methods (see 2.10) are summarised in Table 8 separately for RCTs and PCSs.

Table 8: Random effects meta-analyses for blood loss (BDL)

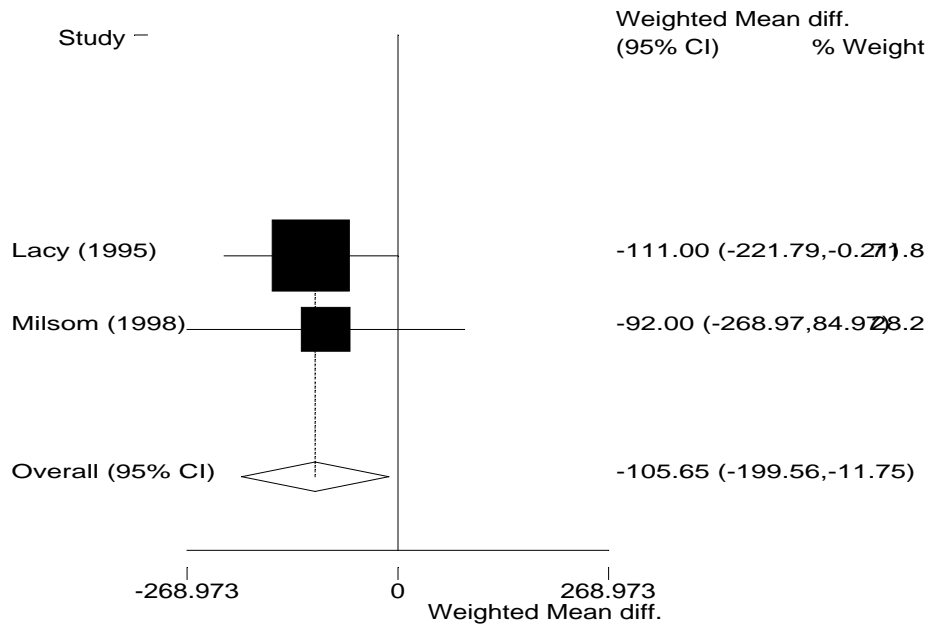
Length of stay (days)	Randomised controlled trials			Prospective cohort studies		
	n	difference	95% CI	n	difference	95% CI
Method^a						
(a)	2	-105.7	-199.6 to -11.7	5	-204.1	-346 to -61.8
(b)	2	-105.7	-199.6 to -11.7	5	-185.3	-303.9 to -66.7
(c)	4	-87.9	-161.3 to -14.4	8	-195.6	-300.0 to -91.2

^a Methods (see 2.10): (a) random effects using published estimates of average BDL and SD of BDL; (b) random effects using estimates of average BDL, combining conversion data for average BDL with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average BDL on SD(BDL).

Again, we focus on the results for method (b). Weighted mean differences and confidence intervals for this method for RCTs and PCSs are shown in the ‘forest plots’ in Figure 7. For both RCTs and PCSs, the pooled estimates indicated a significant reduction in blood loss of 100 to 200 mls ($p = 0.03$ and $p = 0.002$ respectively) when laparoscopic techniques were used.

Figure 7: Random effects meta-analysis of blood loss (method (b))

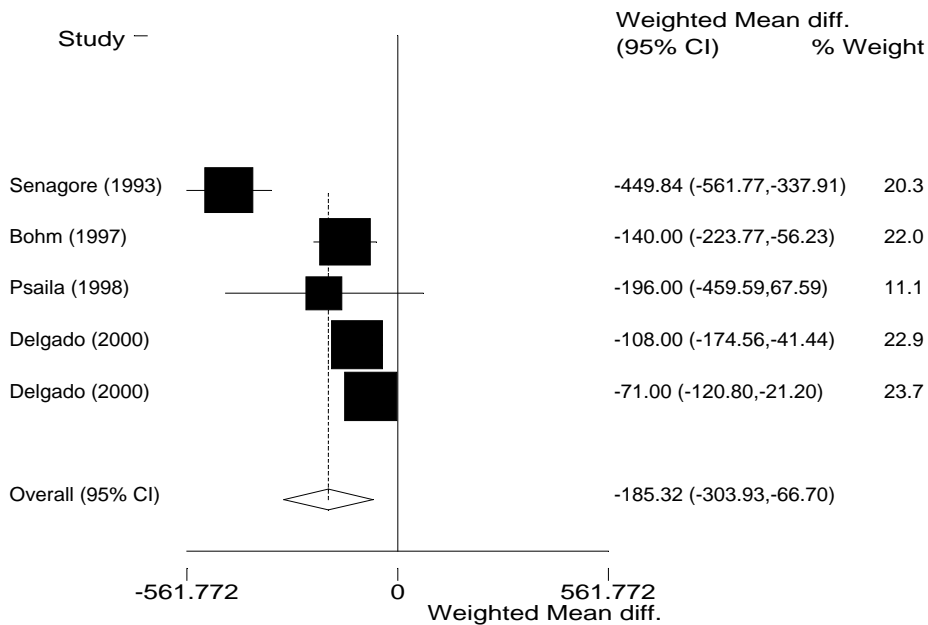
(a) RCTs only



Heterogeneity chi-squared = 0.03 (d.f. = 1) p = 0.858

Test of WMD = 0 : z = 2.21 p = 0.027

(b) PCSs only



Heterogeneity chi-squared = 37.47 (d.f. = 4) p < 0.001

Test of WMD = 0 : z = 3.06 p = 0.002

There was significant heterogeneity between PCSs (p<0.001), which was explored as before.

High and low quality PCSs yielded similar estimates of the WMD (n = 1, WMD = -196.0 and

n = 3, WMD = -202.0), with significant heterogeneity remaining between the latter three studies. When patients with benign lesions were included in the studies, the WMD was much larger (n = 1, WMD = -449.8) than when only patients with malignant tumours were included (n = 4, WMD = -96.4), and there was no heterogeneity between PCSs in the latter sub-group; the WMD estimate of -96 mls is also similar to the pooled estimate for the two RCTs. In studies of older patients, the WMD between groups was smaller (n = 2, WMD = -75.3) than in studies of younger patients (n = 3, WMD = -227.7), although there was still significant heterogeneity between PCSs in the latter sub-group. Early studies yielded a larger WMD (n=2, WMD = -292.6) than for recent studies (n = 3, WMD = -86.8), with significant heterogeneity remaining between PCSs in the former sub-group. All studies used laparoscopically-assisted techniques to some extent. As can be seen from Figure 7, the heterogeneity arose largely because of one study⁽³³⁾. It may be the idiosyncratic aspects of this study that are important, rather than the fact that it recruited relatively young patients, with both benign and malignant lesions, and was carried out early in the development of laparoscopic surgery for colorectal surgery.

In summary, blood loss was consistently less for laparoscopic surgery. Estimates of the WMD varied from 90 to 205 mls, for different study designs and meta-analyses. Considering the extreme nature of one PCS study, we conclude that the reduction in blood loss with laparoscopic techniques is about 100 mls.

3.2.6 Time to restart diet

Two RCTs and eight PCSs reported the time taken by patients to start eating after the operation (TRD: mean or median) for laparoscopic and open groups; both RCTs but only four PCSs reported standard deviations (SDs). Pooled differences in TRD using the three different methods described in the Methods (see 2.10) are summarised in Table 9 separately for RCTs and PCSs.

Table 9: Random effects meta-analyses for time to restart diet (TRD)

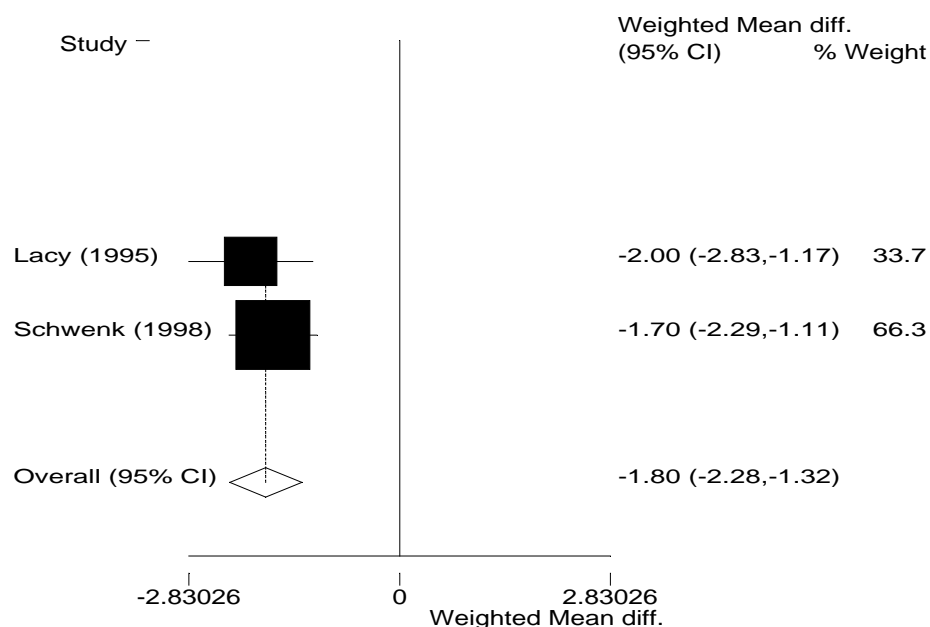
Length of stay (days)	Randomised controlled trials			Prospective cohort studies			
	Method ^a	n	difference	95% CI	n	difference	95% CI
(a) & (b)		2	-1.80	-2.28 to -1.32	4	-1.03	-1.35 to -0.72
(c)		2	-1.80	-2.28 to -1.32	8	-0.91	-1.27 to -0.55

^a Methods (see 2.10): (a) random effects using published estimates of average TRD and SD of TRD; (b) random effects using estimates of average TRD, combining conversion data for average TRD with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average TRD on SD(TRD).

For TRD, methods (a) and (b) gave the same results because of the paucity of studies of each kind; including PCSs with interpolated SDs did not alter the WMD substantially but did introduce significant heterogeneity. Weighted mean differences and confidence intervals for methods (a) and (b) for RCTs and PCSs are shown in the ‘forest plots’ in Figure 8. For both RCTs and PCSs, the pooled estimates indicated a significant reduction in TRD of one to two days ($p < 0.001$) when laparoscopic techniques were used; unusually, the pooled estimate for the two RCTs was larger than for the four PCSs.

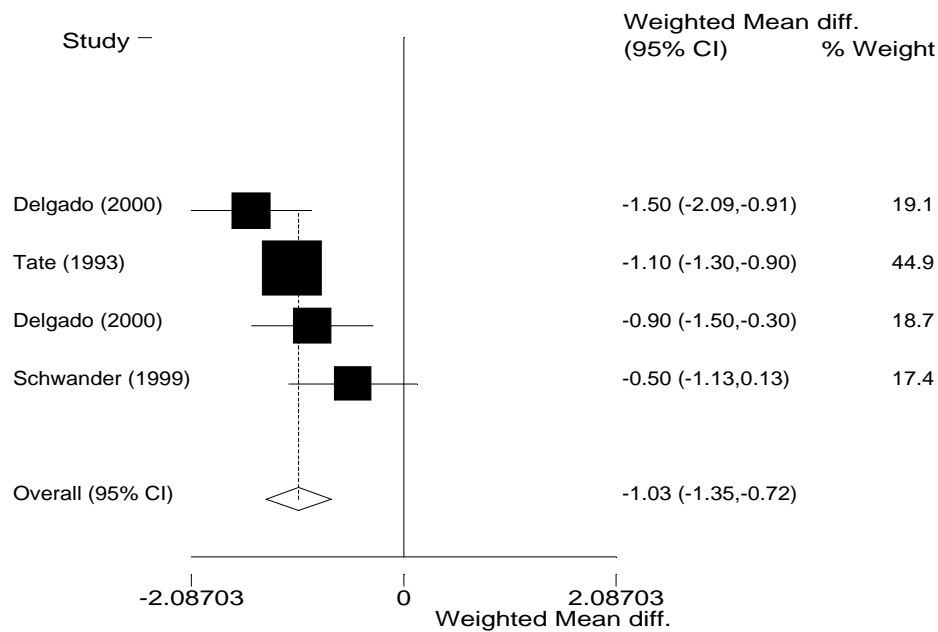
Figure 8: Random effects meta-analysis of time to restart diet (methods (a) and (b))

(a) RCTs only



Heterogeneity chi-squared = 0.33 (d.f. = 1) $p = 0.564$
 Test of WMD = 0 : $z = 7.32$ $p < 0.001$

(b) PCSs only



Heterogeneity chi-squared = 5.60 (d.f. = 3) p = 0.133

Test of WMD = 0 : z = 6.36 p = 0.000

There was no significant heterogeneity between the four PCSs (p = 0.13) used for method (b) and potential heterogeneity was only explored as a function of study quality. The low and high quality PCSs yielded similar estimates of the WMD (n = 2, WMD = -1.20 and n = 1, WMD = -1.10); a quality score was not available for one foreign language PCS.

In summary, time to restart diet was consistently less for laparoscopic surgery. Estimates of the WMD varied from 1 to 2 days for different study designs. It is difficult to choose between these estimates because of the paucity of evidence. Although one would expect the RCTs to have greater validity, the two studies included a total of only 111 patients, compared to over 500 in the PCSs.

3.2.7 Time to bowel movement

Two RCTs and six PCSs reported the time to patients opening their bowels (TBM: mean or median) for laparoscopic and open groups, but only one RCT and four PCSs reported standard deviations (SDs). Pooled differences in TBM using the three different methods described in the Methods (see 2.10) are summarised in Table 10 separately for RCTs and PCSs.

Table 10: Random effects meta-analyses for time bowel movement (TBM)

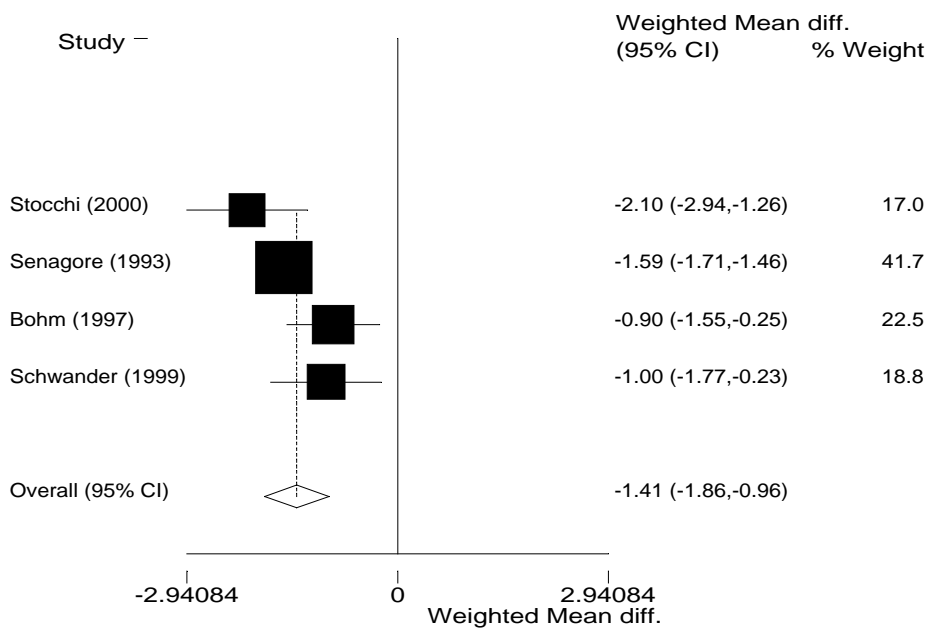
Length of stay (days)	Randomised controlled trials			Prospective cohort studies		
	Method ^a	n	difference	95% CI	n	difference
(a)	1	-0.90	-1.47 to -0.33	4	-1.50	-2.10 to -0.90
(b)	1	-0.90	-1.47 to -0.33	4	-1.41	-1.86 to -0.96
(c)	2	-0.40	-0.78 to -0.02	6	-1.24	-1.74 to -0.74

^a Methods (see 2.10): (a) random effects using published estimates of average TBM and SD of TBM; (b) random effects using estimates of average TBM, combining conversion data for average TBM with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average TBM on SD(TBM).

For TBM, methods (a) and (b) gave virtually the same results because of the paucity of studies of each kind; including studies with interpolated SDs altered the WMD estimates and introduced heterogeneity both for RCTs and PCSs, so we focus on method (b) again.

Weighted mean differences and confidence intervals for method (b) for RCTs and PCSs are shown in the ‘forest plot’ for PCSs in Figure 9. For both the RCT and the PCSs, the WMD estimates indicated a significant reduction in TBM of 1 to 1.5 days ($p=0.002$ and $p<0.001$ respectively) when laparoscopic techniques were used.

Figure 9: Random effects meta-analysis of time to bowel movement (method (b)) PCSs only)



Heterogeneity chi-squared = 7.77 (d.f. = 3) $p = 0.051$

Test of WMD = 0 : $z = 6.20$ $p = 0.000$

The heterogeneity between PCSs was of borderline significance ($p = 0.05$). All PCSs for which quality scores were available were of low quality. When patients with benign lesions were included in the studies, the WMD was larger ($n = 2$, $WMD = -1.67$) than when only patients with malignant tumours were included ($n = 2$, $WMD = -0.94$), and there was no heterogeneity between PCSs in either sub-group; the WMD estimate of -0.94 for patients with malignancies also similar to the pooled estimate for the single RCT, which also only included patients with malignant tumours. The WMD estimates for studies which recruited younger and older patients were similar ($n = 2$, $WMD = -1.32$ and $n = 2$, $WMD = -1.54$ respectively), and there was still significant heterogeneity in both sub-groups; the four PCSs were split into the same pairs based on mid-point date, i.e. early vs. recent. All four studies used laparoscopically-assisted techniques to some extent.

In summary, time to bowel movement was consistently less for laparoscopic surgery. Estimates of the WMD varied from 1 to 1.5 days, for different study designs and meta-analyses. We conclude that the reduction in time to bowel movement for patients with CRC is about 1 day.

3.2.8 Number of lymph nodes harvested

One RCT and 13 PCSs reported the number of lymph nodes harvested (NLN: mean or median) for laparoscopic and open groups, but standard deviations (SDs) were reported for only six PCSs. Pooled differences in NLN using the three different methods described in the Methods (see 2.10) are summarised in Table 11 separately for RCTs and PCSs.

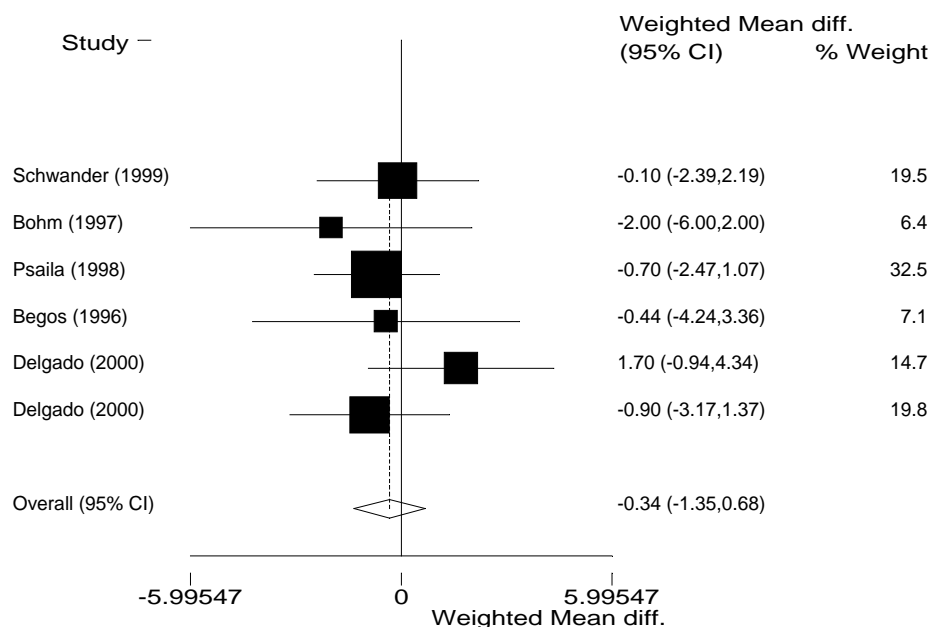
Table 11: Random effects meta-analyses for number of lymph nodes harvested

Length of stay (days)	Randomised controlled trials			Prospective cohort studies			
	Method ^a	n	difference	95% CI	n	difference	95% CI
(a)	-	-	-	-	6	-0.36	-1.38 to 0.66
(b)	-	-	-	-	6	-0.34	-1.34 to 0.68
(c)	1	-6.00	-8.59 to -3.41	13	0.07	-1.61 to 1.74	

^a Methods (see 2.10): (a) random effects using published estimates of average NLN and SD of NLN; (b) random effects using estimates of average NLN, combining conversion data for average NLN with laparoscopic data where data for conversions was reported separately; (c) as for (b), but also interpolating SDs where they were not reported, from a regression of average NLN on SD(NLN).

For methods (a) and (b), pooled estimates of the WMD for NLN were only available for PCSs and were very similar since there was no significant heterogeneity between studies; including studies with interpolated SDs yielded an extreme estimate from a single RCT but did not substantially alter the WMD estimate for PCSs. Weighted mean differences and confidence intervals for method (b) for PCSs are shown in the ‘forest plot’ in Figure 10. The WMD estimate for PCSs indicated no difference in the number of lymph nodes harvested ($p = 0.52$) when laparoscopic techniques were used.

Figure 10: Random effects meta-analysis of number of lymph nodes harvested (method (b)), PCSs only



Heterogeneity chi-squared = 3.39 (d.f. = 5) $p = 0.640$

Test of WMD = 0 : $z = 0.65$ $p = 0.516$

There was no significant heterogeneity between the six PCSs ($p = 0.64$) used for method (b) and potential heterogeneity was only explored as a function of study quality. The low and high quality PCSs yielded similar estimates of the WMD ($n = 2$, WMD = 0.31 and $n = 1$, WMD = -0.70); a quality score was not available for three foreign language PCSs.

In summary, there was little evidence that the number of lymph nodes harvested differed for laparoscopic and open surgical techniques. The estimate from the single RCT that reported relevant data was extremely different from the pooled PCS estimate, and indicated that on

average six fewer lymph nodes were harvested when a laparoscopic technique was used; however, this study did not report any statistical test of the difference between groups nor any measure of the variability of the estimates for each group. We conclude that there is no substantive evidence that fewer lymph nodes are harvested when using a laparoscopic technique.

3.3 Long-term outcomes

There is no *a priori* reason for expecting laparoscopic surgery to be more effective than open surgery with respect to long-term outcomes since, after the immediate post-operative period, long-term outcomes are determined by the completeness of the resection and distant metastases. Rather, the main concern about laparoscopic surgery is the danger of ‘port site metastases’, i.e. seeding tumour cells around the multiple sites of access for laparoscopic instruments.

A total of 57 studies followed up patients who had undergone laparoscopic colorectal surgery for malignancies but two reported no useful data. Characteristics of the studies are summarised in Table 12.

3.3.1 Comparative data on long-term outcomes

Seventeen studies reported one or more long-term outcomes for both laparoscopic and open surgical groups; eight studies reported overall survival, five studies reported disease-free survival, eight studies reported cancer-related deaths, 15 studies reported frequencies of local recurrence and 14 studies reported frequencies of distant metastases (see Table 13). Six studies reporting local recurrences and five studies reporting distant metastases found no events in either group.

Table 13 shows the proportions of patients with stage 2, 3 and 4 tumours and the length of follow-up in laparoscopic and open groups. The proportions of patients with tumours at different stages are reasonably similar across groups for the majority of studies. The weighted average duration of follow up for laparoscopic and open groups was also similar (25.6, 95% CI 23.3-27.9, and 26.3, 95% CI 22.6-30.0, months respectively), although there were differences between groups in individual studies of up to 10 months.

Table 12 : characteristics of studies reporting long-term data

	Comparative: n=20	Case series: n=37
Publication dates	1998 (1994 to 2000)	1997 (1993 to 2000)
Mid point date (years: median & range)	1994 (1992 to 1995)	1993 (1989 to 1998)
Study duration (months: median & range)	36 (14 to 72)	36 (12 to 180)
Non- English language	1	7
Laparoscopic sample size (median & range) ^a	36 (18 to 191)	56 (10 to 399)
Open sample size (median & range)	42 (7 to 224) ^c	-
Study type:		
Randomised controlled trial	2	-
Prospective cohort study	11	-
Retrospective cohort study	5	-
Historically controlled cohort study	2	-
Case series	-	37
Laparoscopic technique:		
Laparoscopic only	8	12
Laparoscopically-assisted	11	19
Either laparoscopic or assisted	1	4
‘Average’ age of laparoscopic group (median & range) ^b	67 (58 to 72)	64 (48 to 76)
‘Average’ of open group (median & range)	67 (59 to 74)	-
‘Average’ duration of laparoscopic follow-up (months) ^b	21 (8 to 42)	22 (7 to 40) ^d
‘Average’ duration of open follow-up (months)	24 (8 to 42)	-
Intention-to-treat analyses reported	6	10 ^e

^a Sample size was calculated as the sum of laparoscopic and open cases unless the paper clearly identified and reported converted cases separately, when the number of converted cases were included in the total.

^b Average age and duration were sometimes reported as a mean and sometimes as a median.

^c One cohort study did not report the sample size for patients treated with open surgery.

^d Six case series did not report the average length of follow-up for patients treated with laparoscopic surgery.

^e For case series, intention-to-treat refers to the inclusion of converted cases in the results from laparoscopic case series

Table 13: Characteristics of and types of comparisons reported by studies that included both laparoscopic and open groups

	Outcome ^a					Number of cases ^b		t (surv) ^c	t (follow up) ^d		% stage 2		% stage 3		% stage 4	
	S	D	C	R	M	Lap	Open		Lap	Open	Lap	Open	Lap	Open	Lap	Open
Buchmann et al., 1995			Y	Y	Y	45	44	-	10.5	10.5	22	36	11	11	0	0
Fleshman et al., 1999	Y		Y	Y	Y	42	125	27.5	20.5	27.5	26	40	43	39	14	10
Lacy et al., 1998			Y	Y	Y	31	40	-	21.4	21.4	45	60	26	30	13	5
Franklin et al., 1996			Y			191	224	-	34.0	24.8	39	50	32	34	14	5
Milsom et al., 1998			Y	Y	Y	55	54	-	18.0	20.4	24	20	29	26	6	7
Bouvet et al., 1998	Y	Y	Y	Y	Y	91	57	24.0	26.0	26.0	15	21	12	21	3	5
Psaila et al., 1998			Y	Y	Y	25	29	-	30.0	26.0	36	45	32	41	0	0
Ramos et al., 1997			Y	Y	Y	20	18	-	18.0	22.0	15	28	50	56	10	6
Leung et al., 1999	Y	Y		Y	Y	28	56	60.0	21.4	23.5	43	43	25	25	24	21
Khalili et al., 1998	Y			Y	Y	80	90	60.0	21.0	18.0	40	51	34	33	0	9
Leung et al., 1997	Y	Y		Y	Y	50	50	48.0	32.8	39.1	48	48	30	30	10	12
Stage et al., 1997				Y	Y	18	14	-	14.0	14.0	44	29	11	14	11	29
Schwander et al., 1999	Y					32	32	36	33.1	31.0	3	3	38	38	0	0
Santoro et al., 1999	Y	Y		Y	Y	50	50	60.0	42.0	42.0	42	46	22	20	10	14
Gray et al., 1994 ^e				Y		22	74	-	24.0	24.0	-	-	-	-	-	-
Buchmann et al., 1996 ^e				Y		39	27	-	9.5	8.0	-	-	-	-	-	-
Leung et al., 2000	Y	Y		Y	Y	25	s34	48.0	29.0	28.5	52	35	20	35	24	29

^a S – patient survival; D – disease-free survival; C – cancer-related deaths; R – local recurrence; M – distant metastasis.

^b Number of laparoscopic cases includes converted cases where converted cases were reported separately.

^c Post-operative months for which patient survival estimates were reported.

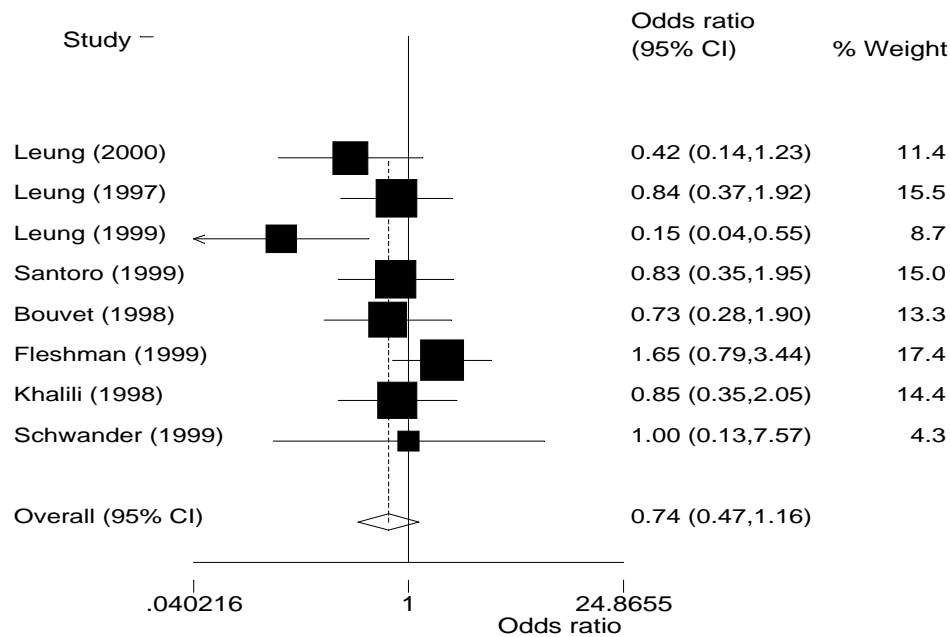
^d Average (mean or median) follow-up time in months reported for laparoscopic and open cases.

^e Numbers of patients with tumours of different stages were not reported.

In attempting to synthesise these outcome data, there is no straightforward method of taking account of the modest imbalances in duration of follow-up and tumour staging within and between studies. Nevertheless, given that these imbalances were of modest size and their direction was not consistent across studies (i.e. the imbalances ‘favoured’ the laparoscopic group in about half of the studies and the open group in the other half), we decided to carry out formal syntheses with a view to ruling out a substantial increase in risk of adverse long-term outcomes with laparoscopic surgery. Overall patient survival and disease-free survival estimates were converted into frequencies of patients surviving to the time for which survival estimates were reported for the meta-analyses, which may result in confidence intervals for the pooled estimates that are too narrow.

Four prospective and four retrospective cohort studies reported survival estimates. The numbers of patients in laparoscopic and open groups in these studies are shown in Table 13. Survival estimates ranged from 61% to 93% for laparoscopic groups and from 46% to 93% for open groups, and were reported for durations ranging from 24 to 60 months. Surprisingly, there was no relationship between survival and duration of follow-up. All studies reported no significant difference in survival between groups, with a minority adjusting for imbalance in covariates between groups using Cox regression. The forest plot for a random effects meta-analysis of the studies is shown in Figure 11, showing that the pooled OR does not differ significantly from unity; the pooled OR certainly does not suggest any decreased survival following laparoscopic surgery.

Figure 11:random effects meta-analysis of comparative studies reporting overall patient survival

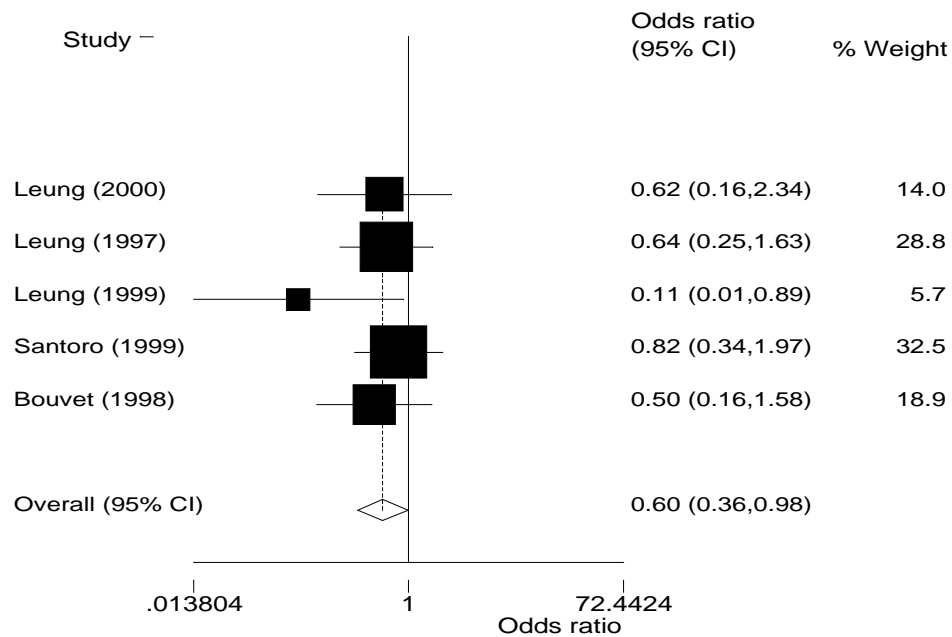


Heterogeneity chi-squared = 11.62 (d.f. = 7) p = 0.114

Test of OR = 1 : z = 1.30 p = 0.192

Three prospective and two retrospective cohort studies reported disease-free survival estimates. The numbers of patients in laparoscopic and open groups in these studies are shown in Table 13. Disease-free survival estimates ranged from 21% to 85% for laparoscopic groups and from 26% to 50% for open groups, and were reported for durations ranging from 24 to 60 months. All studies reported no significant difference in survival between groups. The forest plot for a random effects meta-analysis of the studies is shown in Figure 12, showing that the pooled OR is just significantly less than unity; in all five studies disease-free survival was slightly higher after laparoscopic surgery, without any obvious imbalances in the proportions of patients with different tumour stages (see Table 13). The finding of long-term benefit from laparoscopic surgery may be improbable, as discussed above, but the pooled OR make the possibility of decreased disease-free survival following laparoscopic surgery extremely unlikely.

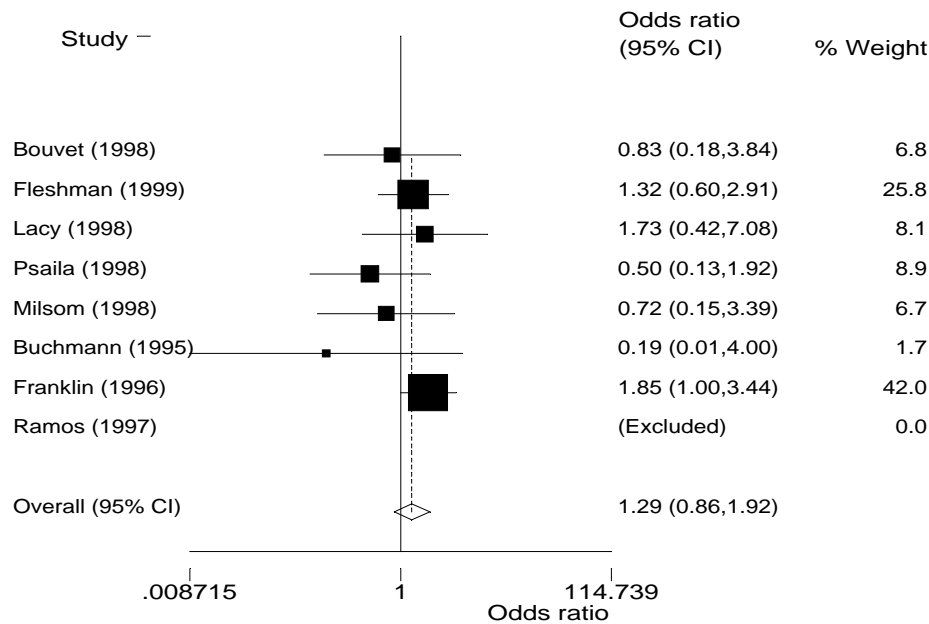
Figure 12: random effects meta-analysis of comparative studies reporting disease free survival



Heterogeneity chi-squared = 3.21 (d.f. = 4) p = 0.523
 Test of OR = 1 : z = 2.02 p = 0.043

Five prospective and three retrospective cohort studies reported the frequency of cancer-related deaths. The numbers of patients in laparoscopic and open groups in these studies are shown in Table 13. The proportion of patients dying from cancer ranged from 0% to 28% for both laparoscopic and open groups, and for durations ranging from 11 to 34 months (maximum 28 months for open groups). Once again, there was no relationship between outcome, i.e. the frequency of cancer-related deaths, and duration of follow-up. The forest plot for a random effects meta-analysis of the studies is shown in Figure 13, showing that the pooled OR does not differ significantly from unity. There was no statistically significant heterogeneity. However, the pooled OR is greater than one, and a 30% increase in the frequency of cancer-related deaths would be considered clinically important if this point estimate were to be confirmed by larger and higher quality studies in the future.

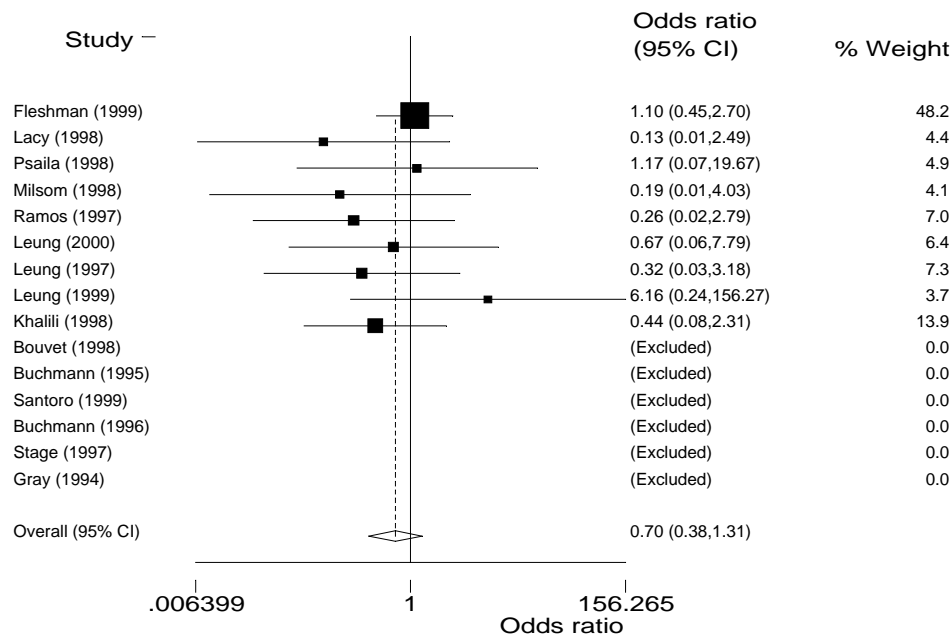
Figure 13: random effects meta-analysis of comparative studies reporting the frequency of cancer-related deaths



Heterogeneity chi-squared = 5.81 (d.f. = 6) p = 0.445
 Test of OR = 1 : z = 1.23 p = 0.219

Ten prospective and five retrospective cohort studies reported the frequency of local recurrences. The numbers of patients in laparoscopic and open groups in these studies are shown in Table 13. The proportion of patients with local recurrences ranged from 0% to 19% for laparoscopic groups and 0% to 17% for open groups, although only one study reported rates greater than 10% for either group. Duration of follow-up ranged from 14 to 33 months and 8 to 39 months for laparoscopic and open groups respectively. Again, there was no relationship between outcome, i.e. the frequency of local recurrences, and duration of follow-up. The forest plot for a random effects meta-analysis of the studies is shown in Figure 14, showing that the pooled OR does not differ significantly from unity; note that six studies were excluded from the meta-analysis because they reported no recurrences for either group. There was no statistically significant heterogeneity. The pooled OR does not suggest any increase in the frequency of local recurrences following laparoscopic surgery.

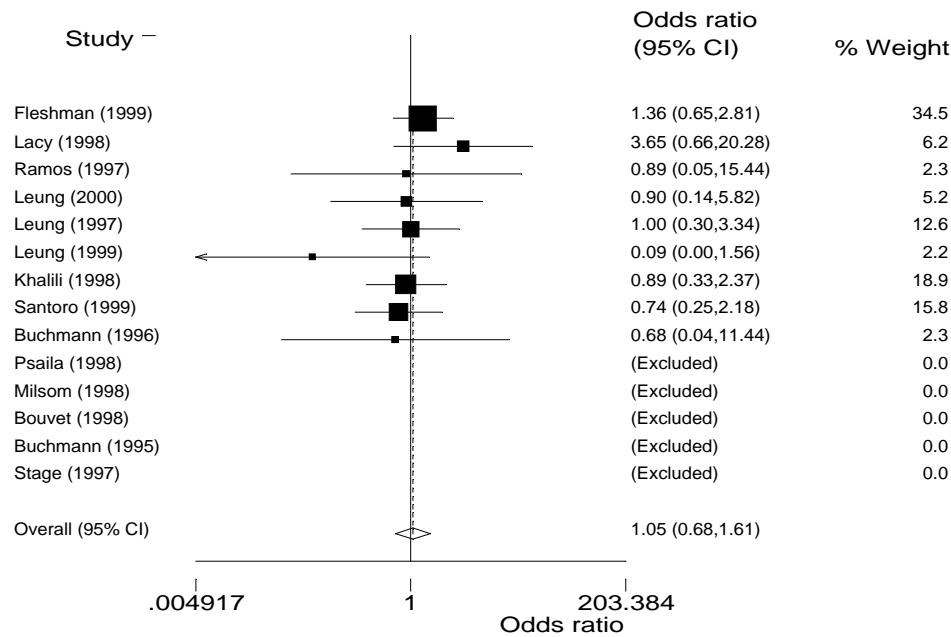
Figure 14: random effects meta-analysis of comparative studies reporting the frequency of local recurrences



Heterogeneity chi-squared = 6.28 (d.f. = 8) p = 0.616
 Test of OR = 1 : z = 1.12 p = 0.262

Nine prospective and five retrospective cohort studies reported the frequency of distant metastases. The numbers of patients in laparoscopic and open groups in these studies are shown in Table 13. The proportion of patients with distant metastases ranged from 0% to 38% for laparoscopic groups and 0% to 31% for open groups. Duration of follow-up ranged from 10 to 33 months and 8 to 39 months for laparoscopic and open groups respectively. There was no obvious relationship between outcome, i.e. the frequency of local recurrences, and duration of follow-up. The forest plot for a random effects meta-analysis of the studies is shown in Figure 15, showing that the pooled OR does not differ significantly from unity; note that five studies were excluded from the meta-analysis because they reported no recurrences for either group. There was no statistically significant heterogeneity. The pooled OR was very close to unity, providing no evidence of any increase in the frequency of distant metastases following laparoscopic surgery.

Figure 15: random effects meta-analysis of comparative studies reporting the frequency of distant metastases



Heterogeneity chi-squared = 6.11 (d.f. = 8) p = 0.635
 Test of OR = 1 : z = 0.21 p = 0.834

These analyses relied on the authors' choices about which long-term outcomes to document and report and there is a danger that authors' choices might have been influenced by the outcome frequencies observed. Clearly, the survival estimates (46% to 93%) are not entirely consistent with the low rates of local recurrence and distant metastasis. This inconsistency may be explained by the inclusion of more studies in the analyses of local recurrence and distant metastasis combined with the substantial variation in the proportion of patients included with stage 4 tumours (0-29%, see Table 13). Also, authors of some studies excluded patients with stage 4 tumours from analyses of long-term outcomes, since operations for such patients are considered to be palliative.

No exploration of factors associated with variation in effect size between studies was attempted for three reasons. First, none of the meta-analyses found significant heterogeneity. Second, few studies reported some of the outcomes, i.e. overall patient survival and disease-free survival. Third, weighted regression analyses of case series that investigated reporting quality variables found no consistent associations between quality criteria and outcome frequency.

3.3.2 Case series data on long-term outcomes

All 57 studies reported one or more long-term outcomes for patients who had undergone laparoscopic surgery, although the total number of laparoscopic patients was missing for one study, precluding its inclusion in the following analyses. Nine studies reported overall survival, five studies reported disease-free survival, 35 studies reported cancer-related deaths, 42 studies reported frequencies of local recurrence, 43 studies reported frequencies of distant metastasis and 50 studies reported the frequencies of port site metastases (see Table 14). Table 14 shows the total numbers of patients, the proportions of patients with stage 2, stage 3 and stage 4 tumours and the average duration of follow at which outcome frequencies were reported.

Table 14: Outcomes ^a reported in case series of patients who underwent laparoscopic surgery (including laparoscopic groups in cohort studies)

	S	D	C	R	M	P	n ^b	FU ^c	%S2	%S3	%S4 ^d
Fleshman et al., 1999	Y		Y	Y	Y	Y	42	20.5	26	43	14
Lacy et al., 1998			Y	Y	Y	Y	31	21.4	45	26	13
Ramos et al., 1997			Y	Y	Y	Y	20	18.0	15	50	10
Leung et al., 2000	Y	Y		Y	Y	Y	25	29.0	52	20	24
Leung et al., 1997	Y	Y		Y	Y	Y	50	32.8	48	30	10
Leung et al., 1999	Y	Y		Y	Y	Y	28	21.4	43	25	24
Khalili et al., 1998	Y			Y	Y	Y	80	21.0	40	34	0
Santoro et al., 1999	Y	Y		Y	Y	Y	50	42.0	42	22	10
Buchmann et al., 1996 ^e				Y	Y	Y	39	9.5	-	-	-
Psaila et al., 1998			Y	Y	Y	Y	25	30.0	36	32	0
Milsom et al., 1998			Y	Y	Y	Y	55	18.0	24	29	6
Bouvet et al., 1998	Y	Y	Y	Y	Y	Y	91	26.0	15	12	3
Buchmann et al., 1995			Y	Y	Y	Y	45	10.5	22	11	0
Stage et al., 1997				Y	Y	Y	18	14.0	44	11	11
Gray et al., 1994 ^e				Y	Y	Y	22	24.0	-	-	-
Franklin et al., 1996			Y				191	34.0	39	32	14
Schwander et al., 1999	Y						32	33.1	3	38	0
Wexner et al., 1996						Y	19	24.0	? ^f	? ^f	16
Verzaro et al., 1994				Y	Y	Y	15	30.0	53	13	0
Baca et al., 1997			Y	Y	Y	Y	52	18.0	27	25	21
Go et al., 1996 ^e			Y	Y	Y	Y	38	10.0	-	-	-
Vara-Thorbeck			Y	Y	Y	Y	17	6.5	35	41	24
Ramos et al., 1994 ^e						Y	208		-	-	-
Schiedeck et al., 2000			Y	Y	Y	Y	399	29.8	9	54	0
Fleshman et al., 1996			Y	Y	Y	Y	372	22.6	25	18	17
Fielding et al., 1997			Y	Y	Y	Y	139	33.0	29	23	25
Morino et al., 1999 ^e			Y	Y	Y	Y	93	40.0	-	-	-

Table 14 (continued.): Characteristics of and types of comparisons reported by studies that included both laparoscopic and open groups

	S	D	C	R	M	P	n	FU	%S2	%S3	%S4
Bruch et al., 1999			Y	Y	Y	Y	60	22.0	? ^f	? ^f	27
Champault et al., 1997				Y	Y	Y	23	17.7	22	26	30
Kwok et al., 1996			Y	Y	Y	Y	83	15.2	47	29	34
Bohm et al., 1999			Y	Y	Y	Y	55	27.1	33	31	0
Petropoulos et al., 1997 ^e			Y	Y	Y	Y	58	-	-	-	-
Lumley et al., 1996				Y	Y		103	16.0	32	27	16
Delgado et al., 1999				Y	Y	Y	50	21.0	34	36	18
Fowler et al., 1995			Y	Y	Y	Y	25	18.0	44	12	8
Gibson et al., 2000 ^e						Y	179	-	-	-	-
Huscher et al., 1996			Y	Y	Y	Y	146	16.0	49	14	6
Poulin et al., 1999			Y			Y	172	24.0	30	25	12
Barlehner et al., 1998			Y	Y	Y	Y	61	17.5	28	39	11
Trebuchet, et al., 1998	Y						218	35.0	39	28	15
Fingerhut et al., 1995 ^e				Y		Y	94	-	-	-	-
Wu et al., 1997			Y		Y	Y	14	17.0	50	14	0
Scott et al., 1995			Y			Y	19	12.0	37	47	0
Hoffman et al., 1996			Y	Y	Y	Y	39	30.0	59	23	15
Adachi et al., 1998					Y	Y	16	34.0	6	6	0
Rhodes et al., 1996			Y	Y	Y	Y	27	15.0	48	30	7
Khoury et al., 1999			Y		Y	Y	10	7.4	50	10	30
Molenaar et al., 1998			Y	Y	Y	Y	35	33.0	40	29	11
Buchmann et al., 1995 ^e			Y	Y	Y	Y	12	21.0	-	-	-
Melotti et al., 1999 ^e			Y		Y	Y	163	36.0	-	-	-
Boulez et al., 1997			Y	Y	Y		45	22.0	16	9	29
Guillou et al., 1993			Y	Y	Y	Y	57	-	37	44	11
Vukasin et al., 1996 ^e						Y	-	-	-	-	-
Bokey et al., 1997			Y	Y	Y	Y	66	29.0	39	29	12
Goh et al., 1997							20	8.0	25	55	5
Kakisko et al., 2000						Y	20	36.3	0	0	0
Lord et al., 1996			Y	Y		Y	55	16.7	53	18	15

^a S – patient survival; D – disease-free survival; C – cancer-related deaths; R – local recurrence; M – distant metastasis.

^b n - number of laparoscopic cases; includes converted cases where converted cases were reported separately.

^c Average (mean or median) post-operative months for which estimates of outcome frequency were reported; where these data are missing and only survival was reported, refer to Table X for the time at which survival estimates were calculated.

^d Proportion of all included laparoscopic patients with stage 2, stage 3 and stage 4 tumours.

^e Numbers of patients with tumours of different stages were not reported.

^f Numbers of patients with stage 1, 2 and 3 tumours were not reported separately.

Pooled estimates of outcome frequency were calculated, and possible sources of variation in outcome frequencies across studies were explored, using weighted regression (see 2.10). Possible sources of variation included distribution of patients by tumour stage, duration of follow-up, mid-point date of study, laparoscopic technique, average age, and quality factors. The analyses of possible sources of variation were hampered by the small number of studies (and consequently patients), i.e. patient or disease-free survival, or by the low frequency of the outcome, i.e. local recurrence, distant and port site metastasis. No significant effects were observed even for distribution of patients by tumour stage and duration of follow-up and therefore we simply report the pooled estimates across studies (see Table 15).

Table 15: pooled rates of long-term outcome from case-series

Outcome	n_s^a	FU^b	% stage 4 (range)	Failure / sample size	Pooled estimate	95% CI
Patient survival	9	49.8	0 to 24%	461 / 616	74.8%	64.9% to 82.9%
Disease-free survival	5	42.9	3 to 24%	176 / 210	86.1%	74.6% to 92.9%
Cancer-related death	35	25.3	0 to 34%	288 / 2812	10.2%	7.2% to 14.4%
Local recurrence	42	23.8	0 to 34%	74 / 2840	2.6%	1.9% to 3.7%
Distant metastasis	43	24.6	0 to 34%	214 / 2958	7.2%	5.5% to 9.4%
Port site metastasis	50	24.8	0 to 34%	43 / 3512	1.2%	0.8% to 1.8%

^a n_s – number of studies.

^b FU – weighted average follow-up in months across studies reporting the outcome.

3.4 Quality of the data

3.4.1 Short-term data

The quality of the 20 English language papers describing RCTs and PCSs with short-term data was again generally poorer than expected. Reporting of studies was fairly consistent however, with most scoring well for descriptive questions with detailed sections on their aims, methods and results. Papers did not score highly on the more specific outcomes, with only two papers distinguishing between primary and secondary outcomes and only two offering a power calculation for the primary outcome.

The number of ineligible patients and the number refusing to participate in these studies was only mentioned in two out of five RCTs and three of 15 PCSs. In PCSs, it was

impossible to determine whether the numbers presented were the number recruited at the beginning of the study or the number who participated. Generalisability therefore scored very badly with only 5 papers getting any marks for this section. Questions on bias scored much better with mean and median scores of 4.8 and 5 out of 7 respectively. All studies described the proportion of patients receiving allocated treatment, but none blinded the observers to the type of surgery allocated. Most papers presented evidence that the laparoscopic and open groups were sufficiently comparable or alternatively made adequate adjustment for potential confounders in their analyses. 50% of papers based their analyses on the type of surgery allocated, rather than that received, or presented data on conversions separately thus allowing analysis by 'intention to treat'. Mean and median scores for all studies were both 16 out of 30.5 with a range of 12-25.5.

3.4.2 Long-term data

In order to appraise the relative quality of each paper in its presentation of long-term data, seven questions were asked and scored 0 (no) or 1 (yes). (This particular instrument has been used previously by Vardulaki et al for the assessment of quality and bias in non-randomised studies). All long-term studies except one documented their aims and objectives clearly. Papers were scored positively for a full description of their study population, both inclusions and exclusions e.g. diagnosis, mean age. Again, this was provided in all but one study. As we have discussed elsewhere, the categorisation of data collection over time i.e. whether prospective or retrospective, was often inaccurate or ambiguous, requiring all the papers to be double-checked and reclassified, if necessary. Few papers calculated either confidence intervals, estimates of random variability of the data, or standard errors.

In the papers providing both short and long-term data, none scored more than five for the seven questions. The majority, 60%, scored only four. In the 39 long-term only studies, one third were rated with four points, with 30% scoring five and 20% achieving six points. 15% only merited three points. Few papers reported confidence intervals and few gave an explicit definition of the outcomes in which they were interested. Overall, therefore, the data was disappointing and limited our analyses, through inconsistent reporting that lacked statistical rigour.

3.5 Economic review

Eight studies were identified that contained some economic data, mainly on costs of treatment and hospital stays. Only one paper reported a study in the UK⁽³⁴⁾ and one reported work from Australia⁽³⁵⁾. The other papers were all based on work in the USA^(33;36-40). This section assesses the quality of the studies in terms of accepted quality criteria for economic evaluation studies^(27;28). Table 16 summarises the findings of this review of quality which are discussed more fully in the sections below.

Only in the Australian study was it possible to work out how the cost data had been collected and analysed. In five studies it was possible to work out how much of it was done, but in two cases there was almost no description of how the economic data had been collected. A particular concern was that in some cases it was not clear if the costs of laparoscopic procedures were calculated on the basis of actual treatment given or intention to treat. Three studies calculated unit costs from a single hospital using accounting data. Three studies used hospital charges or fees. In the remaining two hospitals the source of unit cost data was not stated. No study calculated unit costs from more than one hospital. No study specified the price level for the quoted unit costs.

Although many of the studies stressed the importance of benefits to patients of the use of laparoscopic procedures, all cost data related to hospital treatment and care, suggesting the viewpoint taken was that of funders. No costs to patients, families or society more widely were included. In four studies some data were presented on the differences in the physical volumes of resources. In others only estimates of costs were given. Unless physical volumes are given it is difficult to pool data on resource use. In six studies there was no attempt to assess benefits, although it was ascertained that patients benefited from quicker recovery following laparoscopic surgery. One study used the SF36 questionnaire to assess effect on patients, but summarised the results only in the text. One study used a specially developed outcome tool, but did not give any detail of any attempt to validate the instrument.

Three studies gave confidence intervals or standard errors for cost estimates. In three other cases data were shown that allow significance of differences to be assessed. Two studies presented no statistical analysis of costs (although in one of these some tests were performed on differences in services provided).

None of the studies here present economic data that would meet guideline standards for economic evaluation studies for JAMA^(29;31) or BMJ⁽³⁰⁾. Several present useful detail on costs of hospital care, but care must be taken generalising from these studies. No consistent pattern was 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 the relative cost of hospital days and hours in theatre used in the papers. Table 17 shows the cost differences.

Table 16: Assessing the quality of papers reporting cost-effectiveness

Author	Methods explained	Source of unit cost data	Viewpoint	Volume of resources shown	Benefit measured	Statistical tests carried out
Psaila	Partly	Not given, probably hospital accounts	Funders	Yes	SF36, not fully reported	Yes
Philipson	Yes	Single hospital	Funders	No	No	Yes
Senegore	No	Not specified	Funders	Some	Karnofsky	Yes
Pfeifer	No	Single hospital	Funders	No	No	Yes
Musser	No	Charges	Funders	Partly	No	Yes
Van Ye	No	Not specified	Funders	Partly	No	No
Tucker	No	Charges	Funders	No	No	No
Bouvet	No	Charges	Funders	No	No	Yes

Table 17: Differences in cost between laparoscopic and open surgery

Author	Average cost of surgery (SD if given)			
	Laparoscopic	Open	Converted	P- value
Psaila	£2900 (£1500)	£3300 (£1700)	Not shown	Not shown
Philipson	Aus. \$9064	Aus. \$7881	Not shown	<0.001
Senegore	\$12131 ± 612 ^a	\$14449 ± 696 ^a	\$17583 ± 1731 ^a	Not shown
Pfeifer ^b	\$26926 ± 3990 ^a	\$26903 ± 5370 ^a	\$19702 ± 1591 ^a	>0.005
Musser	\$9800	\$11411	Not shown	0.3
Van Ye ^c	\$18300	\$18200	Not shown	Not shown
Tucker	\$9200	\$14000	\$16000	Not shown
Bouvet	\$12000	\$11000	\$15000	0.3 (for open vs. closed)

^a SE of mean

^b This paper also quotes results from five other studies

^c In both groups the cost was raised by one patient who had a second operation

Since only one published study has attempted to calculate costs of open versus laparoscopic surgery in the NHS, a simple model has been developed using HRG based Reference Cost data. Data were taken from a sample of 139 hospitals that perform more than 20 complex surgical procedures per year on the lower gastrointestinal tract for cancer. This represents 71 % of all such surgery in England and Wales. Since data are available only at aggregated levels, costs of pathology and non-theatre drugs and disposables have been taken from Psaila et al ⁽³⁴⁾, to allow costs of the surgical procedure to be identified (Table 18).

A number of assumptions are necessary. First, it is assumed that pathology costs are independent of length of stay. Second, it is assumed that extra days in hospital can be costed at the average cost since discharge thresholds are the same for each group. This may produce a small bias in favour of open procedures as the mean dependency of laparoscopic patients may be lower than that of those having open procedures. In the hospitals in the sample the average length of stay was 13.09 days (range 7.85-17.96), which is longer than the current average length of stay for CRC patients (~8 days). If the HRG data used here represent on average more dependent patients (the likeliest reason for the difference in the average length of stay), the cost of a bed day may be slightly

overestimated. For open procedures the theatre consumables were taken to cost £100 for open surgery and £300 for laparoscopic procedures ⁽³⁵⁾.

Table 18: Mean unit costs used for the simulations.

Mean unit cost	£ (at 1999 prices)
Operating theatre (including staff)	447.50 per hour
Pathology pharmacy and other consumables	400 per admission
Bed days	153 per day
Theatre consumables (laparoscopic)	300 per case
Theatre consumables (open)	100 per case

The average cost per case for an open procedure using these data comes to a total of £3284, which can be compared to the estimate of £3 300 per case in Psaila et al ⁽³⁴⁾. However, it should be noted that using the Reference Cost data puts a heavier weight on treatment costs and a lower weight on ward costs. This is because a more restrictive definition is used of ward costs, and a larger share of costs is attributed to treatment.

3.6 Economic modelling: the additional cost of laparoscopic surgery

The mean effect on cost from the estimates of increased theatre time and length of stay from the trials data, is an additional cost for laparoscopic surgery of £227. It should be remembered that this uses the reference cost estimates of ‘costs per bed day’ and treatment costs, and these place a higher relative cost on theatre time than do some other estimates, so if anything, the estimates are conservative (ie open procedures appear relatively cheaper).

95% confidence intervals are available for the estimates of length of stay, theatre time and for the estimates of unit costs of theatre and wards. However, it is not feasible with these data to combine them to obtain confidence intervals for the difference in costs in modelling the consequences of a change to laparoscopic surgery. Instead, the confidence intervals for differences in length of stay and theatre time estimates have been used to carry out three sensitivity tests. Since the confidence intervals around unit cost estimates are narrow, no tests were done on sensitivity to this variation. Finally, the effects on cost

of all these at the values that make laparoscopic procedures more expensive is shown with those that show the lowest estimate.

Table 19: sensitivity analyses of the net cost of changing from open to laparoscopic surgery

	Mean	High	Low
Theatre time	226.9208	458.195	18.10583
Length of stay	226.9208	497.3938	-62.3922
Highest and Lowest^a	226.9208	678.275	-220.814

^a Worst and best scenarios, ie upper limit for difference in theatre time and lower limit for difference in LOS vs. lower limit for difference in theatre time and upper limit for difference in LOS

Although the mean values show a slightly higher overall cost of laparoscopic work this result must be treated with caution. It is clearly sensitive to the size of the effect on length of stay, and shortening theatre times in laparoscopic work might offset the effects of higher treatment costs.

Notes on methods used

Costs of theatre consumables are estimated from a single study, and no confidence intervals can be given. It is assumed that the variations in these costs are the same as for other operating theatre costs. Similarly it is assumed that variation in costs of pathology and ward consumables vary in the same way as ward costs.

Length of stay in the reference cost data at 13.09 days may be longer than the average for procedures where laparoscopic surgery is common. Since the longer stay indicates a slightly higher average dependency this will bias any results against laparoscopic surgery.

4 Discussion

4.1 Summary of evidence

With respect to short-term outcomes, laparoscopic colorectal surgery is associated with a reduction in the length of stay and other markers of post-operative recovery, and an increase in operating time. The increase in operating time is unlikely to arise from bias, but the findings of a reduction in length of stay and faster recovery are more difficult to interpret. None of the studies included in this review blinded medical and other health care staff to the type of intervention patients received, so bias may have been introduced, as illustrated by RCTs of laparoscopic cholecystectomy^(41;42). The consistency between short-term measures of recovery may also be misleading since these outcomes are likely to be strongly correlated.

Any colorectal procedure, whether open or laparoscopic, is followed by a period of time when the bowel does not function, called the ileus; the return of bowel sounds or of bowel opening indicates the end of the ileus. The more rapid return of bowel function observed after laparoscopic surgery is consistent with less surgical trauma and less operative manipulation. Less postoperative pain, and consequently a reduction in the use of analgesia, would also be expected to be associated with a more rapid return of bowel function. These factors combined are likely to result in earlier mobilisation and consequently a reduction in length of stay. However, these collective differences could also arise from changes in the pattern of care prompted by expectation of benefits from laparoscopic surgery. For example, patients known to have had open surgery tend to be prescribed more analgesia and re-start their diet later than laparoscopic patients; whether this is due to patients' requirements for more analgesia and an inability to eat or the perception by health care staff of the need for more conservative management is unknown. Observation that early feeding after laparoscopic colectomy is safe and well tolerated has recently led people to challenge the more conservative approach traditionally applied to open colectomy patients, highlighting the susceptibility of these outcomes to bias. The clinical consequences of patients re-starting their diet earlier is unclear, however, since there is evidence that patients who have had open surgery can tolerate diet earlier without a shortening in the duration of their ileus^(43;44).

Our results suggest that on average 13% of laparoscopic procedures are converted, although this overall figure is biased upwards by a higher conversion rate for mixed groups of patients (benign and malignant cases) than for those with only malignant cases. The conversion rate in patients with CRC is likely to be less than 10%. A higher conversion rate for the mixed groups is not unexpected because inflammatory conditions such as diverticular disease, although benign, are frequently more technically challenging to the surgeon⁽⁴⁵⁾. Conversions will increase the average cost difference between laparoscopic and open surgery since the consumable costs of laparoscopic surgery and some increase in operating time will be incurred without the reduction in length of stay.

The evidence on major post-operative complications is unclear, with the data from trials suggesting an increase in the risk of major complications and the data from PCSs suggesting a decrease in the risk of major complications. An increase in major complications, e.g. anastomotic leaks, enterotomies, visceral injuries, with laparoscopic surgery might be expected during the learning curve. However, skilled laparoscopic surgeons might also expect a decrease in major complications, e.g. deep wound infections and chest infections. Both types of study design indicate a lower risk of minor complications, e.g. urinary tract infections and retention, atelectasis and other *sequelae* of major surgery. This finding is intuitive given the less invasive nature of the surgery and the reduced length of stay.

With respect to short-term costs, our best estimate is that the net cost of laparoscopic surgery compared to open surgery is £227 per admission. This net cost mainly reflects the extra cost of theatre consumables, since the increase in theatre time is approximately balanced by a reduction in the length of stay compared to open patients. There are no specific cost-benefit analyses in the literature and only very rudimentary cost-effectiveness analyses have been published. Specifically, health-related quality of life benefits of laparoscopic surgery to patients have been assumed by researchers but have not been measured or reported. The net increase in the cost of laparoscopic surgery is small relative to the imprecision of the estimate and it is sensitive to changes in operating time and length of stay, as demonstrated by the economic model. Modelling theatre time as an average cost also does not take into account that this is a finite resource in the short-term future. From experience in the field of cardiac bypass surgery⁽⁴⁶⁾ one would expect the additional cost of laparoscopic surgery to disappear within the next 5 years as the

result of increasing expertise and micro developments of technology, leading to shorter operating times, fewer conversions and complications and a further reduction in average length of stay.

Short-term benefits of laparoscopic compared to open colorectal surgery are of no consequence if the laparoscopic technique confers a disadvantage in survival. In the management of malignant disease it is the effect of a new intervention on the long-term prognosis that determines its success or failure. Unfortunately, the data for disease recurrence and survival is limited.

The average length of follow-up in the literature reviewed was found to be short at around 26 months. Within this limited follow-up period, there was no significant difference for cancer-related deaths, local recurrence or the distant metastasis rate between the two groups. Laparoscopic surgery appeared to improve disease-free survival time, but this did not reach statistical significance; the relatively few studies reporting this outcome may also have been chosen to report the outcome because the results favoured laparoscopic surgery (see 4.2.5). There is evidence that laparoscopic surgery has immunological benefits when compared to open surgery for cholecystectomy⁽⁴⁷⁾ but whether this has any relevance to tumour behaviour in laparoscopic colectomy is unknown⁽⁴⁸⁾.

Recurrences, and associated shorter survival times, may occur if the specimen resected during laparoscopic colectomy is not as complete as in laparotomy. Standard oncological surgical technique involves an en-bloc resection, 'no-touch' technique, primary ligation of vessels and a systematic lymphadenopathy. There is considerable debate as to whether these criteria are properly met during laparoscopic surgery. Ideally the proximal and distal margins (and lateral in rectal cancer surgery) should not be compromised, nor should the extent of lymph node resection. If the specimen is compromised with respect to the excision margin then recurrence is likely to occur more often.

Data on lymph node retrieval was extracted from papers as a proxy measure of adequacy of resection. Extent of lymphadenectomy is vital for the correct staging of the tumour and to enable adjuvant therapy options to be considered. The number of lymph nodes involved in the disease, combined with the degree of mural penetration, remain the best predictive factors for survival. Data were commonly, but often inadequately, collected in

studies. Only one of three RCTs provided data on the number harvested and none reported standard deviations. Based on the available data, there was no significant difference in the number of lymph nodes excised between the two procedures.

Using the number of lymph nodes excised as a proxy measure of adequacy of resection is not without criticism, as the method of histo-pathological processing affects lymph node yield as well as the extent of surgical resection⁽³⁴⁾. Nevertheless, assuming that the method of processing was similar for both groups within studies, the finding of no difference in the number of lymph nodes excised provides some evidence that laparoscopic surgery is as effective as open surgery in resecting the tumour. The adequacy of resection with laparoscopic surgery is also supported by a number of studies which have demonstrated equivalent oncological specimens with laparoscopic and open techniques. Indeed, pathologists blinded to the nature of the operation are often unable to differentiate between the laparoscopic and open specimens^(49;50).

The risk of port site metastases (PSMs) and the likely adverse effect of PSM on the overall survival remains the primary concern with laparoscopic colorectal surgery⁽⁵¹⁾. Port site metastases are tumour recurrences at sites used for instrument access during a laparoscopic procedure, and were noted early in the development of laparoscopic surgery for CRC⁽⁵¹⁻⁵³⁾.

The aetiology of these unusual wound recurrences remains unknown despite considerable research. They demonstrate aggressive behaviour and most are apparent within 1 year of the procedure. They can occur in both curative and palliative operations⁽⁵¹⁾.

The pooled estimate of the incidence of port site metastases from case series is 1.2% (95% CI 0.8% to 1.8%). Estimates of PSM incidence from other sources vary considerably, from 0 – 21⁽⁵⁴⁻⁵⁷⁾ because the denominator for the total number of laparoscopic procedures performed for CRC is hard to ascertain. However, our estimate is consistent with the wound recurrence rate at 1 year follow-up for 480 patients of 1.1% reported recently by the American Society of Colon and Rectal Surgeons Laparoscopic Registry⁽⁵⁸⁾. No comparative studies reported wound metastasis rates for both procedure types, but it is interesting to note that this type of recurrence is not unique to minimally invasive procedures^(59;60). PSM rates of about 1% are comparable to the reported

incidence of wound site metastases after open surgery⁽⁶⁰⁾. It is also suspected that the wound site metastases after open surgery are under-reported, since this has only become an issue with the advent of laparoscopic surgery.

The relatively short duration of follow-up in the studies reviewed is unlikely to have caused the review to underestimate the incidence, since port site metastases are usually apparent within a year (see above). The fact that authors of case series are more likely to be experienced laparoscopic surgeons means that the estimate may be unrepresentative. Nevertheless, it indicates that port site metastases are unlikely to be a significant problem for experienced surgeons.

4.2 Limitations of study

4.2.1 Literature searching

Several limitations relating to the database indexing of relevant papers were taken into account in the development of search strategies. Inconsistent use of thesaurus terms (possibly due to the relatively recent introduction of laparoscopic procedures) meant that some articles were incorrectly indexed, for example, under the MeSH term 'Endoscopy' rather than 'Laparoscopy'. This was overcome by incorporating various truncated freetext terms into the strategy (e.g. laparoscop\$, minimal\$, inasiv\$). Searches frequently retrieved irrelevant references to the diagnostic use of laparoscopes so the strategy was refined by including MeSH terms and freetext terms relating specifically to surgery. Lastly, depending on the subject under review, papers could legitimately be indexed under many different terms relating to 'laparoscopy', 'surgery', 'colorectal' and 'cancer' etc. In order to achieve a comprehensive retrieval of relevant references, it was necessary, therefore, to use as wide a combination of these concepts as possible.

Citation searches of the included studies using the Science Citation Index identified 151 citations. Only one was potentially relevant to the objectives of this review, but was excluded as it did not fulfil our inclusion criteria (a retrospective cohort study with no long-term data presented).

4.2.2 Data extraction

Our description and analyses are constrained by inadequate and inconsistently reported data in the 69 papers included in this review. For example, some papers failed to report the duration of the study whilst others did not fully outline the stage of disease. If one mean age was calculated for the whole study population only, we accepted this figure to be true for each surgical category. Both means and medians were presented in papers, as were age ranges. In our databases, means and medians have been used interchangeably.

Numerical and computational mistakes within the paper and inconsistencies between the main text and the abstract occurred and in such cases information was extracted from the text, not the abstract.

The reporting of study design by authors was sometimes ambiguous, if not incorrect, and methods of data collection were not always clearly defined. Studies purported to be, for example, case-control, merely because both laparoscopic ‘cases’ and open ‘controls’ were included. When study types were wrongly described, we defined them independently.

The distinction between retrospective and prospective data collection caused particular problems. Some researchers appear to have recorded data prospectively for laparoscopic cases and then retrospectively reviewed a ‘matched’ sample of open cases carried out during the same period. In such studies, open and laparoscopic cases are concurrent in time but the nature of data collection (i.e. retrospective or prospective) is completely confounded with the surgical interventions. A decision was made to call these studies ‘retrospective’. Similarly, any study claiming to be a retrospective review of a prospectively collected database was termed ‘retrospective’, because we considered it unlikely that the databases were designed for the purpose of evaluating the effectiveness of laparoscopic compared to open surgery.

4.2.3 Repeat publication of data

We excluded publications where data were clearly presented more than once. Some centres published reports of specific laparoscopic operation types, e.g. patients undergoing laparoscopic right hemicolectomy and subsequently published papers describing their entire series of patients undergoing surgery. Seven papers were therefore excluded from analyses, five of which described long-term data. Those with overlapping

time periods were included, otherwise large periods of data collection would often have been lost. Unless we were certain that the same data were repeated in more than one paper, the studies remained in the dataset.

The problem of duplicate publications is familiar to reviewers carrying out meta-analyses of randomised control trials and the Cochrane Collaboration has strongly criticised this practice. If anything, we believe that the problem is more acute when reviewing case series since it was our experience that authors rarely acknowledged that data had been published before or referenced previous publications. If data collection start dates and duration are not reported, or two papers report for overlapping periods, it is impossible to exclude duplicate data.

4.2.4 Limitations of the data analyses

Limitations of the analyses arise for two main reasons, (a) the availability and quality of data reported by studies and (b) the assumptions we made to overcome the limitations of the data that were reported.

There were several limitations imposed by the availability and quality of data. Studies rarely reported outcomes by tumour stage, although the numbers of patients in the study with different tumour stages were usually described. This lack of data was particularly important when considering long-term outcomes. In attempting to adjust for case-mix differences between studies in analyses of outcome frequencies, we had to resort to simple methods, i.e. entering the proportion of patients with each tumour stage as covariates. In studies that reported short-term outcomes, a similar problem was observed in the reporting of the results for patients with malignant and benign pathologies; although the numbers of patients in each group were often described, studies rarely reported outcomes separately.

For some outcomes, e.g. complications, recurrences and metastases, authors tended to report the total number of 'events', rather than the number of participants experiencing an event. We inferred that few patients had multiple outcomes but could not quantify how frequently this occurred. This limitation will have led us to overestimate the frequency of these outcomes from case series of laparoscopic patients, and may have biased

comparisons between laparoscopic and open groups if the risk of multiple outcomes differed between groups.

Continuous data were inconsistently reported across studies or not reported, which required us to make assumptions for the meta-analyses. Omissions, especially, highlight the need for authors to report raw data in sufficient detail to allow readers to check the main findings, as recommended for the reporting of randomised controlled trials ⁽⁶¹⁾.

Five studies reported that there were no conversions of laparoscopic cases. Of the 16 studies in which conversions were known to have occurred, only seven reported intention-to-treat analyses. Three studies reported data for conversions separately, but this leaves six studies in which the treatment of conversion cases was not specified.

Several assumptions were made when carrying out the analyses. We assumed that the sampling variances of the means of continuous outcomes were normally distributed, despite evidence that the distributions of raw data were positively skewed. This assumption is justified for large sample sizes by the central limit theorem. Medians were assumed to be equal to means, for the purposes of analyses. Given the skewed nature of the distributions of most outcomes, this assumption is manifestly untrue. However, the difference between two medians is approximately the same as the difference between two means, which is the important point with respect to the analyses. Either medians or means were reported for both groups within a study, so this assumption should not introduce bias, except in so much as the difference between two medians may slightly underestimate the difference between two means for positively skewed distributions.

Medians were also considered to be equivalent to means with respect to the duration of follow-up and, where only a range of follow-up duration was reported, the mean was assumed to be the mid-point of the range, i.e. recruitment was assumed to be constant across study period. Again, since individual studies reported the same types of data consistently for both groups, no bias should have been introduced for comparative analyses. Survival data were also treated in a simplistic manner but similarly for both groups for comparative analyses; survival estimates for both groups within a study were always reported for the same time. Expressing survival as a simple risk of failure will

tend to overestimate precision, since the time at which survival estimates were reported tended to be longer than the mean duration of follow-up.

The assessment of quality for RCTs and PCSs included important questions on RCT quality⁽²⁵⁾, but these proved irrelevant in the context of this review since there were so few RCTs. Nevertheless, there was a reasonable spread of quality scores. There were insufficient studies to explore the effect of each quality dimension separately and the score was dichotomised when investigating heterogeneity in meta-analyses. The cut-off point for classifying studies as ‘better’ and ‘poorer’ quality was merely designed to maximise power, i.e. to give an equal number of studies in each sub-group, not on the basis of any validation of a ‘step’ change in quality. However, the validity of the score is supported by the observation, during exploration of heterogeneity, that pooled estimates for better quality studies tended to be closer to the null effect than pooled estimates for poorer quality studies. The quality criteria for case series have face validity but have not validated empirically; the amount of data and frequency of outcomes precluded any meaningful analysis of the impact of the quality of case series on outcome frequencies.

Given these limitations, one should perhaps reflect on the decision to carry out meta-analyses in the first place. The usual concern of meta-analysts (albeit in the context of RCTs) is that studies may not be comparing like-with-like. We were satisfied that studies included the same kinds of patients and evaluated similar interventions and outcomes. Therefore, in so far as heterogeneity exists between studies, it is likely to arise from differences in study design, quality of execution and quality of reporting, the effects of which we explored. Meta-analysis of non-randomised studies has been discouraged, because of the danger of a pooled estimate simply representing a more precise estimate of the biases inherent in observational studies. We tried to guard against this possibility by comparing pooled estimates from RCTs and PCSs wherever possible. With one or two exceptions, the results of the meta-analyses were broadly consistent across RCTs and PCSs and for different assumptions. We therefore believe that our attempts to quantify the relative effects of laparoscopic surgery compared to open surgery, and the frequencies of certain long-term outcomes following laparoscopic surgery, are valuable in reviewing the costs and benefits of this technology to CRC patients.

The extent of economic evaluation that could be carried out was severely limited by the paucity of both the economic and effectiveness data, especially high quality data on important long-term outcomes and short-term health related quality of life.

Three additional issues not explicitly covered by this review merit consideration. Other *sequelae* of laparotomy are the associated long-term complications, eg. adhesions and incisional hernias. It has been suggested that minimally invasive surgery is associated with a reduced risk of adhesions, which are estimated to occur in approximately 10% of patients at any time after a laparotomy. They cause serious morbidity to patients and high costs to the NHS in treating them, with patients typically being admitted for 4-5 days even for conservative medical management for adhesions.

Currently the introduction of a national screening programme for CRC is being considered. If established, a screening programme would be expected to detect predominantly pre-malignant pathologies and early malignant tumours (Dukes' Stage A). Laparoscopic surgery is widely considered to be more appropriate for the overtly 'well' patients, rather than those with more advanced tumours⁽²¹⁾. Ensuring the availability of acceptable methods of treatment, and the facilities to deliver them, to those who are detected, is one of the conditions for establishing a national screening programme.

Patients with non-curable, stage Dukes' D tumours represent an exception to the consensus view described above. Since the aim of the operation is palliative for these patients, laparoscopic surgery is seen to be more appropriate than open surgery because it minimises post-operative morbidity and increases quality of life when only a few months of life remain. These patients already have disseminated disease so concerns about possible seeding of metastases following laparoscopic surgery do not apply.

4.2.5 Publication Bias

Publication bias could have affected this review in several ways. First, we may have failed to identify important literature. Second, there may have been biases in the literature that has been published. Third, given the number of outcomes that authors could have reported, they may have been influenced in their choice of those to report by the findings they observed.

We believe that we successfully identified all of the relevant literature. This view is supported by the SCI search of all included papers, which did not identify any eligible papers that had been missed. However, within the time frame for the review, we were unable to include certain non-English language papers. The exclusion of these papers is unlikely to have influenced our findings.

Statistical methods have been developed to attempt to quantify the effect of publication bias in meta-analysis of randomised controlled ⁽⁶²⁾. Funnel plots, plotting effect size against sample size, will be asymmetrical if publication bias is present. However, in order to attribute asymmetry of the funnel plot to publication bias, the method assumes that included studies are essentially bias free. This assumption is justifiable for RCTs but may not be so for non-randomised study designs, which constituted the majority of the studies in this review. Hence, we have not applied this method to our data. Moreover, the concept of unpublished data has a different meaning in the context of case series. Data for unpublished comparative study designs are likely to exist in some form whereas data are unlikely to be available in a useable format from centres that have not published case series.

Published case series may be subject to bias, although not in the conventional sense. The concept of unpublished data is difficult to apply to case series since these would, in principle, include data for all patients who have ever undergone laparoscopic CRC surgery. However, the institutions that publish large case series are atypical and more likely to be 'centres of excellence'. There may also be a tendency for centres to select cases in a way that minimises complication and conversion rates, e.g. by including non-consecutive patients or by carefully choosing the reporting period to exclude unfavourable results. 'Publication bias could be serious with respect to the findings of this review in the context of trends over time; for example, once an implicit 'standard' has been set through previous publications, centres may choose to publish only those case series which give better, or similar, results.

Finally, the number and choice of outcomes reported varied considerably between papers. We also noted possible inconsistencies between pooled estimates of, for example, overall patient survival and disease recurrence. It seems plausible to us that studies may have

selected the outcomes they reported depending on the findings observed, possibly favouring results that showed benefits of laparoscopic surgery.

4.3 Continuing work on the role of laparoscopic surgery in colorectal cancer

More definitive answers regarding the safety of laparoscopic surgery in CRC will be more apparent when two large randomized clinical trials have been completed. The MRC funded CLASICC Trial (Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer) ⁽⁴⁾, a multi-centre study in the UK, and the American National Institute of Health Trial ⁽⁶³⁾ are randomizing more than 1000 patients each. Unfortunately they are still recruiting and their keenly awaited results are unlikely to be reported until 2004. In addition, there are several other small RCTs in progress.

5 Conclusions

The key focus of this review, given that its scope was limited to laparoscopic surgery for colorectal *cancer*, must be long-term outcomes. In this context, the main concern is that laparoscopic surgery could result in poorer long-term outcomes by disseminating metastases at the time of surgery, especially at the port sites. However, there are also theoretical reasons for postulating that laparoscopic surgery may lead to better long-term outcomes, since minimally invasive surgery results in a reduced level of immunosuppression from the operation relative to open surgery, which may in turn help to prevent metastatic recurrence arising from excision of the tumour.

Evidence was compared between laparoscopic groups for five long-term outcomes, without any clear results emerging. No consistent and significant differences were found but there were few comparative studies, the confidence intervals around the estimates were wide, and the study designs and reporting of data were generally of poor quality. The pooled estimate of the incidence of PSM was low and very similar to that reported for metastases at wound sites following open surgery. We cannot *exclude* the possibility of an elevation in the incidence of wound site metastases with laparoscopic surgery but can state that any such elevation must be small. Any study designed to detect this difference in rate would have to be very large; for example, 3000 participants in both laparoscopic and open groups would be required to have 90% power to detect a doubling in the wound site metastasis rate from 1% to 2%. There was also no evidence of inadequacy of resection of the tumour using laparoscopic methods, as judged by the number of lymph nodes harvested. We conclude that the existing evidence suggests open and laparoscopic techniques have broadly equivalent long-term outcomes, although the existing evidence cannot exclude the possibility that laparoscopic surgery for colorectal surgery has clinically important benefits *or* harms compared to open surgery. High quality evidence on survival, probably the most relevant test of long-term outcome, will become available on completion of the CLASSIC and NIH trials but these studies are not likely to report before 2004.

The evidence on short-term outcomes is more straightforward. Studies have consistently shown that laparoscopic surgery reduces the use of analgesia, length of stay and the time to other markers of recovery but increases the duration of the operation. The reductions

in length of stay and other markers of recovery are likely to be strongly correlated and they may arise from changes in patterns of care either *in response to* the improved clinical status of patients or *as the result of* expectation of benefits from less invasive surgery. The health-related quality of life effects of laparoscopic surgery for patients have not been quantified.

At the current stage of development of the technology, laparoscopic surgery has a net increased cost compared to open surgery in the short-term of about £200 per operation. This difference would be completely swamped by any difference in long-term outcomes. By analogy with other health technology innovations, the difference would be expected to disappear over the next five years if uptake and development of the technology continues.

Finally, there are two other issues that have not been considered in the review but which are potentially relevant. The first is that laparoscopic surgery may reduce long-term complications, e.g. adhesions and incisional hernias, which are associated with laparotomy. This issue was not addressed by any of the papers that were reviewed and we do not believe that it is being considered in the two large current RCTs. The second is the use of laparoscopic surgery for the removal of pre-malignant and early cancers should a national screening policy be implemented. This consideration might justify maintaining a critical mass of surgeons with the expertise to carry out laparoscopic surgery for colorectal pathologies.

In summary:

- There is no evidence of long-term harms or benefits from laparoscopic compared to open surgery. There is a need for higher quality evidence about long-term outcomes with adequate precision to detect clinically important differences. Two large, high quality trials are in place, which will report in 4-5 years. There is no action that can be taken at present to provide high quality evidence about long-term outcomes sooner.
- There is a need for quantification of the health related quality of life gains for patients during the peri-operative and recuperation periods. This information could be gathered relatively easily in the context of a new study, if not already being collected alongside the CLASSIC or NIH trials. However, care would need to be taken in the design of such a study to avoid bias arising from patients' preconceptions about the advantages of minimally invasive surgery.
- Laparoscopic surgery for colorectal cancer currently costs more than open surgery, although the difference is relatively small in relation to the imprecision of the estimate and would be expected to disappear as expertise and uptake of the technology increases. The opportunity to exploit the technology promptly in the future probably depends on maintaining a critical mass of expertise during its development.
- Colorectal surgeons in the UK carrying out laparoscopic surgery for colorectal cancer should recruit patients to the CLASSIC trial wherever possible. When this is not possible, they should contribute data for laparoscopic patients to the national registry⁽²¹⁾.
- Given the concerns about PSMs during the early development of laparoscopic surgery for colorectal cancer, and the experience of an increase in serious complications during the rapid uptake of laparoscopic cholecystectomy, it may be advisable to institute a formal accreditation process in non-commercial centres for laparoscopic surgery for colorectal cancer and to carry out this type of surgery only in specialist centres.

6 Contributions from the authors

All members of the review team have read, edited and commented on a number of drafts of this review and are all in agreement with the conclusions drawn and the recommendations made herein. Specifically, Suzy Paisley carried out all literature searches, while papers were chosen for the review, read and data extracted by Katerina Vardulaki, Bethan Bennett-Lloyd and Jeremy Parfitt. Katerina Vardulaki and Bethan Bennett-Lloyd also constructed the databases.

Clinical advice and an insight into the broader issues of laparoscopic surgery was provided by Jeremy Parfitt and Ara Darzi, both of whom advised throughout the course of the review and drafted all clinical sections. Barney Reeves was the lead investigator and as well as guiding on the results, discussion and conclusions, undertook all the statistical analyses of the data and drafted all sections pertaining to the results. Charles Normand carried out the cost-effectiveness analysis and drafted the economic sections of the review. The rest of the review was written and edited by Katerina Vardulaki and Bethan Bennett-Lloyd.

7 Conflicts of interest

There were no conflicts of interest. However, Prof. Ara Darzi has been approached by the Association of Endoscopic Surgeons of Great Britain and Ireland to contribute to their submissions to NICE, and is also acting as a clinical expert on the NICE appraisals committee.

8 Appendices

Appendix A: The Staging of Colorectal Cancer

Stage	Description	Duke's
Stage 0	Carcinoma in situ (Tis,N0,M0)	
Stage 1	Tumour invades submucosa (T1,N0,M0) Tumour invades muscularis propria (T2,N0,M0)	Duke's A
Stage II	Tumour invades into subserosa or into pericolic Or perirectal tissues (T3,N0,M0) Tumour perforates visceral peritoneum or directly Invades other organs/structures (T4,N0,M0)	Duke's B
Stage III	Any degree of bowel wall perforation with regional lymph node metastases N1 - 1-3 pericolic/perirectal nodes involved N2 - 4 or > nodes involved N3 – lymph nodes along named vessel involved (Any T,N1-3,M0)	Duke's C
Stage IV	Distant metastases present with any degree of Bowel wall invasion, with or without lymph Node involvement	Duke's D

*table reproduced from Poulin et al ⁽⁶⁴⁾

Appendix B : Search strategies for Medline (using OVID BIOMED) Clinical effectiveness review. 1966- 2000

1 Laparoscopes/
2 Laparoscopy/
3 laparoscop\$.tw.
4 videolaparoscop\$.tw.
5 celioscop\$.tw.
6 key hole.tw.
7 keyhole.tw.
8 minim\$ invasive.tw.
9 or/1-8
10 su.fs.
11 Surgical procedures, operative/
12 Reoperation/
13 Surgery/
14 Surgical equipment/
15 Surgical instruments/
16 operation\$.tw.
17 resect\$.tw.
18 surgery.tw.
19 surgical.tw.
20 surgeon\$.tw.
21 or/10-20
22 exp Colorectal neoplasms/
23 (carcinoma adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
24 (neoplasia\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
25 (neoplasm\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
26 (adenocarcinoma\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
27 (cancer\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
28 or/22-27
29 exp Colonoscopes/
30 exp Colonoscopy/
31 29 or 30
32 Video-assisted surgery/
33 Surgical procedures, minimally invasive/
34 or/32-33
35 Colorectal surgery/
36 exp Colectomy/
37 colotomy.tw.
38 hemicolect\$.tw.
39 colectom\$.tw.
40 or/35-39
41 Neoplasms/
42 Carcinoma/
43 Adenocarcinoma/
44 or/41-43
45 Colonic diseases/
46 Rectal diseases/
47 exp Colon/
48 exp Rectum/
49 or/45-48
50 44 and 49
51 9 and 21 and 28
52 9 and 21 and 50
53 34 and 28
54 34 and 50
55 34 and 40 and 44
56 40 and 9 and 44
57 40 and 9 and 28
58 or/51-57

Appendix C: Medline search strategy (using OVID BIOMED). Cost effectiveness review. 1966-2000

1 Laparoscopes/
2 Laparoscopy/
3 laparoscop\$.tw.
4 videolaparoscop\$.tw.
5 celioscop\$.tw.
6 key hole.tw.
7 keyhole.tw.
8 minim\$ invasive.tw.
9 or/1-8
10 su.fs.
11 Surgical procedures, operative/
12 Reoperation/
13 Surgery/
14 Surgical equipment/
15 Surgical instruments/
16 operation\$.tw.
17 resect\$.tw.
18 surgery.tw.
19 surgical.tw.
20 surgeon\$.tw.
21 or/10-20
22 exp Colorectal neoplasms/
23 (carcinoma adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
24 (neoplasia\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
25 (neoplasm\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
26 (adenocarcinoma\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
27 (cancer\$ adj3 (colorectal or colon\$ or rect\$ or intestin\$ or bowel)).tw.
28 or/22-27
29 exp Colonoscopes/
30 exp Colonoscopy/
31 29 or 30
32 Video-assisted surgery/
33 Surgical procedures, minimally invasive/
34 or/32-33
35 Colorectal surgery/
36 exp Colectomy/
37 colotomy.tw.
38 hemicolect\$.tw.
39 colectom\$.tw.
40 or/35-39
41 Neoplasms/
42 Carcinoma/
43 Adenocarcinoma/
44 or/41-43
45 Colonic diseases/
46 Rectal diseases/
47 exp Colon/
48 exp Rectum/
49 or/45-48
50 44 and 49
51 9 and 21 and 28
52 9 and 21 and 50
53 34 and 28
54 34 and 50
55 34 and 40 and 44
56 40 and 9 and 44
57 40 and 9 and 28

58 or/51-57
59 Economics/
60 exp "Costs and cost analysis"/
61 Economic value of life/
62 exp Economics, hospital/
63 exp Economics, medical/
64 Economics, nursing/
65 exp models, economic/
66 Economics, pharmaceutical/
67 exp "Fees and charges"/
68 exp Budgets/
69 ec.fs.
70 (cost or costs or costed or costly or costing\$.)tw.
71 (economic\$ or pharmaco-economic\$ or price\$ or pricing).tw.
72 Quality-adjusted life years/
73 or/59-72
74 58 and 73

Appendix D: Proforma for collection of data

prospective cohort with concurrent/ historical controls

retrospective cohort

case-series

case-control study

randomised controlled trial

Study id:

Publication date:

First author:

Language of publication:

Country:

Centre:

Number of centres:

Study year:

Study duration:

Number randomised:

Lap.group:

Open group:

Number with malignant disease:

Lap.group:

Open group:

Number of conversions:

Reasons for conversions:

Mean age: Lap. group:

Open group:

Converted group:

Staging: Dukes/UICC/TMN:

Lap. group:

Open group:

Converted group:

Outcome	Units	Lap. cases Mean/med.	range	Open cases Mean/med.	range	Conversions Mean/med.	range
Length of stay							
Operating time							
Analgesia use							
Drug type							
Days post op							
Op. blood loss							
Time to mobilisation							
Time to oral/normal intake							
Time to opening of bowels							
Excision margin							
Complications: • Major • Minor							

	Laparoscopic cases	Open cases	Conversions
Mean follow-up			
Patient survival: years K-M : Hazard ratio/RR			
Recurrence: Local (pelvic, anastomotic) Distant (wound, liver etc) PSM			

Appendix E: Classification of post-operative complications

Major complications:

- bleeding
- anastomotic leak
- enterotomy
- visceral damage/ereteric damage
- ileus/small bowel obstruction
- myocardial infarction
- deep venous thrombosis/ pulmonary embolism
- chest infection/pulmonary problems
- peritonitis
- stoma stenosis
- stricture
- fistula
- port site hernia
- deep wound infection

Minor complications:

- urinary tract infection
- urinary retention
- wound infection
- renal failure
- rectal bleeding
- hypoxia
- atelectasis

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Appendix G: Quality assessment of papers describing short-term outcomes

Study ID:

- | REPORTING OF THE STUDY | | (score) |
|-------------------------------|---|----------------|
| 1 | Is the hypothesis/aim/objective of the study clearly described? | |
| | <p>This question refers to a clear statement of the objective, i.e. to measure the effectiveness of x in population y with respect to z, even if x, y and z are not clearly described (see Qs 2, 3 and 4).</p> | |
| | a) Yes | (1) |
| | b) No | (0) |
| 2 | Are the inclusion and exclusion criteria clearly stated in the Introduction or Methods section? | |
| | <p>If the inclusion and exclusion criteria are implicitly given in the description of the characteristics of the population (Q.3a), answer 'yes'.</p> | |
| | a) Yes | (1) |
| | b) No | (0) |
| 3 | Are the interventions of interest described in detail in the Introduction or Methods section or is reference given to a previous paper in which they were published? | |
| | <p>Treatments, e.g. intervention and control, that are to be compared should be clearly described.</p> | |
| | a) Yes | (1) |
| | b) No | (0) |
| 4 | Did authors distinguish between primary and secondary outcomes? | |
| | a) Yes | (1) |
| | b) No | (0) |
| 5 | Was a power calculation reported for the primary outcome? | |
| | a) Yes | (1) |
| | b) No | (0) |
| | c) Can't tell | (0) |
| 6 | Are the main findings of the study clearly described? | |
| | <p>Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests, which are considered below.)</p> | |
| | a) Yes | (2) |
| | b) No | (0) |

7 Are estimates of the random variability of the main outcomes clearly described for each group of patients to be compared?

In non parametric data the inter-quartile range should be reported. In parametric data the standard error and/or standard deviation, or confidence intervals should be reported.

Intervention group

- a) Yes (0.5)
- b) No (0)
- c) Can't tell (0)

Control group

- a) Yes (0.5)
- b) No (0)
- c) Can't tell (0)

8 Are the distributions of principle confounders clearly described ?

- a) Yes (1)
- b) No (0)

9 Have the numbers of patients lost to follow-up been described?

- a) Yes (1)
- b) No (0)
- c) No loss to follow-up (1)

10 Have the main adverse events that may be a consequence of the intervention been reported in either the Methods or Results section ?

If the authors describe a list of possible complications in the Methods and Results sections (1)

If complications are described in text or table (0.5)

If complications are described as 'minor' or 'major' (0)

11 Have 95% confidence intervals and/or actual probability values (i.e. 0.035 rather than <0.05) been reported for the main outcomes, except where the probability value is less than 0.001?

This is a measure of effect

- a) Both CI and p values (1)
- b) Either CI or p values (0.5)
- c) Neither (0)

EXTERNAL VALIDITY

1 What proportion of subjects who were approached were *ineligible* to participate?⁴

Ineligible' are those who do not meet the inclusion criteria

- What is the actual % of ineligibles reported in the paper?: (1)
OR What numbers were reported as being ineligible? (x/n): (1)
OR If a number is not reported in the paper, answer ' No': (0)

2. What proportion of subjects who were eligible *refused* to participate? ^d

- What is the actual % of refusal reported in the paper?: (1)
OR What numbers were reported for refusal? (x/n): (1)
OR If a number is not reported in the paper, answer 'No': (0)

INTERNAL VALIDITY – BIAS

1 Was an attempt made to blind those measuring the outcomes of interest?

- a) Yes (1)
b) No (0)
c) Can't tell (0)

2 If any of the results of the study were based on “data dredging”, was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective or unplanned subgroup analyses were reported, then answer 'yes'.

- a) Yes
b) No

3 What proportion of patients in each group completed the allocated treatment regime?

This question is about the proportion of subjects who “crossed over” with respect to the treatment they received or who did not comply with their allocated treatment, rather than loss to follow-up.

Intervention group

- What % completed the allocated treatment regime? (2: >95%)
OR What number completed the allocated treatment regime? (x/n) (1: 85-95%)
OR Answer 'CT' if it is impossible to tell. (0: <85%)

Control group

- What % completed the allocated treatment regime? (2: >95%)
OR What number completed the allocated treatment regime? (x/n) (1: 85-95%)
OR Answer 'CT' if it is impossible to tell. (0: <85%)

4 Were the patients in the different intervention groups recruited from the same source population?

For example, patients for all comparison groups should be selected from the same hospitals. The question should be answered ‘can’t tell’ for cohort studies where there is no information concerning the source of the patients included in the study.

- a) Yes (1)
- b) No (0)
- c) Can’t tell (0)

INTERNAL VALIDITY – CONFOUNDING

(score)

1 Were patients randomised to intervention groups?

Studies should be classified by method of randomisation. Group randomised study should be ticked if, for example, units of health care delivery such as general practices have been randomised rather than individual patients.

- a) Truly random **and** concealed (1)
- b) Truly random but **not** concealed (0.5)
- c) Group randomised study (1)
- d) Not random/cohort (0)

2 If not randomised, is there a description of the basis for treatment allocation?

- a) Yes (1)
- b) No (0)
- c) Randomised study (1)

3 Was there adequate adjustment for the effects of confounding in the analysis from which the main findings were drawn or alternatively evidence that the groups were comparable?

- age* (0.5)
- ASA score (Co-morbidity)* (0.5)
- stage* (0.5)
- site of tumour* (0.5)
- history of previous surgery* (0.5)

4 Are the main conclusions of the study based on an intention to treat analysis rather than on an analysis of treatments actually received?

For studies in which all patients received the treatment to which they were allocated, answer ‘yes’ rather than ‘not applicable.’

- a) Yes (1)
- b) No (0)
- c) Not applicable i.e. no conversions (1)

5 How many subjects were lost to follow up?

If the number of patients lost to follow up is not reported, the question should be answered as 'can't tell.'

Intervention group

What is the percentage of patients lost to follow up? (2: <5%)

OR What is the number of patients lost to follow up? (x/n) (1: 5-15%)

OR Can't tell: CT (0: >15%)

Control group

What is the percentage of patients lost to follow up? (2: <5%)

OR What is the number of patients lost to follow up? (x/n) (1: 5-15%)

OR Can't tell: CT (0: >15%)

Appendix H: Quality assessment of papers describing long-term outcomes

Study id:

Are aims of the study are clear?

Is case-definition clear?

Was the data collected retrospectively or prospectively ?

Are patients in the study population consecutive?

Use of confidence intervals/standard error ? (estimate of random variability)

Are outcomes (recurrence/death) stratified by disease stage ?

Is there a clear definition of the outcomes reported ?

Yes = 1

No = 0

Score: 7

Appendix I: Inter-rater agreement for coding data variables

Inter-rater agreement for coding of short-term data variables

Question	Agreement	Expected agreement	Kappa
Reporting:			
1	80%	82%	-0.11
2	50%	62%	-0.32
3	90%	74%	0.62
4	90%	74%	0.62
5	90%	74%	0.62
6	50%	56%	-0.13
7a	90%	90%	0.00
7b	90%	90%	0.00
8	60%	66%	-0.18
9	70%	70%	0.00
10 ^a	75%	75%	0.00
11 ^a	50%	50%	0.00
External validity:			
1	80%	66%	0.41
2	70%	70%	0.00
Internal validity(bias):			
1	80%	80%	0.11
2	90%	74%	0.62
3a ^a	70%	55%	0.33
3b ^a	90%	74%	0.62
4	100%	100%	-
Internal validity(confounding):			
1 ^a	100%	63%	1.00
2	50%	50%	0.00
3 ^a	68%	63%	0.12
4	90%	50%	0.80
5a ^a	55%	46%	0.17
5b ^a	65%	68%	-0.09

^a A weighted kappa value was calculated for these questions because the response categories were ordinal.

Inter-rater agreement for coding of long-term data variables

Question	Agreement %	Expected agreement %	Kappa score
Clear aims/objectives	90	90	0
Case definition clear ^α	100	82	1
Use of consecutive cases	80	66	0.41
Prospective or retrospective data	100	52	1
Use of Confidence Intervals	100	82	1
Outcomes stratified by stage	100	68	1
Well defined outcomes	60	48	0.23
Total score	70	28	0.58

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