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[Intervention Review]

Laparoscopic versus open total mesorectal excision for rectal cancer

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ABSTRACT

Background

Colorectal cancer including rectal cancer is the third most common cause of cancer deaths in the western world. For colon carcinoma, laparoscopic surgery is proven to result in faster postoperative recovery, fewer complications and better cosmetic results with equal oncologic results. These short-term benefits are expected to be similar for laparoscopic rectal cancer surgery. However, the oncological safety of laparoscopic surgery for rectal cancer remained controversial due to the lack of definitive long-term results. Thus, the expected short-term benefits can only be of interest when oncological results are at least equal.

Objectives

To evaluate the differences in short- and long-term results after elective laparoscopic total mesorectal excision (LTME) for the resection of rectal cancer compared with open total mesorectal excision (OTME).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2013, Issue 2), MEDLINE (January 1990 to February 2013), EMBASE (January 1990 to February 2013), ClinicalTrials.gov (February 2013) and Current Controlled Trials (February 2013). We handsearched the reference lists of the included articles for missed studies.

Selection criteria

Only randomised controlled trials (RCTs) comparing LTME and OTME, reporting at least one of our outcome measures, was considered for inclusion.

Data collection and analysis

Two authors independently assessed study quality according to the CONSORT statement, and resolved disagreements by discussion. We rated the quality of the evidence using GRADE methods.

Main results

We identified 45 references out of 953 search results, of which 14 studies met the inclusion criteria involving 3528 rectal cancer patients. We did not consider the risk of bias of the included studies to have impacted on the quality of the evidence. Data were analysed according to an intention-to-treat principle with a mean conversion rate of 14.5% (range 0% to 35%) in the laparoscopic group.

There was moderate quality evidence that laparoscopic and open TME had similar effects on five-year disease-free survival (OR 1.02; 95% CI 0.76 to1.38, 4 studies, N = 943). The estimated effects of laparoscopic and open TME on local recurrence and overall survival were similar, although confidence intervals were wide, both with moderate quality evidence (local recurrence: OR 0.89; 95% CI 0.57 to1.39 and overall survival rate: OR 1.15; 95% CI 0.87 to1.52). There was moderate to high quality evidence that the number of resected lymph nodes and surgical margins were similar between the two groups.

For the short-term results, length of hospital stay was reduced by two days (95% CI -3.22 to -1.10), moderate quality evidence), and the time to first defecation was shorter in the LTME group (-0.86 days; 95% CI -1.17 to -0.54). There was moderate quality evidence that 30 days morbidity were similar in both groups (OR 0.94; 95% CI 0.8 to 1.1). There were fewer wound infections (OR 0.68; 95% CI 0.50 to 0.93) and fewer bleeding complications (OR 0.30; 95% CI 0.10 to 0.93) in the LTME group.

There was no clear evidence of any differences in quality of life after LTME or OTME regarding functional recovery, bladder and sexual function. The costs were higher for LTME with differences up to GBP 2000 for direct costs only.

Authors' conclusions

We have found moderate quality evidence that laparoscopic total mesorectal excision (TME) has similar effects to open TME on long term survival outcomes for the treatment of rectal cancer. The quality of the evidence was downgraded due to imprecision and further research could impact on our confidence in this result. There is moderate quality evidence that it leads to better short-term post-surgical outcomes in terms of recovery for non-locally advanced rectal cancer. Currently results are consistent in showing a similar disease-free survival and overall survival, and for recurrences after at least three years and up to 10 years, although due to imprecision we cannot rule out superiority of either approach. We await long-term data from a number of ongoing and recently completed studies to contribute to a more robust analysis of long-term disease free, overall survival and local recurrence.

PLAIN LANGUAGE SUMMARY

Keyhole laparoscopic or open surgery for rectal cancer

Colorectal (large bowel) cancer including rectal cancer is the third most common cause of cancer deaths in the western world. The risk of developing rectal cancer increases with age and is most common in people around 70 years of age. The treatment consists of complete surgical resection of the tumour and surrounding tissue by a technique called total mesorectal excision (TME), sometimes combined with chemotherapy and radiotherapy. This surgery can be performed by either normal open abdominal surgery with a large incision or by keyhole laparoscopic surgery with several small incisions for the instruments and camera. For colon cancer, laparoscopic surgery is proven to result in faster postoperative recovery, fewer complications and better cosmetic results. These results are expected to be equal for rectal surgery. However, surgery for rectal cancer is technically more difficult than for colon cancer due to the location deeper in the pelvis and close to important nerves. Therefore a complete and safe resection of the tumour should be guaranteed, this is important to reduce the risk of recurrence of the tumour and could be tested by assessing recurrence rates and patient survival in the long term.

In this updated review, we have assessed all randomised studies of laparoscopic and open TME for rectal cancer, to compare and combine their results. We included 14 trials reporting on a total of 3528 patients undergoing rectal cancer surgery. In 14.5% of those having laparoscopic surgery needed conversion to open surgery by a large incision in the abdomen due to difficulties or problems during the procedure.

There is currently moderate quality evidence that laparoscopic total mesorectal excision (LTME) has similar effects to open TME (OTME) on long term survival outcomes for the treatment of rectal cancer. The estimated effect was imprecise and further research could impact on our confidence int this result. There is moderate quality evidence that it leads to better short-term post-surgical outcomes in terms of length of hospital stay. We found that pain was lower in the LTME group and that resumption of diet was better. We did not find clear evidence of a difference in quality of life between the two groups, but costs were higher for LTME. We await long-term data from a number of ongoing and recently completed studies to contribute to our understanding of the effects of these surgical approaches on long-term disease free, overall survival and local recurrence.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Laparoscopic versus open total mesorectal excision (TME) for rectal cancer

Patient or population: people with Rectal Cancer
Settings:
Intervention: Laparoscopic TME
Comparison: Open TME

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open TME	Laparoscopic TME			
Disease-free survival at 5 years	718 per 1000	722 per 1000 (659 to 778)	OR 1.02 (0.76 to 1.38)	943 (4 studies)	⊕⊕⊕◯ moderate[1]
Overall survival at 5 years	679 per 1000	709 per 1000 (648 to 763)	OR 1.15 (0.87 to 1.52)	987 (4 studies)	⊕⊕⊕◯ moderate[2]
Local recurrences	54 per 1000	48 per 1000 (31 to 73)	OR 0.89 (0.57 to 1.39)	1538 (8 studies)	⊕⊕⊕◯ moderate[3]
Lymph nodes retrieved		The mean number of lymph nodes retrieved in the intervention groups was 0.43 lower (1.13 lower to 0.26 higher)		3682 (11 studies)	⊕⊕⊕⊕ high
CRM positivity	61 per 1000	60 per 1000 (44 to 83)	OR 0.99 (0.71 to 1.4)	2313 (8 studies)	⊕⊕⊕◯ moderate[4]
30-day morbidity (total)	275 per 1000	263 per 1000 (233 to 295)	OR 0.94 (0.8 to 1.1)	3397 (11 studies)	⊕⊕⊕◯ moderate[5]

Hospital stay (days)		The mean length of hospital stay in the intervention groups was **2.16 days shorter** (3.22 to 1.1 days shorter)	3084 (11 studies)	⊕⊕⊕○ **moderate**[6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Statistical inaccuracy with wide confidence interval at both sides
[2]Statistical inaccuracy with wide confidence interval at both sides, but a tendency for a higher overall survival for LTME
[3]Statistical inaccuracy with wide confidence interval at both sides, but a tendency for a lower recurrence rate for LTME
[4]Only 8 studies provided data on CRM positivity
[5]Definition of overall morbidity varied or was unclear
[6]Length of hospital stay depends on postoperative protocols and implementation of enhanced recovery programmes

BACKGROUND

Description of the condition

The incidence of rectal cancer in the western world is 28% to 35% of the total colorectal cancer incidence, with 15 to 25/100,000 new patients per year for both men and women. The risk increases with age, with a median age of 70 years at the time of diagnosis; the associated mortality is between 4 and 10 per 100,000 per year (Glimelius 2013). Symptoms suggesting rectal cancer typically include changes in bowel habits, the feeling of incomplete emptying, rectal bleeding, anaemia or weight loss. The diagnosis can be made by tumour biopsy during colonoscopy or sigmoidoscopy. If rectal cancer is confirmed, the extent of the disease is examined by imaging of the chest and liver for signs of metastases, and magnetic resonance imaging (MRI) of the pelvis and/or endorectal ultrasound (ERUS) are done to determine the degree of rectal wall and mesorectal fascia invasion. The majority of rectal carcinomas are adenocarcinoma (95% to 98%), usually arising from an adenoma (Glimelius 2013; Monson 2013).

Description of the intervention

Complete resection of rectal cancer can be achieved by a sphincter-preserving anterior resection (AR, rectosigmoid resection) or an abdominoperineal resection (APR). Both had high local recurrence rates until the introduction of the total mesorectal excision (TME) (Heald 1986). Total mesorectal excision achieves a complete removal of the rectum together with its draining lymphatics, and results in low rates of recurrence. Despite the successful introduction of laparoscopic and laparoscopic-assisted procedures for the resection of colonic cancer, surgeons have been more reluctant to introduce laparoscopic TME due to the technically demanding resection plane.

How the intervention might work

Laparoscopic and laparoscopic-assisted TME offers several theoretical advantages compared to open resection. It may be associated with less blood loss, faster recovery, early feeding and a lower morbidity rate, as shown in laparoscopic colonic surgery (Braga 2002; Pikarsky 2002). The magnified view of the pelvis afforded by the laparoscope may facilitate identification of the autonomic nerves and thus prevent unintentional injury of these nerves. However, these advantages of LTME are only beneficial to people with rectal cancer when local recurrence and disease-free survival rates are at least similar to those achieved with OTME.

Why it is important to do this review

The introduction of laparoscopy 20 years ago has caused major changes in colorectal surgery. For benign disease, such as diverticulitis and inflammatory bowel disease, laparoscopy has become the surgical technique of choice for its benefits in recovery, complication rate and cosmetic results. Only recently, sufficient evidence has become available showing laparoscopic surgery is safe for the treatment of colonic cancer. Four large randomised trials (472 to 1076 participants) could not show any differences in quality of resection and long-term recurrence and survival rates between laparoscopic and open surgery for colon cancer (MRC CLASICC a 2005; COST 2007; COLOR 2009; LAPKON II 2009). Although COLOR 2009 was not able to rule out any difference with their non-inferiority design, the meta-analysis by Kuhry 2008 did not show any differences.

Despite the larger number of randomised trials on laparoscopic surgery for colon cancer, there is still limited evidence for long- and short-term outcomes after LTME due to the lack of high quality randomised controlled trials with sufficient follow up. Now the results of more well designed large randomised controlled trials (RCTs) become available, there is a need for a updated systematic review of these results.

OBJECTIVES

To evaluate the differences in short- and long-term results after elective laparoscopic total mesorectal excision (LTME) for the resection of rectal cancer compared with open total mesorectal excision (OTME).

METHODS

Criteria for considering studies for this review

Types of studies

In contrast to the published protocol and previous version of this review, for this update we have only considered RCTs comparing LTME to OTME, since sufficient RCTs have become available since the publication of the original review. We did not apply any language restrictions.

Types of participants

People with rectal cancer undergoing total mesorectal excision were considered for inclusion. Studies including participants with colorectal cancer are only eligible if the results for those with rectal carcinoma were presented separately.

Types of interventions

These include laparoscopic, laparoscopic-assisted or open total mesorectal excision as (low) anterior resection or abdominoperineal resection. When a primary anastomosis was constructed, it could either be performed intraperitoneally ('double-stapled' colorectal anastomosis) or extraperitoneally (hand-sewn or stapled colorectal anastomosis).

Types of outcome measures

We sought the following outcomes in all included studies:

Primary outcomes

- Disease-free and overall survival

Secondary outcomes

- Recurrences (local, wound/port site and distant)
- Quality of resection (circumferential margin (CRM) positivity and number of lymph nodes)
- Surgical data (surgical time, incision length, conversion rate)
- Intraoperative complications, blood loss and transfusion requirement
- Postoperative morbidity and mortality (overall morbidity, need for reoperation, anastomotic leakage, wound infection, urinary complications, bleeding, chest infection)
- Postoperative pain (use of medication and visual analogue scale (VAS) score)
- Gastrointestinal recovery and hospital stay (time to first bowel movement, time to normal diet, length of hospital stay)
- Long-term morbidity (incisional herniae and bowel obstruction)
- Quality of life (functional recovery, bladder and sexual function)
- Immunologic response
- Costs

Search methods for identification of studies

Electronic searches

We followed the recommendations of the Cochrane Colorectal Cancer Group and searched the following bibliographic databases with no language restrictions in order to identify relevant primary studies:

Cochrane Central Register of Controlled Trials (CENTRAL) (January 1990 to February 2013);
MEDLINE (January 1990 to February 2013);
EMBASE (January 1990 to February 2013).
We conducted searches using medical subject headings (MeSH) and free-text words. The search has been adapted for each database search and is shown in Appendix 1 (CENTRAL), Appendix 2 (MEDLINE) and Appendix 3 (EMBASE).

Searching other resources

We handsearched the reference lists of all selected articles for further relevant studies. There was no language restriction. In addition, we searched for ongoing trials in the ClinicalTrials.gov and the Current Controlled Trials databases.

Data collection and analysis

Selection of studies

Two authors (SV and LP) independently reviewed all abstracts. We retrieved full-text copies of all studies that potentially met the inclusion criteria based on abstract review. If both authors agreed that a study did not meet the eligibility criteria, we excluded it. If we disagreed, we resolved conflicts by discussion and consensus or by consulting a third member of the review team.

Data extraction and management

We collected data according to the outcomes mentioned above. Each author extracted the data independently from each study and compared them, resolving disagreement by discussion. We used Review Manager 5 (RevMan 5.2) software for statistical analysis, provided by the Cochrane Collaboration. Data not suitable for meta-analysis is discussed in the results section.

Assessment of risk of bias in included studies

Two authors (SV and LP) have assessed all the selected studies for methodological quality according to the CONSORT Statement 2010, and have summarised the information in the 'Risk of bias' figure (Figure 2). In addition, we have used the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We measured the treatment effect using the mean difference (MD) or standardised mean difference (SMD) for continuous data and the odds ratio (OR) for dichotomous data. Standardised mean differences were only used when the reported units or drugs varied between the studies, for instance the number of doses of analgesia. All outcomes included 95% confidence intervals (CI).

Unit of analysis issues

For randomised controlled trials for this surgical intervention, we would expect only a simple parallel design. The only possible cross-over would be the conversion of laparoscopy to open surgery. Because worse outcomes for this group can be expected and should be evaluated as a complication of laparoscopic-intended surgery, all analyses should be performed on the intention-to-treat principle.

Dealing with missing data

To avoid missing unpublished studies, we searched clinical trial databases as stated above. We compared reported outcomes to published protocols or to the Methods section of each article. If we found inconsistencies, this is reported in the 'Selective reporting' section of the 'Risk of bias' table. As missing postoperative and follow-up data are common in surgical studies, we assume a random pattern of missingness.

Assessment of heterogeneity

We used the Cochrane Chi² test (Q-test) to assess heterogeneity and the I² statistic to estimate the degree of heterogeneity (Higgins 2003). We considered an I² of between 0% and 40% as probably not important, between 30% and 60% as representing moderate heterogeneity, between 50% and 90% as substantial heterogeneity, and between 75% and 100% as considerable heterogeneity (Higgins 2011). We used a fixed-effect analysis for outcomes with low heterogeneity.

Assessment of reporting biases

We present an overview of all outcomes per study in the table Selective reporting (reporting bias).

Data synthesis

We analysed continuous variables using mean differences with 95% confidence intervals. For dichotomous variables we used odds ratios with 95% confidence intervals. We constructed forest plots, using the Mantel-Haenszel method (fixed- or random-effects) to combine the outcomes. In case of continuous data presented as median and range, we estimated the mean and standard deviation according to the methods described by Hozo 2005. We generated funnel plots to screen for publication bias. In case of inclusion of an original RCT and the additional publication of a subgroup of participants, we included only the most appropriate subgroup data in the meta-analyses, to avoid duplication of data.

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses for abdominoperineal resection (APR) and anterior resection (AR), and for studies allowing and excluding neoadjuvant therapy. These analyses were not performed because too few studies presented separate data for these groups. However, we plan to explore these subgroups if possible in future updates.

Summary of Findings table

We applied methods developed by the GRADE working group to rate the quality of evidence from RCTs, starting at high quality and downgrading for risk of bias, imprecision, inconsistency, indirectness and publication bias.
We rated the quality of the evidence for the following main outcomes:

1. Disease-free survival at 5 years
2. Overall survival at 5 years
3. Local recurrences
4. Lymph nodes retrieved
5. CRM positivity
6. 30-day morbidity
7. Hospital stay (days)

RESULTS

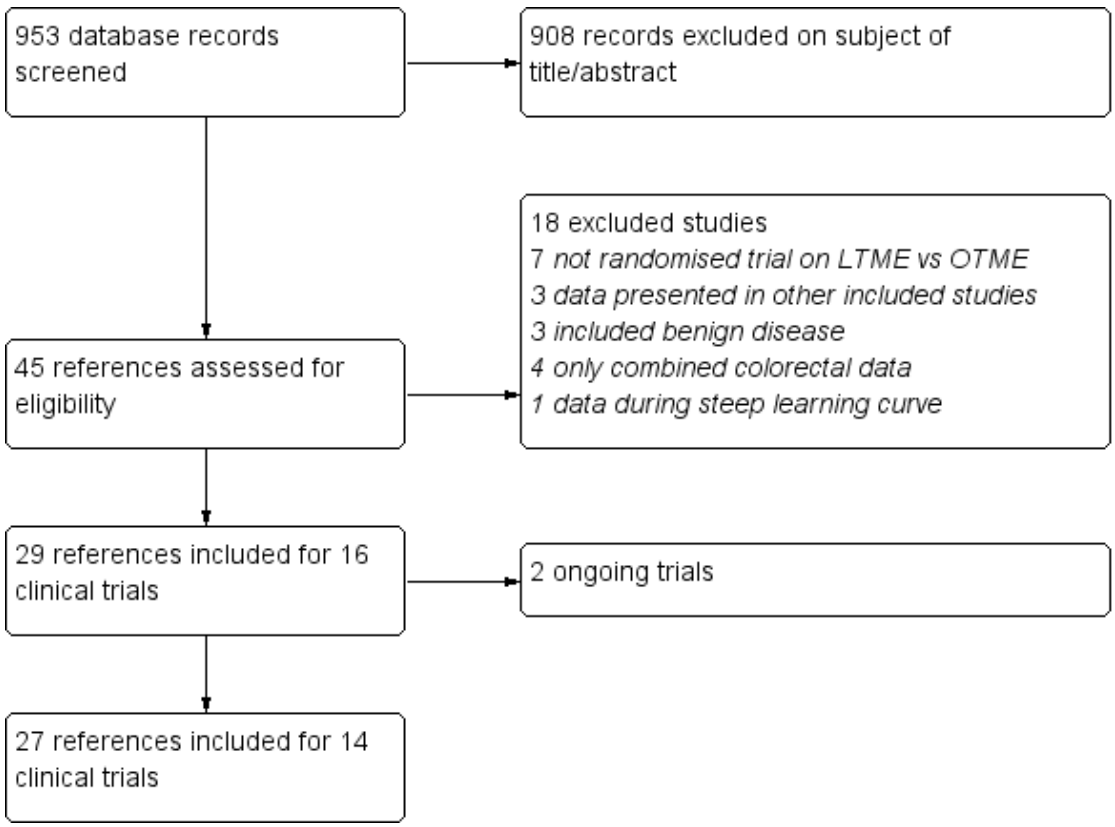
Description of studies

See: Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

Results of the search

Our searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE identified 90, 253 and 852 results respectively. In addition we handsearched MEDLINE for any missed publications for the included trials. After exclusion of duplicates, we screened 953 references and identified 45 eligible references, as shown in the flow chart (Figure 1).

Figure 1. Study selection flow diagram.



Included studies

From the 29 references, we identified two ongoing trials and 14 published clinical trials. Most larger trials have published their results at several stages in different papers. Both ongoing trials (ACTRN12609000663257 and NCT00726622) are still recruiting participants and no results have been published yet. Of the 14 published trials, two (Kang 2010; COLOR 2 a 2013) completed participant recruitment but have not yet published long-term data on survival. The COLOR 2 trial has a second published paper on a local subgroup, referred to as COLOR 2 b 2011 in this review. The Hong Kong trials are divided into the low rectal cancer group in Ng 2008 and the rectosigmoid group in Hong Kong a 2004, with the last subdivided in four papers because results are published for different subgroups as shown in the Characteristics of included studies. Hong Kong a 2004 is the biggest group, presenting upper rectum and sigmoid data, Hong Kong b 2009 is the upper rectal subgroup and reports 10-year follow-up data. Hong Kong c 2000 and Hong Kong d 2003 are both small subgroups of Hong Kong a 2004 and present only short-term data on immunological response.

The UK MRC CLASICC study is presented across nine papers, with six grouped as MRC CLASICC a 2005, giving respectively the short-term, three-year, five-year and 10-year results, the costs and an analysis of long term complications of the same participant group. MRC CLASICC c 2001 (one) and MRC CLASICC b 2005 (two) include papers for a selected or local participant subgroup and are therefore reported separately. King 2006 also consists of two papers, with the second paper focusing on functional recovery in the same participant group. The remaining eight clinical trials have one reference each, with the note that Zhou 2004 and Zhou 2007 are different trials and different authors despite the coincidence of names.

All 14 clinical trials were published as full papers and involved a total of 3528 rectal cancer patients (range 19 to 1044). The characteristics of these trials are described in 20 separate data sets and thus tables to allow for sufficient details on six additional subgroup papers.

All studies had quite similar exclusion criteria. The most common were: T4 rectal cancer, rectal cancer recurrence, people with

synchronous or metachronous colorectal cancer, metastatic disease, emergency surgery, intestinal obstruction or perforation, contraindication for laparoscopy and no informed consent. The majority of the studies described the technique for laparoscopic total mesorectal excision (TME). Perioperative treatment of participants was not described in most of the trials. Six studies had a standardised protocol (Hong Kong a 2004; Braga 2007; Ng 2008; Kang 2010; COLOR 2 b 2011; Liang 2011) and only two had an enhanced recovery protocol (King 2006; Lujan 2009). Data on the type of anaesthesia and analgesia were not given in most studies.

Most studies reported on a range of different outcomes. The most commonly assessed were overall and disease-free survival rates, local recurrence rates, adequacy of oncological resection (margins and number of lymph nodes removed), duration of surgery, conversion rate, mortality, morbidity, anastomotic leakage, postoperative pain, gastrointestinal recovery rate and hospital stay. Most studies lacked a definition of conversion. The most common causes for conversion to open surgery were tumour invasion of adjacent structures or bulky tumours, dense adhesions and technical failure. Few studies evaluated quality of life (MRC CLASICC a 2005; MRC CLASICC b 2005; King 2006; Braga 2007; Kang 2010), immune response (Hong Kong c 2000; MRC CLASICC c 2001; Hong Kong d 2003; Zhou 2007; COLOR 2 b 2011) or costs (Hong Kong a 2004; MRC CLASICC a 2005; King 2006; Braga 2007; Ng 2008).

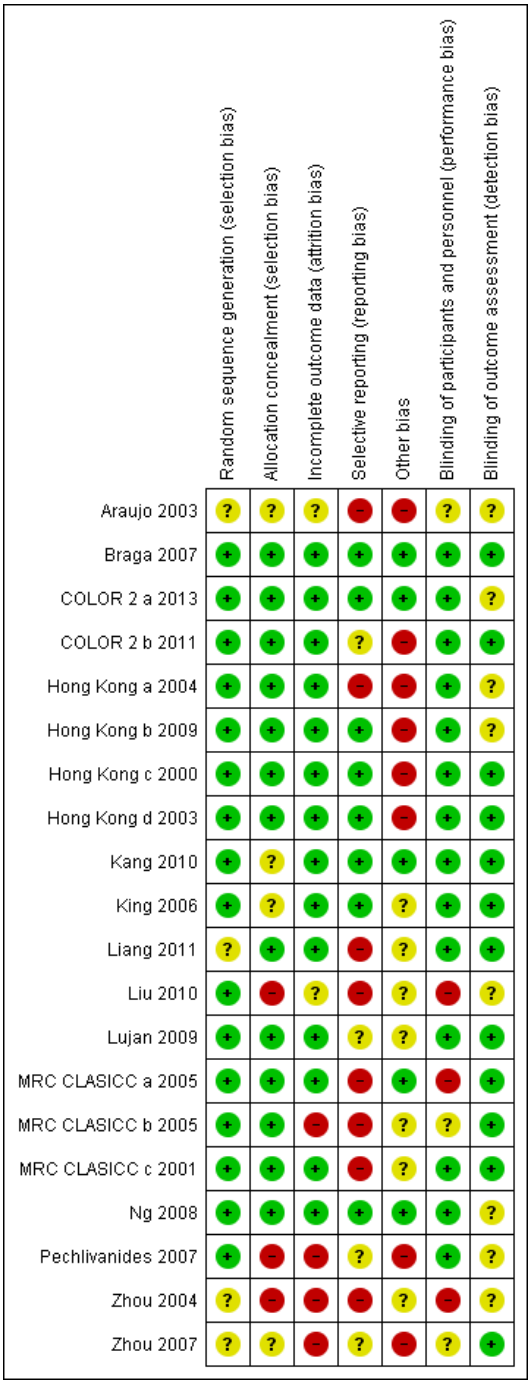
Excluded studies

Sixteen papers were excluded for the following reasons: two studies were not completely randomised (Leung 1999; Mirza 2008) and two other studies presented the same data as another included study (Braga 2002; Braga 2005). Two studies included participants with benign disease (Milsom 1998; Polle 2007) and two other studies excluded people treated with TME for low rectal cancer (Schwenk 1998; Liu 2009). Four studies included colorectal cancer patients, but did not report the number of rectal cancer patients or any separate outcomes for rectal cancer (Kim 1998; JCOG 0404 2005; LAPKON II 2009; LaFa 2011). One study presented low-quality data from a period with a steep learning curve (Pan 2007). Three more studies turned out not to be prospective RCTs, but were a comparison with the national registry (Morris 2011), an economic comparison between UK and USA trials (Stead 2000), and a single-arm phase II trial (Yamamoto 2008).

Risk of bias in included studies

The risk of bias is described in the Characteristics of included studies section, and a summary is shown in Figure 2. Of the included trials, only one had a low risk of bias on all items and three scored low on six out of seven domains. Five were of unclear or low quality, with a high or unclear risk in at least five out of seven domains.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method of randomisation was unclear in four trials, and allocation concealment was not described in seven trials. Only seven trials presented an adequate inclusion and randomisation flow diagram, including a description of the loss to follow-up.

Blinding

Because of the nature of the interventions, blinding is not an option in these trials. Instead of blinding, we assessed whether operative technique and postoperative care were standardised, and how outcome data and pathological data were registered. We assessed standardisation in three studies as inadequate. Outcome registration was adequate in eight studies and unknown in all other studies.

Incomplete outcome data

We did not detect any attrition bias. Not all studies reported on loss to follow-up. Questionnaire response rates were reported for both groups when eligible.

Selective reporting

Comparing the described protocols and methods to the reported results of the different studies, we did not find evidence of any selective reporting, although some studies did not report exact data on non-significant results mentioned in the text sections. An overview of studies and outcomes in Table 1 shows that most studies report on the same outcomes. Five papers reported only one outcome in a subgroup analysis of another trial and one study reported only one outcome for the included participant group.

Other potential sources of bias

An important source of bias is the experience of the surgeons conducting LTME, because of the known steep learning curve. (Schlachta 2001; Tekkis 2005) When only one experienced surgical team is involved, this bias can be limited, but it can be extensive in large multi centre trials or less experienced teams. Only the MRC CLASICC a 2005 and Kang 2010 defined the experience of their surgeons as based on at least 20 procedures. Four other studies only stated that their surgeons were "well experienced" or "the most experienced" (Hong Kong a 2004; Braga 2007; Pechlivanides 2007; Ng 2008;). The remaining eight did not describe surgeons' experience at all or stated only a single surgeon or team performed the procedures.

Effects of interventions

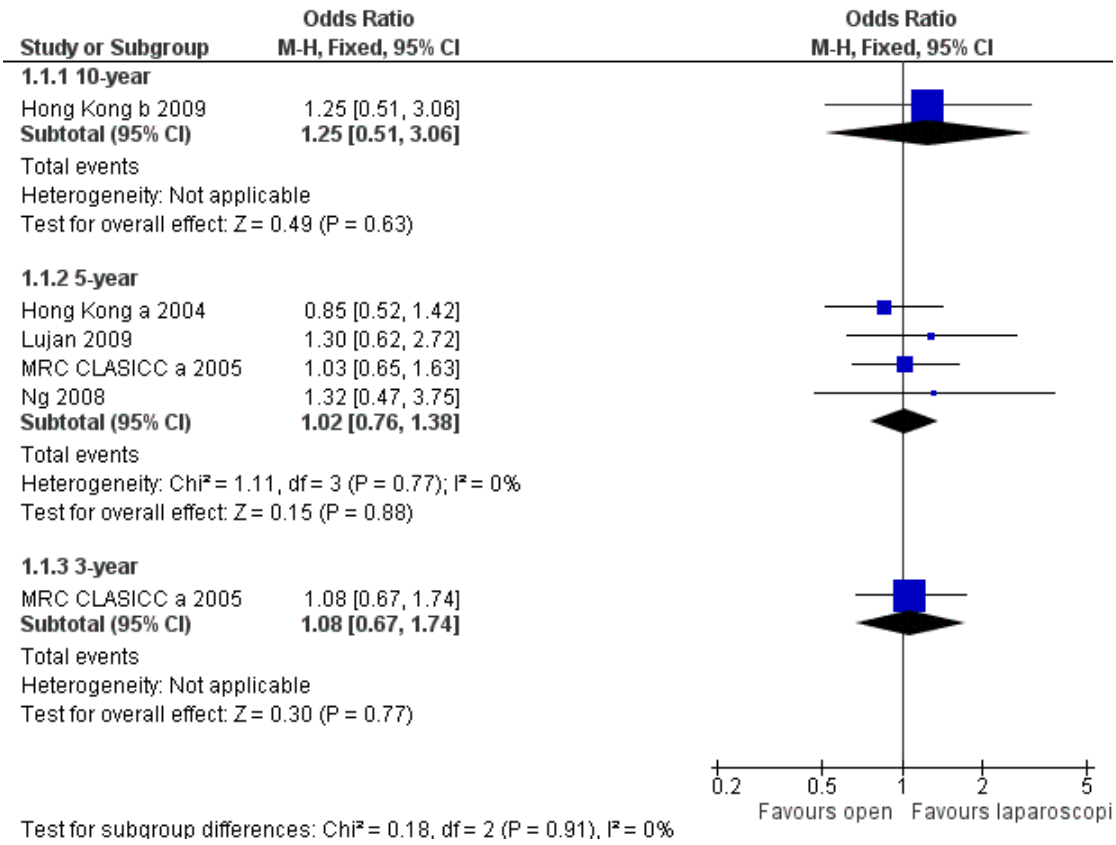
See: **Summary of findings for the main comparison** Laparoscopic versus open total mesorectal excision for rectal cancer

Disease-free and overall survival

The disease-free and overall survival rates have been reported in only six studies including 1494 participants, because of lack of follow-up in the other eight studies. Two of these are trials that will report on these results in the near future (Kang 2010; COLOR 2 b 2011), while the other six did not mention any long-term outcomes in their Methods or protocol.

The combined data for these studies do not show statistical significant differences in disease-free survival at three ((OR 1.08; 95% CI 0.67 to 1.74), five (OR 1.02; 95% CI 0.76 to 1.38) and 10 years ((OR 1.25; 95% CI 0.51 to 3.06) Analysis 1.1) for LTME and OTME. Regarding overall survival at three (OR 1.00; 95% CI 0.70 to 1.42), five (OR 1.15; 95% CI 0.87 to 1.52) or 10 years ((OR 1.15; 95% CI 0.80 to 1.65); Analysis 1.2), again no differences could be found between the groups. Braga 2007 could not be included in the meta-analysis because data were only shown in a Kaplan-Meier curve, but did not show any differences between LTME and OTME groups. See Figure 3.

Figure 3. Forest plot of comparison: 2 Survival and recurrences, outcome: 2.1 Disease free survival.



Ng 2012 has reported the combined 10-year follow-up of Hong Kong a 2004 and Ng 2008 (n = 278) in a conference abstract, and reported no statistically significant differences in survival and recurrences (disease-free survival 82.5% versus 77.6%, P = 0.443, overall survival 63.0% versus 61.1%, P = 0.505 and locoregional recurrences 5.5% versus 9.3%, P = 0.296).

Recurrences

There are no statistical significant differences seen in recurrence rates between LTME and OTME (local OR 0.89; 95% CI 0.57 to 1.39; Analysis 1.3, and distant OR 0.96; 95% CI 0.70 to 1.32; Analysis 1.4). As for port site metastases, only 11 participants (0.9%) in the LTME group developed a port site metastasis (Analysis 1.5). Eight were an extraction site recurrence, leaving only one true port site metastasis. The other two recurrences were not specified. Only three studies described the use of a wound protector in LTME, and reported a similar total of two (0.8%) port site recurrences (Hong Kong a 2004; Zhou 2004; Kang 2010).

Quality of resection: CRM positivity and number of lymph nodes retrieved

One of the most important variables for measuring the quality of the oncological resection and predicting recurrence and survival are circumferential margin involvement and number of lymph nodes retrieved. Eleven RCTs describe the number of retrieved lymph nodes, with no difference between both groups (MD -0.43; 95% CI -1.13 to 0.26; Analysis 2.1). Eight studies reported on circumferential margin positivity, with no difference between LTME and OTME (OR 0.99; 95% CI 0.71 to 1.40; Analysis 2.2).

Duration of surgery, incision length and conversion rate

The duration of surgery was longer for LTME in 11 out of 12 included trials for this analysis, with a difference of 37 minutes (MD 37.48; 95% CI 27.80 to 47.15; Analysis 2.3). Two other studies did not report on surgical time. Four studies reporting on incision length all found a shorter incision length for LTME with a mean difference of 12 centimetres (MD -12.83; 95% CI -14.87 to -10.80; Analysis 2.4).

All studies except two (Zhou 2004; Zhou 2007) describe the conversion rate for the laparoscopic group (Analysis 2.5). The mean conversion rate was 14.5% (0% - 34%), and as described in MRC CLASICC a 2005, is highly dependent on the location of the tumour and the experience of the surgeon. For most studies, the surgeons' experience was not clearly stated and therefore cannot

be compared from these results.

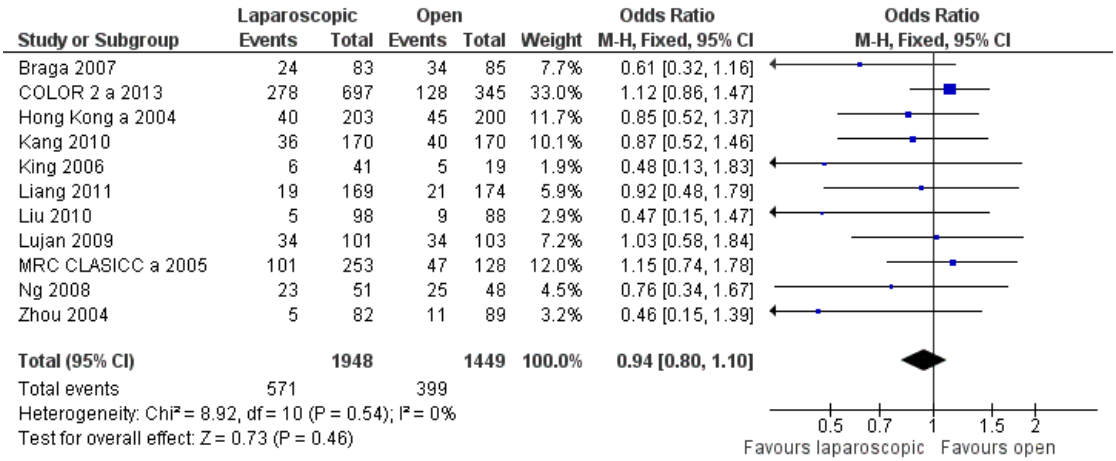
Intraoperative morbidity, blood loss and transfusion requirement

Ten studies described less intraoperative blood loss or transfusion requirement for LTME with a mean difference of 102 millilitres (MD -101.78; 95% CI -147.57 to -55.98; Analysis 2.6) and an odds ratio for transfusion requirement of 0.34 (95% CI 0.19 to 0.62; Analysis 2.7). Only King 2006 described a higher transfusion requirement for LTME, but a lower percentage of participants with over 100 millilitres of blood loss during surgery (27% versus 95%, P < 0.001). The overall intraoperative morbidity was described in four studies and was 11.3% for LTME versus 12.0% for OTME (OR 0.86; 95% CI 0.62 to 1.18; Analysis 2.8). There were insufficient data to compare bowel injury, haemorrhage and solid organ injury separately but individual studies did not show any differences.

Postoperative morbidity and mortality

The overall complication rate was 29.3% (LTME) and 27.5% (OTME) (OR 0.94; 95% CI 0.80 to 1.10; Analysis 3.1), with fewer wound infections and less postoperative bleeding in the LTME group (OR 0.68; 95% CI 0.50 to 0.93 (Analysis 3.2) and OR 0.30; 95% CI 0.10 to 0.93 (Analysis 3.3)). We found no differences in urinary bladder infection or retention (OR 1.23; 95% CI 0.83 to 1.81; Analysis 3.4) and pneumonia (OR 1.32; 95% CI 0.83 to 2.09; Analysis 3.5) between both groups. See Figure 4.

Figure 4. Forest plot of comparison: 4 Short term morbidity and mortality, outcome: 4.1 30d morbidity (total).



Ten studies described similar anastomotic leakage rate for both groups (7.7% vs 6.3% OR 1.01; 95% CI 0.73 to 1.40; Analysis 3.6), while two other trials only included abdominoperineal resection and did not have anastomotic leakage as an outcome. Consequently, the need for reoperation was 5.1% and 5.8% (OR 0.82; 95% CI 0.57 to 1.20; Analysis 3.7) in the LTME and OTME groups respectively. The anastomotic leakage rate has been corrected for participants without an anastomosis.

Data on postoperative mortality were available for 11 studies, with similar mortality rates for the two treatment groups for individual and grouped data (OR 0.81; 95% CI 0.50 to 1.32; Analysis 3.8). Four of them (Zhou 2004; Kang 2010; Liu 2010; Liang 2011) reported no 30-day mortality in either group.

Postoperative pain

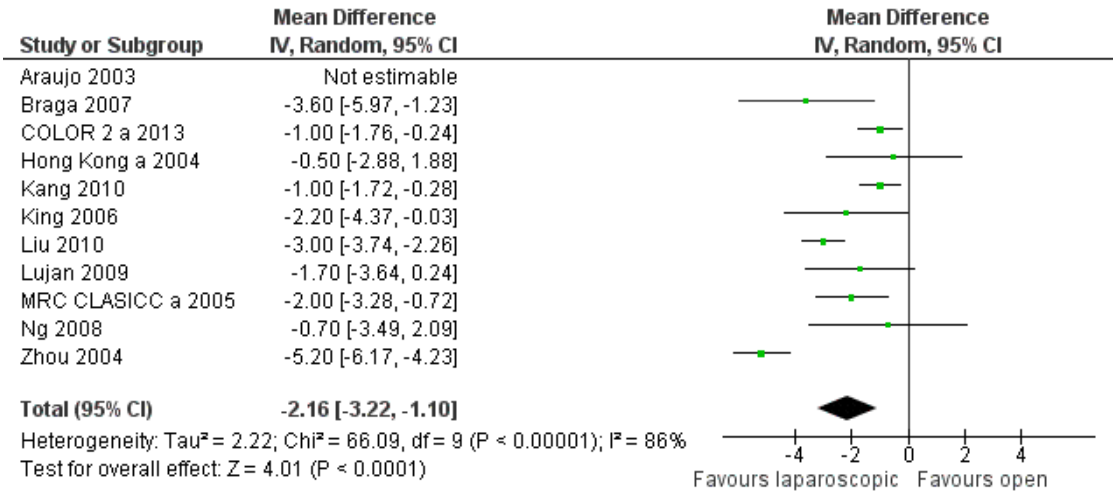
Postoperative pain can be assessed in many different ways. Common measures are a visual analogical scale (VAS) score, patient-controlled anaesthesia (PCA) use, days of morphine use and epidural insufficiency requiring opioid use. Six studies reported results for pain score and analgesic use, and all reported lower analgesic use in the LTME group (standardised mean difference (SMD) -0.60; 95% CI -0.93 to -0.27; Analysis 4.1). COLOR 2 a 2013 reported on the percentage of participants using epidural, opioids or other analgesics, with less epidural use in the LTME group.Three trials reported on VAS pain scores, with a lower pain score for LTME at day one (MD -0.74; 95% CI -1.04 to -0.44; Analysis 4.2).

Gastrointestinal recovery and hospital stay

Length of hospital stay was given in 11 studies, and showed a reduction of two days for the LTME group (MD -2.16; 95% CI -3.22 to -1.10; Analysis 4.3). This is reflected in the gastrointestinal recovery rate to a faster resumption of a normal diet (MD -0.52;

95% CI -0.80 to -0.23; Analysis 4.4), and an earlier first bowel movement (MD -0.86; 95% CI -1.17 to -0.54; Analysis 4.5) in the LTME group. See Figure 5.

Figure 5. Forest plot of comparison: 5 Post op recovery, outcome: 5.3 Hospital stay.



Long-term morbidity: Incisional herniae and bowel obstruction

Only three studies reported on long-term morbidity from incisional hernia and intestinal obstruction (MRC CLASICC a 2005; Braga 2007; Hong Kong b 2009). No statistically significant difference between OTME and LTME was seen (OR 0.84; 95% CI 0.32 to 2.21; Analysis 5.1). Intestinal obstruction occurred less frequently in the LTME group (OR 0.30; 95% CI 0.12 to 0.75; Analysis 5.2).

Quality of life: physical and sexual functioning

Four studies reported on quality of life using questionnaires (MRC CLASICC a 2005; King 2006; Braga 2007; Kang 2010). Only two reported on bladder and sexual functioning (MRC CLASICC a 2005; Kang 2010).

Of the four reporting on physical functioning, three reported significantly better functioning in the LTME group at three, six or 12 months. The MRC CLASICC a 2005 showed return to normal functioning at three months for both groups.

The reports on bladder and sexual functioning suffered from low response rates, varying from 71% overall response rate down to 10% on specific questions about sexual enjoyment and problems. Kang 2010 showed a baseline difference in sexual problems, but better sexual functioning after three months in both groups. In contrast, male sexual problems were worse three months after surgery but there was no difference between both groups. The LTME group had significantly fewer micturition, gastrointestinal and defecation problems at three months after surgery.

MRC CLASICC a 2005 and MRC CLASICC b 2005 both reported on participants in the CLASICC trial, but used different populations, questionnaires and time points. MRC CLASICC b 2005 showed worse sexual functioning after LTME, specifically for erectile dysfunction, but none were statistically significant. No differences in sexual interest, activity and enjoyment were seen at any time point, although for women there was a significant decrease compared to the preoperative baseline for both groups.

Immune response

Five studies described some short-term differences in immune response (MRC CLASICC c 2001; Hong Kong d 2003; Zhou 2007; Hong Kong c 2000; COLOR 2 b 2011). They all reported different parameters, including C-reactive protein (CRP), white blood cell count (WBC) and Interleukin-6 (IL-6). Two studies reported on B-cell, T-cell, cortisol and natural-killer cell (NK-cell) levels.

MRC CLASICC c 2001 had the largest population (n = 161), but did not show any differences in T-cell, B-cell and NK-cell levels at day three. Zhou 2007 included 71 participants and the three other studies around 40 participants each. Hong Kong c 2000 showed higher levels of IL-6 and CRP, with a peak for IL-6 at two hours ($P < 0.001$) and CRP at 48 hours ($P < 0.01$) in the OTME group. The same results were shown by Zhou 2007, but they were measured at one and three days with a difference for IL-6 at day one

and for CRP at day one and three for the OTME group. Cortisol levels and WBC were also higher in the OTME group at day one. COLOR 2 b 2011 expressed results only as ratios compared to preoperative values and showed less increase in IL-6 level at two hours postoperatively in the LTME group. Cortisol, WBC and CRP did not show any differences at 2, 24 and 72 hours. Finally, Hong Kong d 2003 did not show any differences at days one and three for WBC, NK-cell, T-cell and B-cell levels, but for T-cell and B-cell levels there was less suppression in the LTME group at day eight.

Costs

An analysis of costs was included in five studies (Hong Kong a 2004; MRC CLASICC a 2005; King 2006; Braga 2007; Ng 2008). Data were too heterogeneous to be included in a meta-analysis. Braga 2007 only reported the difference in costs in which the benefits of LTME could not compensate for the additional operating room charges, with a mean difference of USD 351 more for LTME. The four other studies calculated the costs per participant randomised. King 2006 and MRC CLASICC a 2005 reported the median direct and indirect costs for LTME. King 2006 reported the costs at GBP 6344 for LTME and GBP 6786 for OTME resulting in a saving of GBP 353 for LTME while being the only study in this analysis that used a fast-track programme. MRC CLASICC a 2005 reported the opposite, with GBP 8259 for LTME and GBP 7820 for OTME, resulting in GBP 439 higher costs for LTME. Neither result achieved a statistically significant difference. Hong Kong a 2004 and Ng 2008 reported only the direct costs, with means of USD 9297 and USD 9588 for LTME and USD 7148 and USD 7517 for OTME with a significant difference of about USD 2000 in favour of OTME.

DISCUSSION

Summary of main results

Nine studies (n = 1877) reported on at least one of the long-term survival or recurrence outcomes and the meta-analyses as well as the separate studies showed similar long-term survival and recurrence rates for laparoscopic and open total mesorectal excision**.**

We found a mean difference in hospital stay of two days, with individual studies reporting a 0.5- to 5-day difference in favour of LTME. Schwenk 2005 found comparable results for colon cancer with a mean difference of 1.5 days in favour of the laparoscopic group. Seven studies standardised their postoperative protocol, but only two implemented an enhanced recovery programme.

Overall completeness and applicability of evidence

Benefits of laparoscopic surgery are attributable to causing less surgical trauma to the patient, which has a positive effect on surgery-induced immunosuppression. This can be demonstrated by taking measurements after surgery, with different peak moments for several parameters. The included studies in this review did not take measurements at the same time point, which may explain why not all of them could show differences in similar parameters. Reduced immunosuppression could be related to a lower complication rate and to shorter hospital stay, and may reduce development of postoperative metastasis (although this has yet to be shown in a randomised trial (Hogan 2011)).

The included RCTs include studies and subgroups of patients with low, mid and high rectal cancer and both APR and anterior resections with and without anastomosis. These differences can affect outcomes, especially the various techniques for low rectal resections can influence the circumferential margins and therefore local recurrences and survival. Lack of reporting of the CRM is an important issue with only eight out of fourteen studies describing this outcome. The number of retrieved lymph nodes is described by eleven studies but is more dependent on difference in high and low vascular ligations of the mesentery than on open or laparoscopic surgery. (Kessler 2013)

With a mean age between 44 and 72, three studies including T4 carcinoma and six offering neoadjuvant treatment in selected cases and a tumour localisation between 15 cm and the anal verge, there is a fair amount of heterogeneity among the included studies. Especially the early and smaller studies included a younger and healthier study population compared to the average rectal cancer patient. Of the four ongoing trials (n = 470 to 1100 participants), three (Kang 2010; ACTRN12609000663257; NCT00726622) require neoadjuvant treatment for selected stages of rectal cancer and the fourth (COLOR 2 a 2013) stratifies the randomisation for neoadjuvant treatment. This might influence both long term and short term outcomes as only six offered neoadjuvant therapy in this review. All ongoing studies include abdominoperineal resections as well as (low) anterior resections, but the maximum distance from the anal verge varies between 9 cm (Kang 2010), 12 cm (NCT00726622) and 15 cm (ACTRN12609000663257; COLOR 2 a 2013).

Another important difference between the included RCTs and current practise are the fast track recovery programmes such as the enhanced recovery after surgery (ERAS) programme. Only two included studies describe an enhanced recovery programme (King 2006; Lujan 2009). COLOR 2 a 2013 referred to local protocols, whereas the other two ongoing studies do not describe their postoperative protocol in the online summary. The LAFA trial (Vlug 2011) showed laparoscopic surgery in combination with fast track recovery resulted in the fastest recovery and hospital discharge compared to regular care and open surgery.

Quality of the evidence

Since 1998, 14 RCTs have been published to answer the question whether LTME results in better short-term results and at least

equal long-term oncological results. The quality of these studies varied extensively, as did the number of included participants. Although the total mesorectal excision principle has been established since 1986, treatment protocols have changed. Surgeons gained more experience in laparoscopic colon and rectal cancer surgery, fast-track protocols were introduced and neoadjuvant treatment became a standard of care in a proportion of cases. All of these factors are able to influence the long-term results of these trials; however they should influence both the laparoscopic and open groups equally, except for the learning curve for laparoscopic procedures.

The quality of the evidence for the most important outcomes was moderate (Summary of findings for the main comparison). This means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The main reason is the imprecision of the confidence intervals, they allow for a variability in odds ratios up to 40% on both sides, which contributes to an absolute increase or decrease of 6% in disease free survival, 5% in overall survival, 2% in local recurrences, and 3% in 30-day morbidity. The COLOR 2 a 2013 trial used a 5% margin for local recurrences for their non-inferiority design, therefore our results remain within those limits.

Potential biases in the review process

Publication bias is a threat for any systematic review. We believe we have missed no important randomised controlled trials after screening reference lists of included trials and other relevant studies and reviews, in addition to the extensive systematic searching of electronic databases and trials registers. We have described all registered ongoing trials.

In the current literature regarding learning curves in laparoscopic colorectal surgery, a wide range of numbers of procedures is reported until a flat curve is achieve, ranging from 11 to 15 colectomies (Simons 1995), 30 colorectal resections (Schlachta 2001) and 60 to 65 colectomies (Tekkis 2005). For the open total mesorectal excision (OTME) technique, the cut-off point for percentage of clear resection margins is defined as around 50 procedures (Oh 2011). This suggests that only the surgeons in Kang 2010 are assumed to have had sufficient experience for a good laparoscopic resection and results may further improve over time.

Agreements and disagreements with other studies or reviews

A meta-analysis of RCTs on laparoscopic and open colorectal surgery (Sammour 2011) has shown a higher intraoperative complication rate for laparoscopic surgery of 6.3% versus 3.9% for open surgery (OR)1.55, 95%CI 1.12 to 2.15). The rate of bowel perforations was 2.1% versus 0.9% (OR 2.28, 95% CI 1.27 to 4.10) across 3018 participants. These differences had limited effect on the outcome, with an average postoperative complication rate of 28%. Compared to the intraoperative complication rate of 11.3% in LTME versus 12.0% in OTME in four included studies in our review (n = 1618), we cannot confirm these previously reported complication rates for LTME.

The results of this review confirm what other colorectal and rectal trials have suggested: short-term results are similar with faster recovery in the LTME group and no statistically significant differences were found in the long-term oncological results. For rectal cancer, non-randomised trials have suggested oncological safe resections as presented in the previous version of this review (Fleshman 1999; Feliciotti 2003; Breukink 2006). Since then, several other reviews have been published describing the same results. Aziz 2006, Gao 2006, Anderson 2008 and Poon 2009 included mainly non-randomised trials, and Row 2010 was a literature review. Ohtani 2011, Huang 2011 and Trastulli 2012 were the first to include only randomised trials. However, Ohtani 2011 also included three non-randomised trials, Huang 2011 included only six trials and Trastulli 2012 nine trials, whereas this systematic review was able to identify 14. In addition, the Cochrane review of laparoscopic colorectal cancer (Kuhry 2008) presented separate meta-analyses for four included rectal cancer RCTs.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently moderate quality evidence that laparoscopic total mesorectal excision (TME) has similar effects to open TME on long term survival outcomes for the treatment of rectal cancer. The quality of the evidence was downgraded due to imprecision and we cannot rule out either approach being superior. There is moderate quality evidence that it leads to better short-term post-surgical outcomes in terms of recovery for non-locally advanced rectal cancer and shorter hospital stay. Currently results are consistent in showing a similar disease-free survival and overall survival, and for recurrences after at least three years and up to 10 years although due to imprecision we cannot rule out superiority of either approach. We await long-term data from a number of ongoing and recently completed studies to contribute to a more robust analysis of long-term disease free, overall survival and local recurrence.

Implications for research

The evidence presented in this systematic review is sufficient to establish the overall and long-term oncological safety of laparoscopic TME. However, at this moment the available data are still insufficient to confirm these results for subgroups such as abdominoperineal resections, following neoadjuvant therapy, in locally advanced disease and in combination with fast track recovery protocols.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Araujo 2003

Methods	Single-centre RCT Sao Paulo, Brazil Number of patients assessed for eligibility but not randomised: unknown Inclusion period: September 1997 to September 2000
Participants	n = 28 (LTME n = 13; OTME n= 15) Inclusion criteria: primary rectal cancer suitable for APR, incomplete response after chemoradiation Exclusion criteria: metastases Age (y): 59.1 vs 56.4 (mean) Dukes stage (%): A 39 vs 43; B 38 vs 21; C 23 vs 36; D 0 vs 0 Tumour location: distal rectum Follow-up: 47.2 months (mean)
Interventions	Laparoscopic vs open TME APR (%): 100 AR (%): 0 Colon (%): 0 Neoadjuvant therapy: all chemoradiation
Outcomes	No primary outcome stated Length of follow-up, local and distant recurrences Duration of surgery, need for transfusion, postoperative hospital stay, postoperative complications, need for reoperation, number of lymph nodes
Notes	Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"were randomised to undergo treatment"
Allocation concealment (selection bias)	Unclear risk	Unknown, moment of randomisation unknown
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described, intention-to-treat not described
Selective reporting (reporting bias)	High risk	No primary outcome stated, not all data given as described in Methods section No sample size calculation

Araujo 2003 (*Continued*)

Other bias	High risk	Published in a non-peer-reviewed journal, Low diversity with distal rectal cancer only Surgeon's experience unknown
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Surgical procedure described according to TME Postoperative protocol unknown
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Braga 2007

Methods	Single-centre RCT Milan, Italy Number of patients assessed for eligibility but not randomised: 28 Inclusion period: unknown
Participants	n = 168 (LTME n = 83; OTME n = 85) Inclusion criteria: age > 18, histologically confirmed rectal cancer, suitable for elective surgery Exclusion criteria: clinical infiltrative cancer, cardiovascular dysfunction, respiratory dysfunction, hepatic dysfunction, ongoing infection, plasma neutrophil level < 2 x10^9 Age (y): 62.8 vs 65.3 (mean) Dukes stage (%): A 30 vs 28; B 19 vs 22; C 38 vs 34; D 13 vs 15 Tumour location: rectum < 15 cm Follow-up: 53.6 months (mean)
Interventions	Laparoscopic vs open TME APR (%): 8 vs 13 AR (%): 92 vs 87 Colon (%): 0 Neoadjuvant therapy: chemoradiation (T3 only)
Outcomes	Primary outcome: Short-term postoperative morbidity Cost benefit analysis, quality of life, oncological outcome
Notes	Enlarged subgroup from Braga 2002 Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated list, sealed envelopes

Braga 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	Opened before induction of anaesthesia
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Survival given per stage, not combined and only in Kaplan-Meier curve Sample size calculation performed
Other bias	Low risk	Same surgical team, "well experienced"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure according to TME Standardised postoperative protocol and discharge criteria, no enhanced recovery
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Complications registered by independent team, weekly clinic visits until 30 days

COLOR 2 a 2013

Methods	Multicentre RCT (30 academic centres) Belgium, Canada, Denmark, Germany, The Netherlands, Spain, South Korea, Sweden Number of patients assessed for eligibility but not randomised unknown Inclusion period: January 2004 to May 2010
Participants	n = 1044 (LTME n = 699; OTME n = 345) Inclusion criteria: Solitary rectal cancer at colonoscopy or barium enema x-ray, distal border within < 15 cm of anal verge, suitable for elective surgery, informed consent Exclusion criteria: Metastatic disease, local resection, T4 tumours, T3 tumours with margins < 2 mm to endopelvic fascia on CT or MRI, other malignancy than adeno-carcinoma, participant < 18 y, acute intestinal obstruction, > 1 colorectal tumour, FAP, HNPCC, Crohn's disease or ulcerative colitis, ASA > III, pregnancy Age (y): 66.8 vs 65.8 (mean) Gender (male): 64% vs 61% Dukes stage (%): A 30 vs 29; B 31 vs 33; C 38 vs 38 Tumour location: rectum <15cm Follow-up: short term data, 28 days
Interventions	Laparoscopic vs open TME APR (%): 29 vs 23 LAR (%): 70 vs 77 Colon (%): 0 Neoadjuvant therapy: radiotherapy 59% vs 58%, chemotherapy 32% vs 34%

COLOR 2 a 2013 (*Continued*)

Outcomes	Primary outcome: local recurrences at 3 years (will be published later) Secondary outcomes: Operating time, conversion rate, blood loss, postoperative recovery of gastrointestinal function, postoperative pain medication, length of hospital stay, morbidity and mortality within 28 days after surgery, histopathological outcomes and anastomotic leakage
Notes	COLOR 2 b 2011 presents a local subgroup of 40 participants focusing on inflammatory response markers Funding or conflicts of interest: Funding by Ethicon Endo-Surgery Europe, Swedish Cancer Foundation, West Gothia Region and Sahlgrenska University Hospital. The authors declare to have no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised via online register with randomisation list stratified for centre, tumour location and preoperative radiotherapy
Allocation concealment (selection bias)	Low risk	Central randomisation after registration in database
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Sample size calculation performed
Other bias	Low risk	Surgeon's technique and resection quality assessed prior to enrolment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Local standardised postoperative protocols
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Objective measurements

COLOR 2 b 2011

Methods	Single-centre RCT (University Hospital) Amsterdam, The Netherlands Number of patients assessed for eligibility but not randomised unknown Inclusion period: June 2006 to December 2008
Participants	n = 40 (LTME n = 22; OTME n = 18) Inclusion criteria: Solitary rectal cancer at colonoscopy or barium enema x-ray, distal border within < 15 cm of anal verge, suitable for elective surgery, informed consent Exclusion criteria: Metastatic disease, local resection, T4 tumours, T3 tumours with margins < 2 mm to endopelvic fascia on CT or MRI, other malignancy than adenocarcinoma, patient < 18 y, acute intestinal obstruction, > 1 colorectal tumour, FAP, HNPCC, Crohn's disease or ulcerative colitis, ASA > III, pregnancy Age (y): 64 vs 67 (median) Gender (male): 73% vs 67% Dukes stage (%): A 50 vs 27.8; B 22.3 vs 38.9; C 22.3 vs 22.2 Tumour location: rectum < 15 cm Follow-up: 72 h
Interventions	Laparoscopic vs open TME APR (%): 18 vs 28 LAR (%): 82 vs 72 Colon (%):0 Neoadjuvant therapy: unknown
Outcomes	Primary outcomes :Postoperative inflammatory response (IL-6, IL-8, CRP), immune status (WBC, HLA-DR), stress response (cortisol, prolactin, growth hormone) Secondary outcomes: Hospital stay, complication rate, lymph nodes resected
Notes	Local subgroup of COLOR 2 a 2013 Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised within COLOR II trial, computer-generated list, stratified for preoperative radiotherapy and location of tumour
Allocation concealment (selection bias)	Low risk	Randomisation after entry of participant details in database
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No sample size calculation for this sub study

COLOR 2 b 2011 (*Continued*)

Other bias	High risk	Surgeon's experience: unknown
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Standardised postoperative protocol per hospital
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measurements

Hong Kong a 2004

Methods	Two-centre RCT Hong Kong, China Number of patients assessed for eligibility but not randomised: 422 Inclusion period: September 1993 to October 2002
Participants	n = 403 (LTME n = 203; OTME n = 200) Inclusion criteria: sigmoid and upper rectal cancer Exclusion criteria: distance from anal verge < 5 cm, tumour size > 6 cm, T4 rectal cancer, previous abdominal operations in lower pelvis, intestinal obstruction or perforation, metastatic disease, no informed consent Age (y): 67.1 vs 66.5 (mean) Dukes stage (%): A 15 vs 14; B 35 vs 37; C 32 vs 35; D 18 vs 14 Tumour location: sigmoid and rectum >5 cm Follow-up: 52.7 vs 49.2 months (median, participants alive)
Interventions	Laparoscopic vs open APR (%): 0 LAR (%): 100 Colon (%):0 (Neo)adjuvant therapy: 8.4 vs 13.5 adjuvant radiotherapy, 18.7 vs 25.0 adjuvant chemotherapy
Outcomes	Primary outcome: 5-year disease-free survival, Secondary outcomes: operation time, disposable instruments used, blood loss, transfusion requirement, analgesic requirement, visual analogue scale, time to flatus, time to opening bowel, time to normal diet, duration of hospital stay, 30-day mortality, morbidity
Notes	Short-term data rectosigmoid subgroup Funding or conflicts of interest: The authors declare no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hong Kong a 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Kept concealed by an independent operating theatre co-ordinator
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up described, intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Sample size calculation performed Ratio between sigmoid and rectal cancer not given
Other bias	High risk	High diversity rectosigmoid carcinoma, ratio not given Surgeon's experience: "Skilled in both laparoscopic and open colorectal surgery"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure described Standardised postoperative protocol (no enhanced recovery programme)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Hong Kong b 2009

Methods	Two-centre RCT Hong Kong, China Number of patients assessed for eligibility but not randomised unknown Inclusion period: September 1993 to October 2002
Participants	n = 153 (LTME n = 76; OTME n = 77) Inclusion criteria: upper rectal cancer Exclusion criteria: distance from anal verge < 5 cm, tumour size > 6 cm, T4 rectal cancer, previous abdominal operations in lower pelvis, intestinal obstruction or perforation, metastatic disease, no informed consent Age (y): 66.5 vs 65.7 (mean) Dukes stage (%): A 14 vs 17; B 38 vs 38; C 26 vs 36; D 21 vs 9 Tumour location: Upper rectum 12 - 15 cm Follow-up: 112.5 vs 108.8 months (median, living participants)
Interventions	Laparoscopic vs open TME APR (%): 0 LAR (%): 100 Colon (%):0 Adjuvant therapy (%): 14.5 vs 32.5 chemotherapy, 17.1 vs 27.3 radiotherapy

Hong Kong b 2009 (*Continued*)

Outcomes	Primary outcome: Long-term morbidity (adhesion-related obstruction, incisional hernia) Secondary outcomes: Recurrence and survival
Notes	Long-term data upper rectal cancer subgroup of Hong Kong a 2004 Short-term mortality not included in long-term morbidity and mortality analysis Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	as Hong Kong a 2004
Allocation concealment (selection bias)	Low risk	as Hong Kong a 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up described, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Low diversity with upper rectal subgroup
Other bias	High risk	as Hong Kong a 2004
Blinding of participants and personnel (performance bias) All outcomes	Low risk	as Hong Kong a 2004
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Hong Kong c 2000

Methods	Single-centre RCT Hong Kong, China Number of patients assessed for eligibility but not randomised unknown Inclusion period: September 1996 to April 1998
Participants	n = 34 (LTME n = 17 ; OTME n = 17) Inclusion criteria: sigmoid and upper rectal cancer Exclusion criteria: distance from anal verge < 5 cm, tumour size > 6 cm, T4 rectal cancer, previous abdominal operations in lower pelvis, intestinal obstruction or perforation, metastatic disease, no informed consent Age (y): 67.0 vs 66.9 (mean) Dukes stage (%): A 0 vs 0; B 59 vs 53; C 41 vs 47; D 0 vs 0 Tumour location: sigmoid and rectum

Hong Kong c 2000 (*Continued*)

	Follow-up: 22.6 vs 20.5 months (median)	
Interventions	Laparoscopic vs open APR (%): 0 LAR (%): 100 Colon (%):0	
Outcomes	Primary outcome: cytokine and CRP response	
Notes	Smaller subgroup rectosigmoid Hong Kong a 2004 Funding or conflicts of interest: No statement	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	as Hong Kong a 2004
Allocation concealment (selection bias)	Low risk	as Hong Kong a 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Sample size calculated
Other bias	High risk	High diversity with sigmoid and rectum carcinoma, ratio not given Low conversion rate compared to Hong Kong a 2004 Surgeon's experience: "Skilled in both laparoscopic and open colorectal surgery"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	as Hong Kong a 2004
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measurements

Hong Kong d 2003

Methods	Single-centre RCT Hong Kong, China Number of patients assessed for eligibility but not randomised unknown Inclusion period: June 1998 to August 1999
Participants	n = 40 (LTME n = 20; OTME n = 20) Inclusion criteria: sigmoid and upper rectal cancer Exclusion criteria: distance from anal verge < 5 cm, tumour size > 6 cm, T4 rectal cancer, previous abdominal operations in lower pelvis, intestinal obstruction or perforation, metastatic disease, no informed consent Age (y): 68.2 vs 69.1 (mean) Dukes stage (%): A 5 vs 5, B 50 vs 55, C 45 vs 40, D 0 vs 0 Tumour location: sigmoid and rectum Follow-up: 8 days
Interventions	Laparoscopic vs open APR (%): 0 LAR (%): 100 Colon (%):0
Outcomes	Primary outcome: lymphocyte subpopulation and natural killer cell cytotoxicity
Notes	Smaller subgroup rectosigmoid Hong Kong a 2004 Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	as Hong Kong a 2004
Allocation concealment (selection bias)	Low risk	as Hong Kong a 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing data reported, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Sample size calculated
Other bias	High risk	High diversity rectosigmoid carcinoma, ratio not given Surgeon's experience: "Skilled in both laparoscopic and open colorectal surgery"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	as Hong Kong a 2004

Hong Kong d 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measurements

Kang 2010

Methods	Multicenter RCT (3 centres) Seoul, South Corea Number of patients assessed for eligibility but not randomised: 39 Inclusion period: April 2006 to August 2009
Participants	n = 340 (LTME n = 170; OTME n =170) Inclusion criteria: Mid and low rectal cancer, after preoperative chemoradiation Exclusion criteria: Distant metastasis, another malignancy, severe cardiac or pulmonary disease, pregnancy, severe medical disease, intestinal obstruction or perforation Age (y): 57.8 vs 59.1 (mean) Dukes stage (%): unknown (cT3 N0-2 M0) Tumour location: mid or lower rectum < 9cm Follow-up: 3 months Response rate for questionnaire 75% vs 77%
Interventions	Laparoscopic vs open TME APR (%): 11.2 vs 14.1 LAR (%): 88.8 vs 85.9 Colon (%): 0 Neoadjuvant therapy: All neoadjuvant chemoradiotherapy and recommended 4 months adjuvant therapy
Outcomes	Primary outcome: 3-year disease-free survival Secondary outcomes: TME quality, CRM, lymph nodes, distance anal verge, surgical time, length of incision, tumour size, gastrointestinal recovery, hospital stay, complications, quality of life
Notes	Long-term data expected in 2013 Funding or conflicts of interest: National cancer centre, South Corea. The authors declared no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Telephone trial co-ordinator, block permutation approach
Allocation concealment (selection bias)	Unclear risk	Telephone trial co-ordinator, moment of randomisation unknown

Kang 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No missing data Sample size calculation performed
Other bias	Low risk	Low diversity with mid/low rectal cancer cT3N0-2 Surgeon's experience: median 75 laparoscopic resections (28 - 150), live demonstrations and video assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure according to TME Standardised postoperative protocol, no enhanced recovery
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pathologists blinded

King 2006

Methods	Single-centre RCT Yeovil, United Kingdom Number of patients assessed for eligibility but not randomised: 32 January 2002 to March 2004
Participants	n = 62 (LTME n = 41; OTME n = 19) (rectal n = 19) Inclusion criteria: adenocarcinoma of the colon or rectum Exclusion criteria:Non-elective admission, distant metastases, age < 18, pregnancy, no informed consent, unsuitable for epidural anaesthesia (from 2nd year on) Age (y): 72.3 vs 70.4 (mean) Dukes stage (%): A 22.0 vs 5.3; B 46.3 vs 57.9; C 31.7 vs 36.8 Tumour location: colon and rectum Follow-up: 6 weeks/12 months Compliance rate for HRQL questionnaires over 95% and response rate of 80%
Interventions	Laparoscopic vs open TME APR (%): 7.3 vs 5.3 LAR (%): 29.3 vs 21.1 Colon (%): 63.4 vs 73.7 Neoadjuvant therapy:12% neoadjuvant chemotherapy, 35% adjuvant chemotherapy
Outcomes	Primary outcome: Hospital stay Secondary outcomes: Morbidity, analgesia requirement, antiemetic requirement, re-admission stay, quality of life, cost, disease recurrence, stoma closure, adjuvant chemotherapy, health-related quality of life and functional outcomes Study-specific questionnaire for functional recovery

King 2006 (*Continued*)

Notes	Funding or conflicts of interest: National Health Service Developments in the Organization of Care Projects Grant Yeovil District Hospital has received funds from Ethicon Endosurgery to support postgraduate training in laparoscopic surgery. One author is supported by a Medical Research Council Clinician Scientist Award

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Telephone trial co-ordinator, moment of randomisation unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up described, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Data reported according to methods described No sample size for these outcomes calculated
Other bias	Unclear risk	High diversity, all colorectal patients Single surgeon, experience unknown
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure described according to TME Postoperative protocol according to enhanced recovery programme
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collection team

Liang 2011

Methods	Single-centre RCT Taiyuan, China Number of patients assessed for eligibility but not randomised: 3 Inclusion period: May 2004 and April 2008
Participants	n = 343 (LTME n = 169; OTME n = 174) Inclusion criteria: rectal cancer confirmed by pathological examination, written informed consent. Suitable for LAR or APR Exclusion criteria: metastatic disease, BMI > 30, acute intestinal obstruction, previous

Liang 2011 (*Continued*)

	abdominal surgery, neoadjuvant chemotherapy Age (y): 57.3 vs 57.4 (mean) Dukes stage (%): A 5.3 vs 4.0; B 42.6 vs 48.3; C 52.1 vs 47.7; D 0 vs 0 Tumour location: rectum Follow-up: 44 months (median)
Interventions	Laparoscopic versus open TME APR (%): 49.1 vs 40.2 LAR (%): 50.9 vs 59.8 Colon(%): 0 (neo)adjuvant therapy: neoadjuvant excluded, adjuvant unknown
Outcomes	Primary outcome: 3-year survival Secondary outcomes: Number of lymph nodes removed, length of specimen, distance between inferior border of tumour and incised margin in LAR, time to first discharge, bowel movement and fluid intake, infectious complications, anastomotic leakage, anastomotic stenosis, deep vein thrombosis, 1-year survival
Notes	Funding or conflicts of interest: No competing financial interests declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not mentioned
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes, day before surgery
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up described, intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Sample size calculation not performed
Other bias	Unclear risk	Distance for anal verge unknown Single surgical team
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure not described, TME principles followed Standardised postoperative protocol (no enhanced recovery programme)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Complications assessed by reviewer unaware of treatment group

Liu 2010

Methods	Single-centre RCT Hangzhou, China Number of patients assessed for eligibility but not randomised unknown Inclusion period: February 2005 and October 2008
Participants	n = 186 (LTME n = 98; OMTE n = 88) Inclusion criteria: rectal carcinoma Exclusion criteria: synchronous cancer, acute intestinal obstruction or perforation Age (y): 59.3 vs 61.5 (mean) Dukes stage (%): A 32.7 vs 28.4 B 35.7 vs 34.1 C 27.6 vs 26.1D 4.1 vs 11.4 Tumour location: rectum Follow-up: 16.3 months (mean)
Interventions	Laparoscopic vs open TME, hand-assisted APR (%): 12.2 vs 15.9 LAR (%): 83.7 vs 79.5 Colon (%): 0 Neoadjuvant therapy: unknown
Outcomes	Primary outcome: "safety and efficacy" Secondary outcomes: Duration of surgery, incision length, blood loss, analgesia requirement, time to flatus, time to oral fluids, hospital stay, complications, number of lymph nodes
Notes	Hand-assisted laparoscopy Funding or conflicts of interest: The authors declared no conflicts of interest in relation to this article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	High risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described, intention-to-treat irrelevant with no conversions
Selective reporting (reporting bias)	High risk	Sample size calculation not performed
Other bias	Unclear risk	Distance from anal verge unknown Single surgical team, experience unknown
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgical procedure described, TME unknown No standardised postoperative protocol

Liu 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Lujan 2009

Methods	Single-centre RCT Murcia, Spain Number of patients assessed for eligibility but not randomised: 31 Inclusion period: January 2002 and February 2007
Participants	n = 204 (LTME n = 103; OTME n = 101) Inclusion criteria: Mid and low rectal adenocarcinoma Exclusion criteria: Locally advanced disease, FAP, emergency surgery Age (y): 67.8 vs 66.0 (mean) Dukes stage (%): A 10.9 vs 14.6 B 34.7 vs 37.9 C 44.6 vs 42.7 D 9.9 vs 4.9 Tumour location: rectum < 9cm Follow-up: 32.8 vs 34.1 months (mean)
Interventions	Laparoscopic vs open TME APR (%): 23.8 vs 21.4 LAR (%): 76.2 vs 78.6 Colon (%): 0 Neoadjuvant therapy: Stage II and III neoadjuvant chemoradiotherapy, stage III and IV adjuvant chemotherapy
Outcomes	Primary outcome: number of lymph nodes harvested Secondary outcomes: 2- and 5-year local recurrence, survival, circumferential margin involvement, complication rate, hospital stay
Notes	Funding or conflicts of interest: The authors declare no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed envelope until day of operation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up described, intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Non-radical resections excluded from analysis

Lujan 2009 (*Continued*)

		Sample size calculation performed
Other bias	Unclear risk	Single surgical team, experience unknown
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure described according to TME Standardised postoperative protocol within enhanced recovery program
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Single experienced pathologist

MRC CLASICC a 2005

Methods	Multicenter RCT (27 centres) United Kingdom Number of patients assessed for eligibility but not randomised unknown Inclusion period: July 1996 to July 2002
Participants	n = 794 (381 rectal LTME n = 253; OTME n = 128) Inclusion criteria: Colorectal carcinoma suitable for right hemicolectomy, left hemicolectomy, sigmoid, anterior resection, APR Exclusion criteria: Transversum, cardiac or pulmonary disease, acute intestinal obstruction, other malignant disease in past 5 years, synchronous adenocarcinoma, pregnancy, associated GI disease needing surgical intervention Age (y): 69 vs 69 (mean) Dukes stage (%): A 16.7 vs 16.4; B 34.6 vs 36.9 C 37.1 vs 34.7 Tumour location: colon and rectum Follow-up: 3 months, 3 years ,5 years and 10 years
Interventions	Laparoscopic vs open colorectal surgery APR (%): 13 vs 12 LAR (%): 37 vs 36 Colon (%): 50 vs 52 Neoadjuvant therapy(%): Adjuvant radiotherapy 5.5 vs 6.7 and adjuvant chemotherapy 28.1 vs 28.7
Outcomes	Primary outcomes: resection margins, Dukes C2 tumours, in-hospital mortality, 3 and 5 year OS/DFS and local recurrence Secondary outcomes: Complication rates, quality of life, transfusion requirements, distant and port site recurrences at 3 and 5 years, short term costs
Notes	Short term results, short-term costs, 3-year, 5-year and 10-year data of the CLASICC Trial across 5 different publications. No reply to request for additional data for meta-analysis Funding or conflicts of interest: The authors declare to have no conflict of interest. The trial was funded by the UK Medical Research Council

MRC CLASICC a 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Telephone trial co-ordinator, stratified by surgeon, site of surgery, presence of metastases and preoperative radiotherapy
Allocation concealment (selection bias)	Low risk	Telephone trial co-ordinator
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up and missing data described, intention-to-treat analysis
Selective reporting (reporting bias)	High risk	High rate of missing participant and pathological data, up to 13% Sample size calculation performed, but not reached
Other bias	Low risk	High diversity with colorectal cancer patients, specific rectal cancer data published separately Surgeons' experience: a minimum of 20 laparoscopic resections
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgical procedure according to surgeons current practice No standardised postoperative protocol described, enhanced recovery unknown
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data monitoring committee

MRC CLASICC b 2005

Methods	Multicenter RCT (27 centres) United Kingdom Number of patients assessed for eligibility but not randomised unknown Inclusion period: July 1996 to July 2002
Participants	n = 148 (LTME n = 98; OTME n =50), n = 347 including laparoscopic colon group Age (y): 66 vs 65 (mean) Questionnaire response rate 71.2% of 347 participants eligible for inclusion Tumour location: rectum > 5 cm
Interventions	Laparoscopic colon versus laparoscopic rectal versus open rectal

MRC CLASICC b 2005 (*Continued*)

Outcomes	Primary outcome: Overall function score for sexual and bladder function I-PSS, IIEF, FSFI questionnaires over the last 4 weeks at a single time point within or after 12 months (up to 76 months) EORTC module QLQ-CR38 questionnaire items at 2 weeks and 3, 6, 18 months
Notes	Subgroup of MRC CLASICC a 2005 Converted patients analysed as open surgery Some comparisons only between laparoscopic rectal and laparoscopic colon Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	as MRC CLASICC a 2005
Allocation concealment (selection bias)	Low risk	as MRC CLASICC a 2005
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Most data only addressed in text, numbers not given Sample size calculated for questionnaire outcome
Other bias	Unclear risk	No other bias identified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unknown
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Validated questionnaires

MRC CLASICC c 2001

Methods	Single-centre RCT Singapore Number of patients assessed for eligibility but not randomised unknown Inclusion period: March 1997 to August 1999
Participants	n = 236 (LTME n = 118; OTME n = 118) Inclusion criteria: > 18 y, elective surgery, left hemi colon, sigmoid or rectum Exclusion criteria: transverse colon, contraindication for pneumoperitoneum, acute intestinal obstruction, any malignancy in previous 5 y, synchronous adenocarcinomas and

MRC CLASICC c 2001 (*Continued*)

	pregnancy Age (y): 64 vs 62 (median) Gender (%): male 52 vs 59 Dukes stage (%): A 8 vs 7; B 41 vs 45; C 38 vs 38; D 13 vs 10 Tumour location: colon and rectum Follow-up: 3 days for immune response
Interventions	Laparoscopic vs open colorectal surgery APR (%): 85 vs 85 AR (%): 6 vs 5 Colon (%):9 vs 10 Neoadjuvant treatment: unknown
Outcomes	Primary outcome: T-cell number Secondary outcomes: CD4, CD8, humoral response, complement level, phagocytosis function
Notes	Singapore subgroup MRC CLASICC a 2005 Funding or conflicts of interest: Funding by the National Reseach Council Singapore, no statement on conflict of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central telephone randomisation
Allocation concealment (selection bias)	Low risk	Blocks of 6 and 4
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis, missing data addressed Sample size calculation performed
Selective reporting (reporting bias)	High risk	High rate of missing data (12 participants preoperative, 44 postoperative)
Other bias	Unclear risk	1:1 randomisation, in contrast to 2:1 randomisation in CLASICC Trial Surgeons' experience as MRC CLASICC a 2005 > 20 procedures
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure described according to TME
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measurements

Ng 2008

Methods	Single-centre RCT Hong Kong, China Number of patients assessed for eligibility but not randomised: 54 Inclusion period: September 1994 to February 2005
Participants	n = 99 (LTME n = 51; OTME n = 48) Inclusion criteria: Low rectal cancer, eligible for APR Exclusion criteria: Tumour > 6 cm, clinical infiltrative cancer, recurrent disease, no informed consent, intestinal obstruction or perforation Age (y): 63.7 vs 63.5 (mean) Dukes stage (%): A 5 vs 4; B 6.5 vs 4; C 8.5 vs 10; D 5.5 vs 6 Tumour location: low rectal cancer < 5 cm Follow-up 87.2 vs 90.1 months (median, participants alive)
Interventions	Laparoscopic vs open TME APR (%): 100 LAR (%): 0 Colon (%):0 Neoadjuvant therapy not offered, adjuvant unknown
Outcomes	Primary outcome: Analgesic requirement and postoperative recovery Secondary outcomes: Recurrence and survival at 5 years Operative time, blood loss, disposable instruments, transfusion, analgesic requirement, pain score, time to flatus, time to bowel movement, time to diet, time to walk independently, hospital stay, morbidity, mortality, circumferential margin involvement, lymph nodes
Notes	Low and mid rectal cancer subgroup Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Kept concealed by an independent operating theatre co-ordinator
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis, loss to follow-up described
Selective reporting (reporting bias)	Low risk	Follow-up for participants alive Sample size calculation performed
Other bias	Low risk	Surgeons' experience: "surgeons experienced in both laparoscopic and colorectal surgery"

Ng 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure, TME unknown Standardised postoperative protocol, no enhanced recovery
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Pechlivanides 2007

Methods	Multicenter RCT (3 centres) Crete and Athens, Greece Number of patients assessed for eligibility but not randomised unknown Inclusion period: unknown
Participants	n = 73 (LTME n = 34; OTME n = 39) Inclusion criteria: low rectal carcinoma < 12 cm Exclusion criteria: Tumours extending to the pelvic walls or organs Age (y): 72 vs 69 (median) Dukes stage (%): only T stage given Tumour location: mid and low rectal carcinoma < 12 cm Follow-up: no follow-up
Interventions	Laparoscopic vs open TME APR (%): 20.6 vs 10.3 LAR (%):79.4 vs 89.7 Colon (%): 0 (Neo) adjuvant therapy: Short-course radiotherapy or long-course chemoradiation
Outcomes	Primary outcome: Oncological clearance (number of lymph nodes) Secondary outcomes: pathological stage, extent of tumour invasion
Notes	Funding or conflicts of interest: No statement

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	High risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up and intention-to-treat not described Only one outcome Limited details on inclusion and exclusion

Pechlivanides 2007 (*Continued*)

		criteria
Selective reporting (reporting bias)	Unclear risk	No sample size calculation
Other bias	High risk	Significantly less anastomoses and more ileostomies in the laparoscopic group Surgeon's experience: "most experienced surgeon"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical procedure described according to TME Postoperative protocol irrelevant for outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding described

Zhou 2004

Methods	Single-centre RCT Sichuan, China Number of patients assessed for eligibility but not randomised unknown Inclusion period: June 2001 to September 2002
Participants	n = 171 (LTME n = 82; OMTE n = 89) Inclusion criteria: primary rectal cancer with lowest margin of tumour located under the peritoneal reflection and 1.5 cm above the dentate line Exclusion criteria: rectal cancer of other pathological type (e.g. lymphoma), emergency surgery, Dukes D tumours with local infiltration affecting adjacent organs, participants unwilling to take part in the study Age (y): 45 vs 44 (mean) Dukes stage (%): A 6 vs 7; B 12 vs 9; C 77 vs 76; D 5 vs 8 Tumour location: mid and low rectal cancer (lowest margin 1 - 8 cm) Follow-up: range 1 - 16 months
Interventions	Laparoscopic vs open TME APR (%): 0 LAR (%): 100 Colon (%):0 (Neo)adjuvant therapy: not described
Outcomes	Primary outcome: Feasibility and efficacy and short-term outcomes Morbidity, mortality, duration of surgery, blood loss, analgesia requirement, time to flatus, time to intake, time to defecation, pain score, hospital stay
Notes	Funding or conflicts of interest: Funded by a National Outstanding Youth Foundation of China grant

Zhou 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The grouping was randomised
Allocation concealment (selection bias)	High risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up and intention-to-treat analysis unknown, conversion rate unknown
Selective reporting (reporting bias)	High risk	No sample size calculation
Other bias	Unclear risk	Surgeons' experience: 4 colorectal surgeons, experience unknown
Blinding of participants and personnel (performance bias) All outcomes	High risk	No standardised postoperative protocol described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Zhou 2007

Methods	Single-centre RCT Shijiazhuang, China Number of patients assessed for eligibility but not randomised unknown, but 4 excluded after randomisation Inclusion period: December 2004 to April 2007
Participants	n = 71 (LTME n = 36; OTME n = 35) Inclusion criteria: Histologically confirmed rectal cancer, suitable for elective surgery Exclusion criteria: Neoadjuvant treatment, metastases, postoperative anastomotic leakage Age (y): 56 vs 55 (mean) Dukes stage (%): A 6 vs 6; B 47 vs 43; C 47 vs 51 Tumour location: rectal cancer > 5 cm Follow-up: 5 days
Interventions	Laparoscopic vs open TME APR (%): 0 LAR (%): 100 Colon (%): 0 Neoadjuvant therapy is exclusion criteria

Zhou 2007 (*Continued*)

Outcomes	Primary outcome not stated Outcomes: Body temperature, WBC count, CRP level, Cortisol level, IL-6 level, VAS score at -1, 1, 3 and 5 days
Notes	Article translated from Chinese Funding or conflicts of interest: Science and Research Fund of The Second Hospital of Hebei Medical University

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random allocation
Allocation concealment (selection bias)	Unclear risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	High risk	Conversion and intention-to-treat unknown
Selective reporting (reporting bias)	Unclear risk	No sample size calculation
Other bias	High risk	Surgeon's experience: unknown
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unknown
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measurements

APR: abdominoperineal resection
AR: anterior resection
ASA: American Society of Anaesthesiologists
CI: Confidence interval
CRP: C-reative protein
CT: computed tomography
EORTC: European Organization for the Research and Treatment of Cancer
FAP: familial adenomatous polyposis
FSFI: Female sexual function index
HLA-DR: Human Leukocyte Antigen D related
HNPCC: hereditary non-polyposis colorectal cancer
HRQL: health-related quality of life
IIEF: Internation index of erectile function
I-PSS: International prostate symptom score
LAR: lower anterior resection

MRI: magnetic resonance imaging
QLQ-CR38: Quality of life questionnaire - colorectal cancer-specific
TME: total mesorectal excision
VAS: visual analogue scale
WBC: white blood cells

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Braga 2002	Colorectal benign disease included, extended subgroup of rectal cancer participants described in Braga 2007
Braga 2005	Data on colorectal participants, extended subgroup of rectal cancer participants described in Braga 2007
JCOG 0404 2005	Colon cancer including rectosigmoid, rectal cancer excluded.
Kim 1998	Mid and low rectum excluded, number of upper rectum within proctosigmoid group unclear
LaFa 2011	Unknown number of rectal cancer participants included (anterior resection, left and right colectomy)
LAPKON II 2009	Colorectal participants, unknown number of rectal carcinoma > 12 cm included
Leung 1999	Only partially randomised and no intention-to-treat analysis
Liu 2009	No TME performed (D3 lymphadenectomy)
Milsom 1998	Benign disease included, no separate analysis on rectal cancer
Mirza 2008	Almost all participants were randomised within 2 other trials (MRC CLASICC a 2005; King 2006), not fully randomised
Morris 2011	Comparison between CLASICC Trial data and national registry
Pan 2007	Surgeon in steep learning curve during study. Significant differences in outcome between early and late inclusion groups. No numerical outcomes provided in abstract, no full-text available
Polle 2007	Benign disease and familial polyposis coli participants included
Schwenk 1998	Sphincter-preserving resection with TME is exclusion criterion
Stead 2000	Economic comparison between UK and USA trials
Yamamoto 2008	Non-randomised, single arm phase II trial

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12609000663257

Trial name or title	A La CaRT: Australasian Laparoscopic Cancer of the Rectum Trial A phase III prospective randomised trial comparing laparoscopic-assisted resection versus open resection for rectal cancer
Methods	Randomised controlled trial Target sample size: 470
Participants	Inclusion criteria: Histological diagnosis of adenocarcinoma of the rectum (<15cm from the anal verge as measured by rigid sigmoidoscopy), T 1-3 N0 M0, T1-3 N1 M0 or T1-3 N0-1 M1 disease as determined by pre-treatment CT scans and pelvic MRI or EUS. For patients with T3 or N1 disease, completion of pre-operative 5FU-based chemotherapy and/or radiation therapy. Capecitabine may be substituted for 5FU, Age >18 years, ECOG Performance Status: 0, 1 or 2, Written informed consent, Life expectancy of at least 12 weeks Exclusion criteria: Medical or psychiatric conditions that compromise the patient's ability to give informed consent or comply with the study protocol. Pregnancy or breast feeding. Any uncontrolled concurrent medical condition. Any co-morbid disease that would increase risk of morbidity. Participation in any investigational drug study within the previous 4 weeks. Evidence of T4 disease extending to circumferential margin of rectum or invading adjacent organs. Evidence of systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude surgery, or other severe incapacitating disease, ASA IV or ASA V. History of conditions that would preclude use of a laparoscopic approach (e.g. multiple previous major laparotomies, severe adhesions) . Concurrent or previous invasive pelvic malignancy (cervical, uterine and rectal) within five years prior to registration
Interventions	Laparoscopic-assisted resection versus open resection
Outcomes	To determine whether laparoscopic-assisted resection is not inferior to open rectal resection as a safe, effective oncologic approach to rectal cancer and secondary from a patient related benefit perspective, based on morbidity, mortality associated with surgery, disease-free survival and disease recurrence and quality of life
Starting date	March 2010
Contact information	Dr. Andrew Stevenson, c/o A La CaRT Trial Coordinator NHMRC Clinical Trials Centre Locked Bag 77, Camperdown, 1450, Australia. alacart@ctc.usyd.edu.au
Notes	Patient recruitment ongoing

NCT00726622

Trial name or title	A phase III prospective randomized trial comparing laparoscopic-assisted resection versus open resection for rectal cancer - ACOSOG Z6051
Methods	Randomised controlled trial Target sample size: 650 Follow-up 5 years

NCT00726622 (*Continued*)

Participants	Inclusion: Histologically confirmed adenocarcinoma of the rectum (<12 cm from the anal verge), T3, N0, M0 or T1-3, N1-2, M0 disease by pre-neoadjuvant therapy CT scans and pelvic MRI or transrectal ultrasound. Completed neoadjuvant fluorouracil-based chemotherapy and/or radiotherapy within the past 4 weeks (Capecitabine may have been substituted for fluorouracil), ECOG performance status 0 - 2, Exclusion: T4 disease, severe incapacitating disease (i.e., ASA IV or ASA V), systemic disease (e.g., cardiovascular, renal, or hepatic) that would preclude surgery, evidence of conditions (e.g., multiple prior major laparotomies or severe adhesions) that would preclude use of a laparoscopic approach, pregnancy, Body mass index > 34, other invasive pelvic malignancy (cervical, uterine, or rectal) within the past 5 years, history of psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements
Interventions	Laparoscopic versus open rectal surgery
Outcomes	Primary outcomes: Circumferential margin > 1 mm, Distal resected margin > 2 cm (or > 1 cm with clear frozen section in the low rectum), Completeness of total mesorectal excision Secondary outcomes: Patient-related benefit, disease-free survival (2 years), Local pelvic recurrence rates, overall survival, quality of life, sexual function and bowel function
Starting date	August 2008
Contact information	James Fleshman, MD. American College of Surgeons Oncology Group. fleshman@wustl.edu
Notes	Patient recruitment ongoing until Dec 2013

DATA AND ANALYSES

Comparison 1. Survival and recurrences

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease-free survival	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 10-year	1	130	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.51, 3.06]
1.2 5-year	4	943	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.76, 1.38]
1.3 3-year	1	326	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.67, 1.74]
2 Overall survival	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 10-year	2	534	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.80, 1.65]
2.2 5-year	4	987	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.87, 1.52]
2.3 3-year	2	682	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.70, 1.42]
3 Local recurrences	8	1538	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.57, 1.39]
3.1 5-year	5	963	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.49, 1.81]
3.2 3-year	3	575	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.46, 1.56]
4 Distant recurrences	6	1341	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.32]
5 Wound/port site metastases	7	2130	Odds Ratio (M-H, Fixed, 95% CI)	2.76 [0.75, 10.20]

Comparison 2. Surgical data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lymph nodes retrieved	11	3682	Mean Difference (IV, Random, 95% CI)	-0.43 [-1.13, 0.26]
2 CRM positivity	8	2313	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.40]
3 Duration of surgery	12	3840	Mean Difference (IV, Random, 95% CI)	37.48 [27.80, 47.15]
4 Incision length	4	1488	Mean Difference (IV, Random, 95% CI)	-12.83 [-14.87, -10.80]
5 Conversion rate			Other data	No numeric data
6 Blood loss	8	2615	Mean Difference (IV, Random, 95% CI)	-101.78 [-147.57, -55.98]
7 Transfusion requirement	5	939	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.19, 0.62]
8 Intraoperative morbidity	4	1618	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.18]

Comparison 3. Short-term morbidity and mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 30-day morbidity (total)	11	3397	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.10]
2 Wound infection	10	3337	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.50, 0.93]
3 Bleeding	5	1181	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.10, 0.93]
4 Urinary complications	8	1756	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.83, 1.81]
5 Pneumonia	8	2668	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.83, 2.09]
6 Anastomotic leakage	10	2505	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
7 Need for reoperation	7	2316	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.20]
8 30-day mortality	11	3812	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.32]

Comparison 4. Postoperative recovery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Analgesia use (number of doses)	5	1199	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.93, -0.27]
2 Day 1 pain score (VAS)	3	776	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.04, -0.44]
3 Hospital stay (days)	11	3084	Mean Difference (IV, Random, 95% CI)	-2.16 [-3.22, -1.10]
4 Time to normal diet (days)	8	2109	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.80, -0.23]
5 Time to first defecation (days)	8	2893	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.17, -0.54]

Comparison 5. Long term morbidity

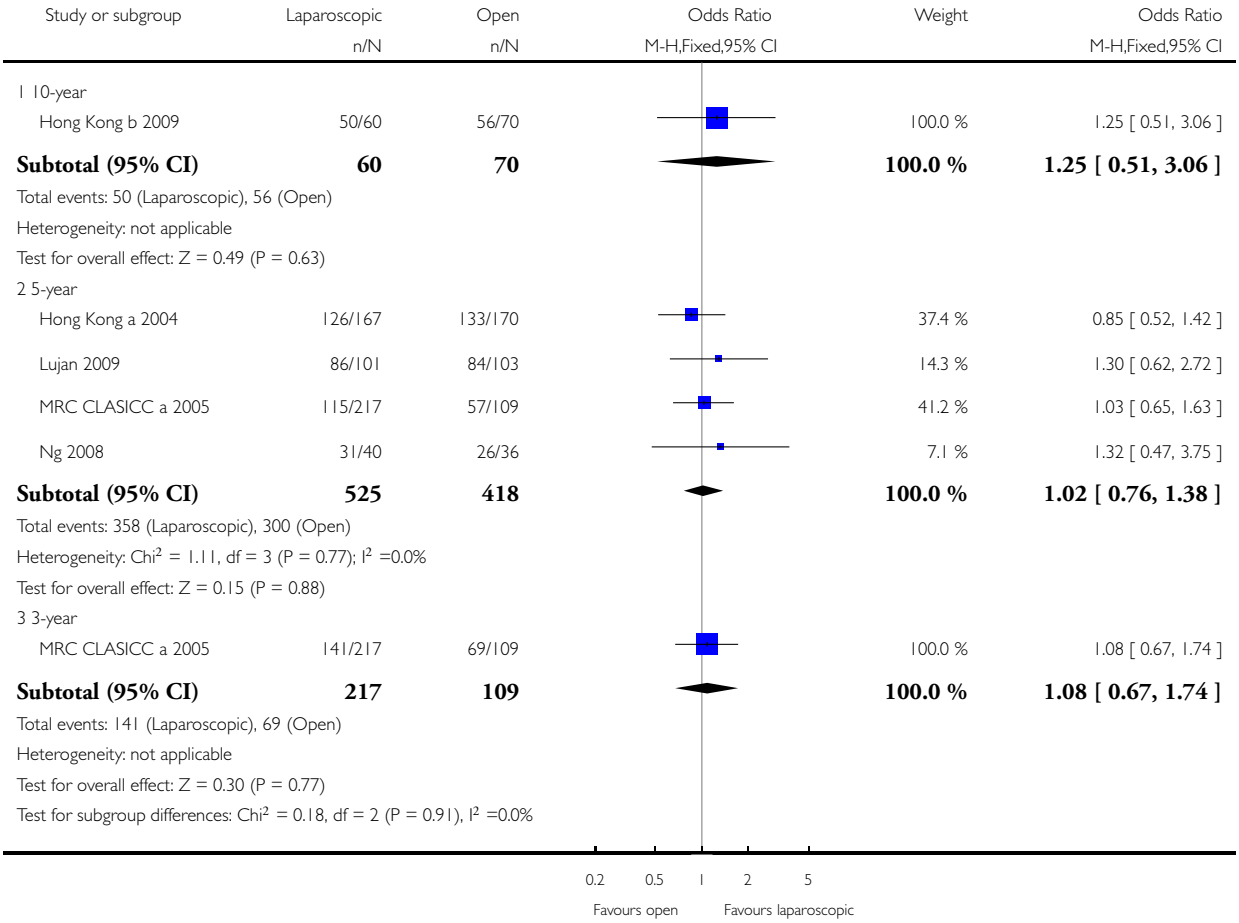
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incisional hernia	3	508	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.32, 2.21]
2 Intestinal obstruction	3	508	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.12, 0.75]

Analysis 1.1. Comparison 1 Survival and recurrences, Outcome 1 Disease-free survival.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 1 Survival and recurrences

Outcome: 1 Disease-free survival

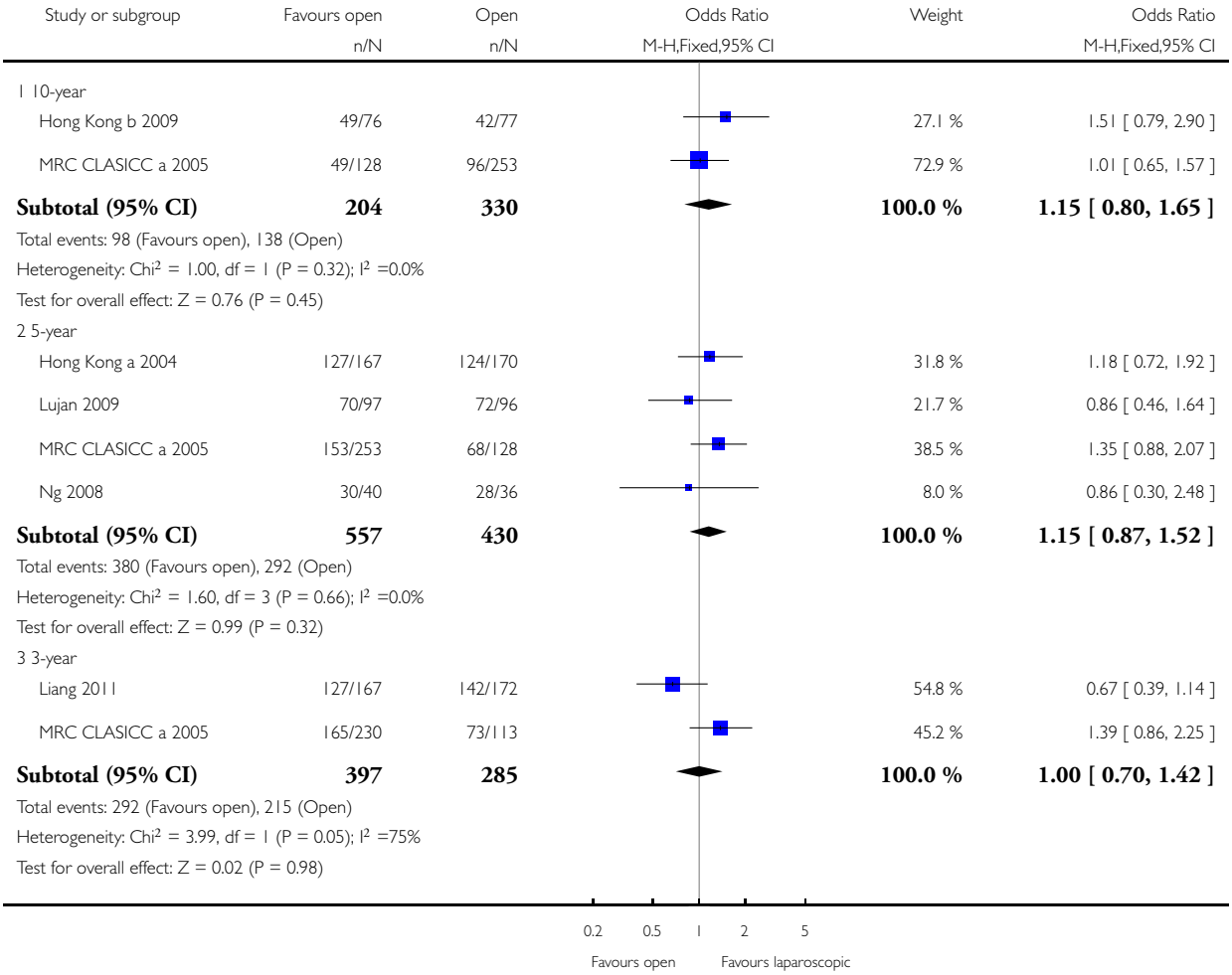


Analysis 1.2. Comparison 1 Survival and recurrences, Outcome 2 Overall survival.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 1 Survival and recurrences

Outcome: 2 Overall survival

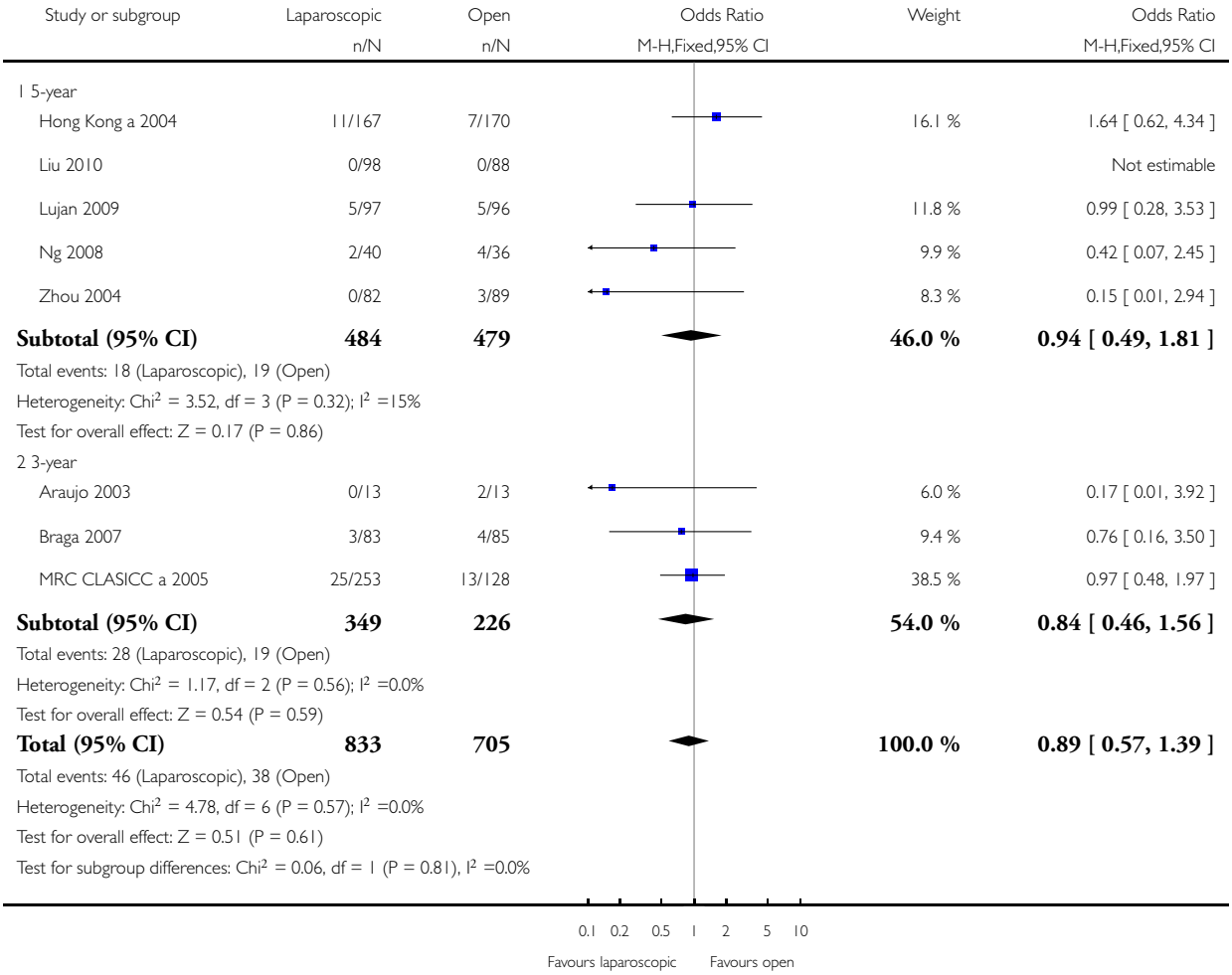


Analysis 1.3. Comparison 1 Survival and recurrences, Outcome 3 Local recurrences.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 1 Survival and recurrences

Outcome: 3 Local recurrences

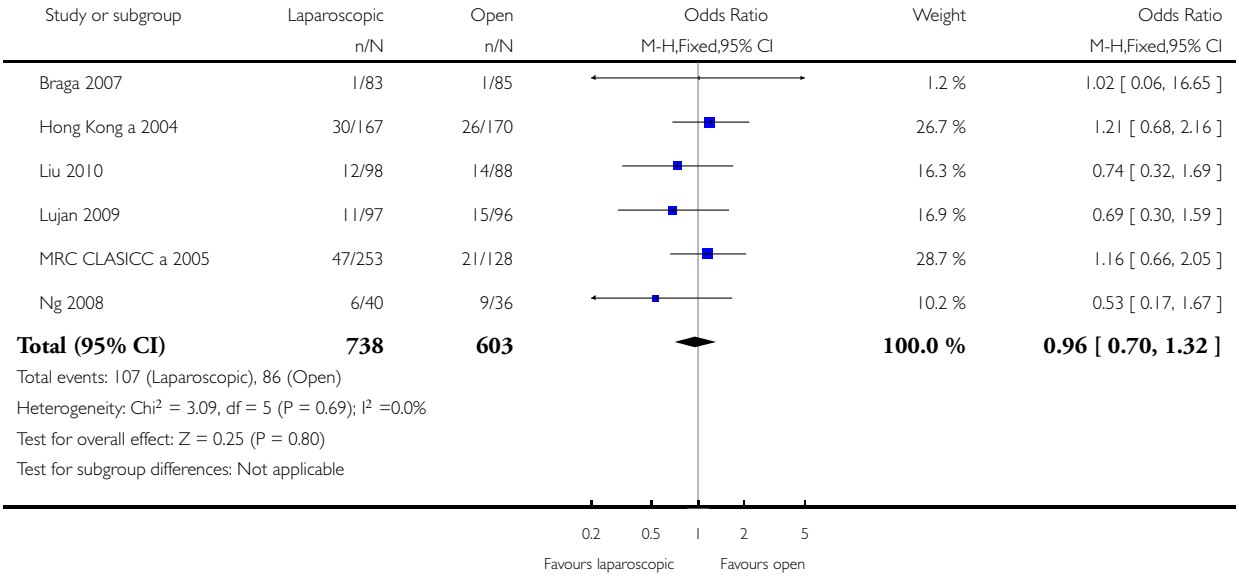


Analysis 1.4. Comparison 1 Survival and recurrences, Outcome 4 Distant recurrences.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 1 Survival and recurrences

Outcome: 4 Distant recurrences



Analysis 1.5. Comparison 1 Survival and recurrences, Outcome 5 Wound/port site metastases.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 1 Survival and recurrences

Outcome: 5 Wound/port site metastases

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Hong Kong a 2004	0/167	0/170			Not estimable
Liang 2011	0/167	0/172			Not estimable
Liu 2010	0/98	0/88			Not estimable
Lujan 2009	0/103	0/101			Not estimable
MRC CLASICC a 2005	9/526	1/268		39.5 %	4.65 [0.59, 36.88]
Ng 2008	0/51	1/48		46.4 %	0.31 [0.01, 7.73]
Zhou 2004	2/82	0/89		14.1 %	5.56 [0.26, 117.53]
Total (95% CI)	**1194**	**936**		**100.0 %**	**2.76 [0.75, 10.20]**

Total events: 11 (Laparoscopic), 2 (Open)

Heterogeneity: $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Surgical data, Outcome 1 Lymph nodes retrieved.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 1 Lymph nodes retrieved

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Araujo 2003	13	5.5 (0)	15	11.9 (0)			Not estimable
Braga 2007	83	12.7 (7.3)	85	13.6 (6.9)		7.1 %	-0.90 [-3.05, 1.25]
COLOR 2 a 2013	699	13 (5.9)	345	14 (6.7)		16.7 %	-1.00 [-1.83, -0.17]
Hong Kong a 2004	203	11.1 (7.9)	200	12.1 (7.1)		11.1 %	-1.00 [-2.47, 0.47]
Kang 2010	170	17 (7.4)	170	18 (8.1)		9.8 %	-1.00 [-2.65, 0.65]
Liang 2011	169	7.05 (5.05)	174	7.44 (4.89)		14.6 %	-0.39 [-1.44, 0.66]
Liu 2010	98	16 (4.4)	88	15 (7.4)		9.0 %	1.00 [-0.77, 2.77]
Lujan 2009	101	13.63 (6.26)	103	11.57 (5.1)		10.3 %	2.06 [0.49, 3.63]
MRC CLASICC a 2005	526	12 (6.7)	268	13.5 (8.1)		13.9 %	-1.50 [-2.63, -0.37]
Ng 2008	51	12.4 (6.7)	48	13 (7)		5.1 %	-0.60 [-3.30, 2.10]
Pechlivanides 2007	34	19.2 (8.3)	39	19.2 (10)		2.4 %	0.0 [-4.20, 4.20]
Total (95% CI)	**2147**		**1535**			**100.0 %**	**-0.43 [-1.13, 0.26]**

Heterogeneity: $Tau^2 = 0.57$; $Chi^2 = 18.32$, df = 9 (P = 0.03); $I^2 = 51\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Surgical data, Outcome 2 CRM positivity.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 2 CRM positivity

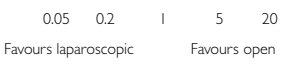
Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	1/83	2/85		2.9 %	0.51 [0.05, 5.69]
COLOR 2 a 2013	56/588	30/300		54.3 %	0.95 [0.59, 1.51]
Hong Kong b 2009	2/76	1/77		1.5 %	2.05 [0.18, 23.14]
Kang 2010	5/170	7/170		10.3 %	0.71 [0.22, 2.27]
Lujan 2009	4/101	3/103		4.3 %	1.37 [0.30, 6.30]
MRC CLASICC a 2005	30/193	14/97		23.8 %	1.09 [0.55, 2.17]
Ng 2008	3/51	2/48		2.9 %	1.44 [0.23, 9.00]
Zhou 2004	0/82	0/89			Not estimable
Total (95% CI)	**1344**	**969**		**100.0 %**	**0.99 [0.71, 1.40]**

Total events: 101 (Laparoscopic), 59 (Open)

Heterogeneity: $Chi^2 = 1.42$, df = 6 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

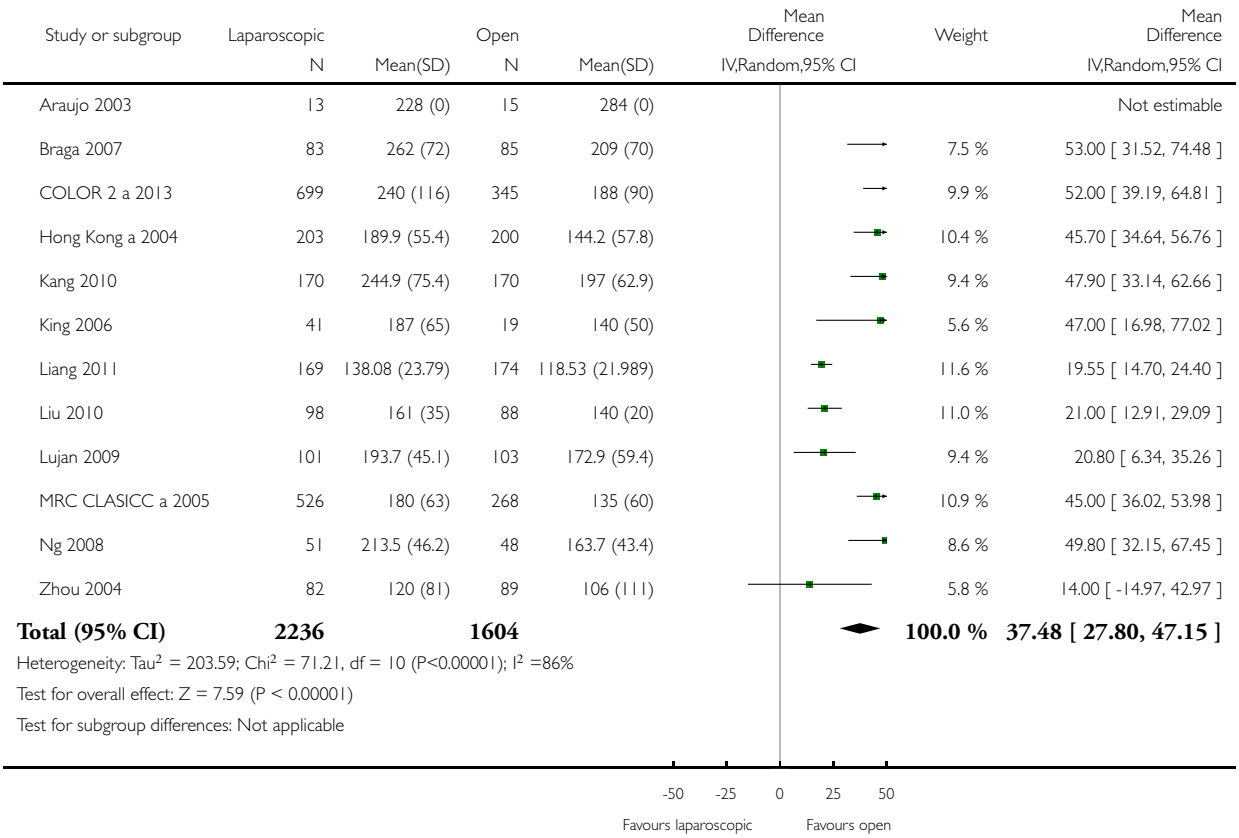


Analysis 2.3. Comparison 2 Surgical data, Outcome 3 Duration of surgery.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 3 Duration of surgery



Analysis 2.4. Comparison 2 Surgical data, Outcome 4 Incision length.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 4 Incision length

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Braga 2007	83	5.8 (0.8)	85	19.1 (3.1)		25.2 %	-13.30 [-13.98, -12.62]
Kang 2010	170	5 (1.1)	170	20 (3.7)		25.4 %	-15.00 [-15.58, -14.42]
Liu 2010	98	6 (1)	88	17 (2)		25.6 %	-11.00 [-11.46, -10.54]
MRC CLASICC a 2005	526	10 (8.1)	268	22 (8.1)		23.8 %	-12.00 [-13.19, -10.81]
Total (95% CI)	**877**		**611**			**100.0 %**	**-12.83 [-14.87, -10.80]**

Heterogeneity: $Tau^2 = 4.17$; $Chi^2 = 116.55$, df = 3 (P<0.00001); $I^2 = 97\%$

Test for overall effect: Z = 12.35 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Surgical data, Outcome 5 Conversion rate.

Conversion rate

Study	
Araujo 2003	0 (0/13)
Braga 2007	7.2 (6/83)
COLOR 2 a 2013	17 (121/695)
Hong Kong a 2004	23.2 (47/203)
Kang 2010	1.2 (2/170)
King 2006	7.3 (3/41)
Liang 2011	0.5 (1/169)
Liu 2010	0 (0/98)
Lujan 2009	7.9 (8/101)

MRC CLASICC a 2005	33.9 (82/242)
Ng 2008	9.8 (5/51)
Pechlivanides 2007	2.9 (1/34)
Zhou 2004	Unknown
Zhou 2007	Unknown

Analysis 2.6. Comparison 2 Surgical data, Outcome 6 Blood loss.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

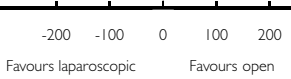
Outcome: 6 Blood loss

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Braga 2007	83	213 (236)	85	396 (367)		10.4 %	-183.00 [-276.09, -89.91]
COLOR 2 a 2013	699	200 (222)	345	400 (370)		15.8 %	-200.00 [-242.37, -157.63]
Hong Kong a 2004	203	169 (500)	200	238 (972)		6.1 %	-69.00 [-220.25, 82.25]
Kang 2010	170	200 (148)	170	217.5 (185)		16.4 %	-17.50 [-53.11, 18.11]
Liu 2010	98	310 (96)	88	380 (85)		17.2 %	-70.00 [-96.01, -43.99]
Lujan 2009	101	127.8 (113.3)	103	234.2 (174.3)		16.0 %	-106.40 [-146.67, -66.13]
Ng 2008	51	321.7 (750)	48	555.6 (1180)		1.3 %	-233.90 [-626.08, 158.28]
Zhou 2004	82	20 (85)	89	92 (111)		16.9 %	-72.00 [-101.50, -42.50]
Total (95% CI)	**1487**		**1128**			**100.0 %**	**-101.78 [-147.57, -55.98]**

Heterogeneity: $Tau^2 = 2998.32$; $Chi^2 = 50.06$, df = 7 (P<0.00001); $I^2 = 86\%$

Test for overall effect: Z = 4.36 (P = 0.000013)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Surgical data, Outcome 7 Transfusion requirement.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 7 Transfusion requirement

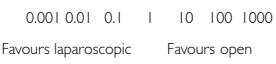
Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Araujo 2003	3/13	10/15		18.4 %	0.15 [0.03, 0.80]
Braga 2007	6/83	22/85		51.9 %	0.22 [0.09, 0.58]
Kang 2010	0/170	1/170		3.9 %	0.33 [0.01, 8.19]
King 2006	6/41	2/19		6.0 %	1.46 [0.27, 7.99]
Liang 2011	4/169	8/174		19.8 %	0.50 [0.15, 1.70]
Total (95% CI)	**476**	**463**		**100.0 %**	**0.34 [0.19, 0.62]**

Total events: 19 (Laparoscopic), 43 (Open)

Heterogeneity: $Chi^2 = 4.85$, df = 4 (P = 0.30); $I^2 = 18\%$

Test for overall effect: Z = 3.52 (P = 0.00043)

Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2 Surgical data, Outcome 8 Intraoperative morbidity.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 2 Surgical data

Outcome: 8 Intraoperative morbidity

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Araujo 2003	2/13	4/15		4.0 %	0.50 [0.08, 3.32]
COLOR 2 a 2013	81/694	49/344		73.0 %	0.80 [0.54, 1.16]
MRC CLASICC a 2005	35/253	16/128		23.1 %	1.12 [0.60, 2.12]
Zhou 2004	0/82	0/89			Not estimable
Total (95% CI)	**1042**	**576**		**100.0 %**	**0.86 [0.62, 1.18]**

Total events: 118 (Laparoscopic), 69 (Open)

Heterogeneity: $Chi^2 = 1.16$, df = 2 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.93 (P = 0.35)

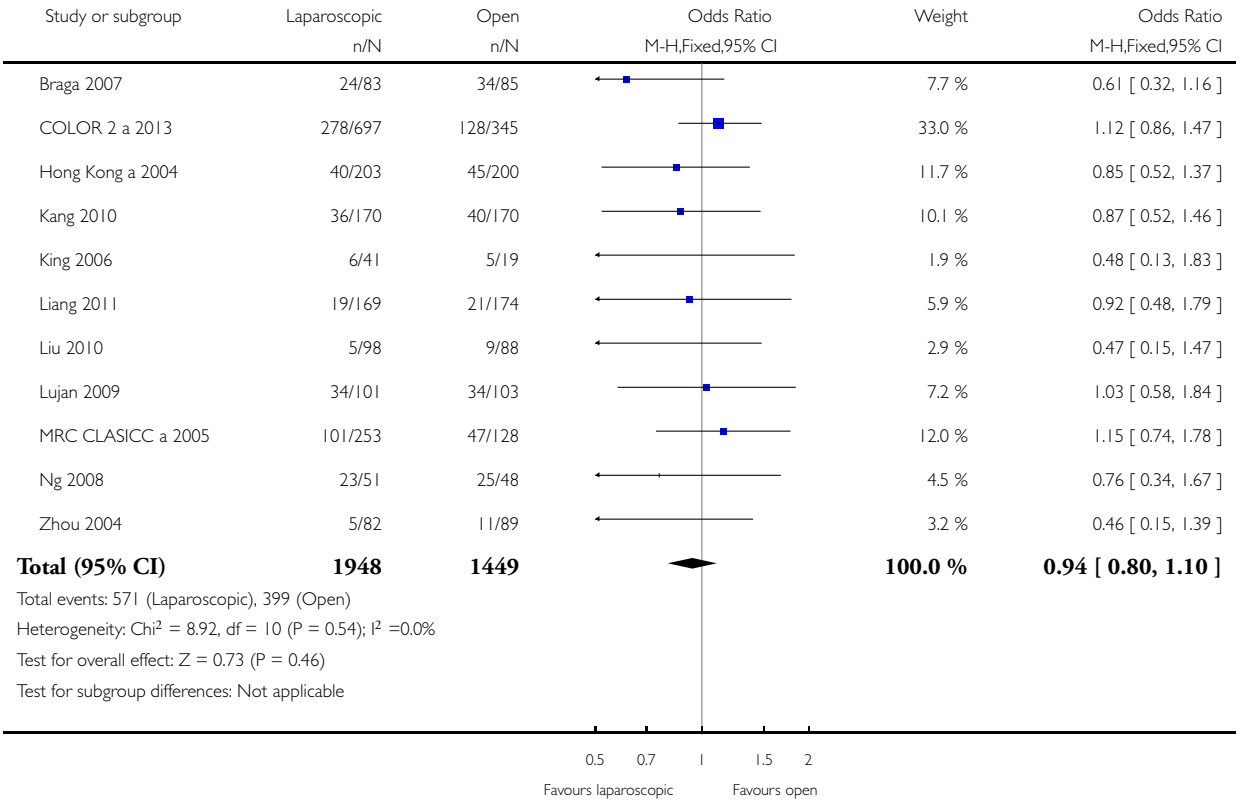
Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Short-term morbidity and mortality, Outcome 1 30-day morbidity (total).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 1 30-day morbidity (total)



Analysis 3.2. Comparison 3 Short-term morbidity and mortality, Outcome 2 Wound infection.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 2 Wound infection

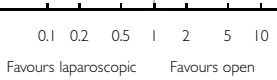
Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	6/83	13/85		12.2 %	0.43 [0.16, 1.20]
COLOR 2 a 2013	28/697	17/345		22.3 %	0.81 [0.44, 1.50]
Hong Kong a 2004	9/203	15/200		14.8 %	0.57 [0.24, 1.34]
Kang 2010	2/170	11/170		11.1 %	0.17 [0.04, 0.79]
Liang 2011	9/169	8/174		7.6 %	1.17 [0.44, 3.10]
Liu 2010	3/98	4/88		4.2 %	0.66 [0.14, 3.05]
Lujan 2009	0/101	2/103		2.5 %	0.20 [0.01, 4.22]
MRC CLASICC a 2005	33/253	15/128		17.7 %	1.13 [0.59, 2.17]
Ng 2008	0/51	4/48		4.7 %	0.10 [0.01, 1.83]
Zhou 2004	2/82	3/89		2.9 %	0.72 [0.12, 4.40]
Total (95% CI)	**1907**	**1430**		**100.0 %**	**0.68 [0.50, 0.93]**

Total events: 92 (Laparoscopic), 92 (Open)

Heterogeneity: Chi^2 = 10.16, df = 9 (P = 0.34); I^2 =11%

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Short-term morbidity and mortality, Outcome 3 Bleeding.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 3 Bleeding

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	0/83	4/85		34.2 %	0.11 [0.01, 2.05]
Hong Kong a 2004	2/203	4/200		30.9 %	0.49 [0.09, 2.69]
Kang 2010	1/170	3/170		23.1 %	0.33 [0.03, 3.20]
Ng 2008	0/51	1/48		11.8 %	0.31 [0.01, 7.73]
Zhou 2004	0/82	0/89			Not estimable
Total (95% CI)	**589**	**592**		**100.0 %**	**0.30 [0.10, 0.93]**

Total events: 3 (Laparoscopic), 12 (Open)

Heterogeneity: $Chi^2 = 0.78$, df = 3 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.036)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Short-term morbidity and mortality, Outcome 4 Urinary complications.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 4 Urinary complications

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Araujo 2003	1/13	1/15		1.8 %	1.17 [0.07, 20.72]
Braga 2007	2/83	5/85		10.4 %	0.40 [0.07, 2.10]
Hong Kong a 2004	13/203	10/200		20.3 %	1.30 [0.56, 3.04]
Kang 2010	17/170	7/170		13.6 %	2.59 [1.04, 6.41]
Liang 2011	1/169	1/174		2.1 %	1.03 [0.06, 16.60]
Lujan 2009	13/101	10/103		18.6 %	1.37 [0.57, 3.29]
Ng 2008	17/51	17/48		25.1 %	0.91 [0.40, 2.09]
Zhou 2004	2/82	4/89		8.1 %	0.53 [0.09, 2.98]
Total (95% CI)	**872**	**884**		**100.0 %**	**1.23 [0.83, 1.81]**

Total events: 66 (Laparoscopic), 55 (Open)

Heterogeneity: Chi^2 = 5.86, df = 7 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Short-term morbidity and mortality, Outcome 5 Pneumonia.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 5 Pneumonia

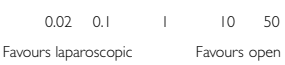
Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Araujo 2003	1/13	0/15		1.3 %	3.72 [0.14, 99.48]
Braga 2007	3/83	2/85		5.9 %	1.56 [0.25, 9.56]
COLOR 2 a 2013	20/697	10/345		40.5 %	0.99 [0.46, 2.14]
Hong Kong a 2004	4/203	3/200		9.2 %	1.32 [0.29, 5.97]
Liang 2011	2/169	2/174		6.1 %	1.03 [0.14, 7.40]
Lujan 2009	1/101	4/103		12.2 %	0.25 [0.03, 2.25]
MRC CLASICC a 2005	25/253	5/128		18.6 %	2.70 [1.01, 7.22]
Ng 2008	2/51	2/48		6.2 %	0.94 [0.13, 6.94]
Total (95% CI)	**1570**	**1098**		**100.0 %**	**1.32 [0.83, 2.09]**

Total events: 58 (Laparoscopic), 28 (Open)

Heterogeneity: Chi^2 = 5.35, df = 7 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3 Short-term morbidity and mortality, Outcome 6 Anastomotic leakage.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 6 Anastomotic leakage

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	8/76	9/74		11.2 %	0.85 [0.31, 2.34]
COLOR 2 a 2013	58/461	25/240		39.5 %	1.24 [0.75, 2.04]
Hong Kong a 2004	1/203	4/200		5.5 %	0.24 [0.03, 2.19]
Kang 2010	2/151	0/146		0.7 %	4.90 [0.23, 102.93]
King 2006	1/12	0/4		0.9 %	1.17 [0.04, 34.52]
Liang 2011	4/86	6/104		7.1 %	0.80 [0.22, 2.92]
Liu 2010	2/72	3/63		4.3 %	0.57 [0.09, 3.53]
Lujan 2009	5/77	10/81		12.5 %	0.49 [0.16, 1.51]
MRC CLASICC a 2005	26/190	9/94		14.3 %	1.50 [0.67, 3.34]
Zhou 2004	1/82	3/89		3.9 %	0.35 [0.04, 3.47]
Total (95% CI)	**1410**	**1095**		**100.0 %**	**1.01 [0.73, 1.40]**

Total events: 108 (Laparoscopic), 69 (Open)

Heterogeneity: $Chi^2 = 7.22$, df = 9 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 0.08 (P = 0.94)

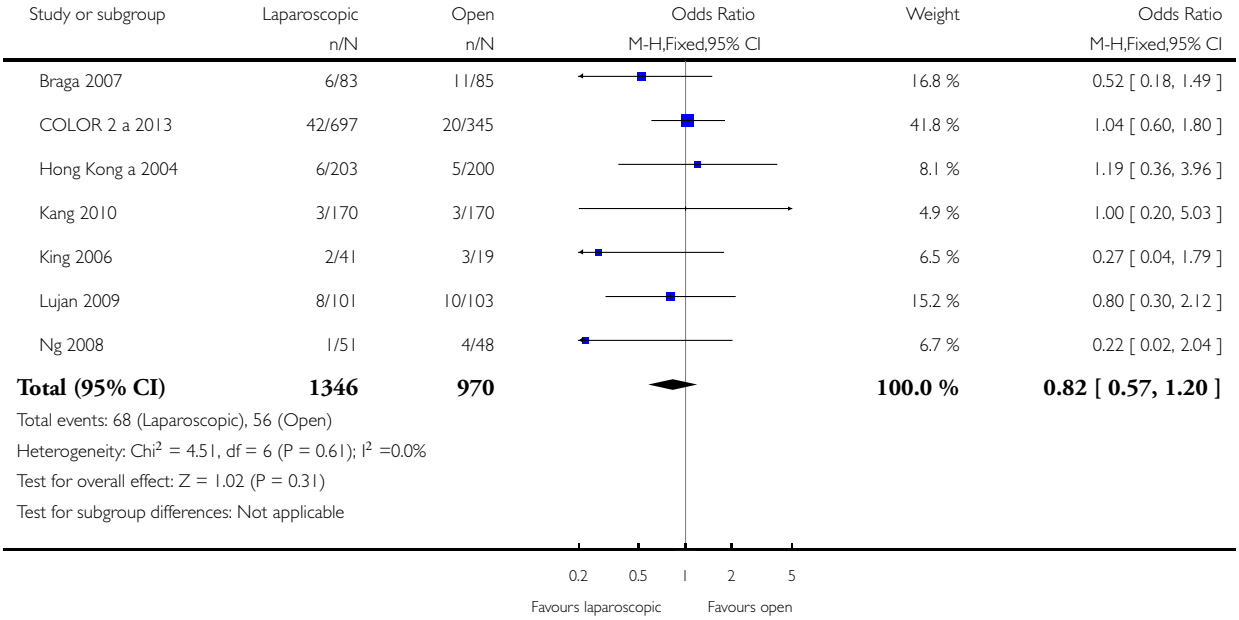
Test for subgroup differences: Not applicable

Analysis 3.7. Comparison 3 Short-term morbidity and mortality, Outcome 7 Need for reoperation.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 7 Need for reoperation



Analysis 3.8. Comparison 3 Short-term morbidity and mortality, Outcome 8 30-day mortality.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 3 Short-term morbidity and mortality

Outcome: 8 30-day mortality

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	1/83	1/85		2.8 %	1.02 [0.06, 16.65]
COLOR 2 a 2013	8/699	6/345		22.9 %	0.65 [0.23, 1.90]
Hong Kong a 2004	5/203	4/200		11.3 %	1.24 [0.33, 4.68]
Kang 2010	0/170	0/170			Not estimable
King 2006	1/41	1/19		3.8 %	0.45 [0.03, 7.60]
Liang 2011	0/169	0/174			Not estimable
Liu 2010	0/98	0/88			Not estimable
Lujan 2009	2/101	3/103		8.4 %	0.67 [0.11, 4.12]
MRC CLASICC a 2005	21/526	13/268		47.7 %	0.82 [0.40, 1.66]
Ng 2008	1/51	1/48		2.9 %	0.94 [0.06, 15.46]
Zhou 2004	0/82	0/89			Not estimable
Total (95% CI)	**2223**	**1589**		**100.0 %**	**0.81 [0.50, 1.32]**

Total events: 39 (Laparoscopic), 29 (Open)

Heterogeneity: $Chi^2 = 0.79$, df = 6 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Postoperative recovery, Outcome 1 Analgesia use (number of doses).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 4 Postoperative recovery

Outcome: 1 Analgesia use (number of doses)

Study or subgroup	Laparopscopic N	Mean(SD)	Open N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Hong Kong a 2004	203	4.5 (3.8)	200	6.9 (8.2)		21.8 %	-0.38 [-0.57, -0.18]
Kang 2010	170	107 (52)	170	157 (50.5)		21.3 %	-0.97 [-1.20, -0.75]
Liu 2010	98	2 (1)	88	3 (1)		19.6 %	-1.00 [-1.30, -0.69]
Ng 2008	51	6 (11.8)	48	11.4 (12.3)		17.5 %	-0.44 [-0.84, -0.05]
Zhou 2004	82	3.9 (0.9)	89	4.1 (1.1)		19.7 %	-0.20 [-0.50, 0.10]
Total (95% CI)	**604**		**595**			**100.0 %**	**-0.60 [-0.93, -0.27]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 29.47$, df = 4 (P<0.00001); $I^2 = 86\%$

Test for overall effect: Z = 3.58 (P = 0.00034)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Postoperative recovery, Outcome 2 Day 1 pain score (VAS).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 4 Postoperative recovery

Outcome: 2 Day 1 pain score (VAS)

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hong Kong a 2004	167	4.6 (2.4)	170	5.4 (2.3)		35.7 %	-0.80 [-1.30, -0.30]
Kang 2010	170	4.7 (2)	170	5.5 (2)		49.8 %	-0.80 [-1.23, -0.37]
Ng 2008	51	4.5 (2.1)	48	4.9 (1.9)		14.5 %	-0.40 [-1.19, 0.39]
Total (95% CI)	**388**		**388**			**100.0 %**	**-0.74 [-1.04, -0.44]**

Heterogeneity: $Chi^2 = 0.85$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 4.85 (P < 0.00001)

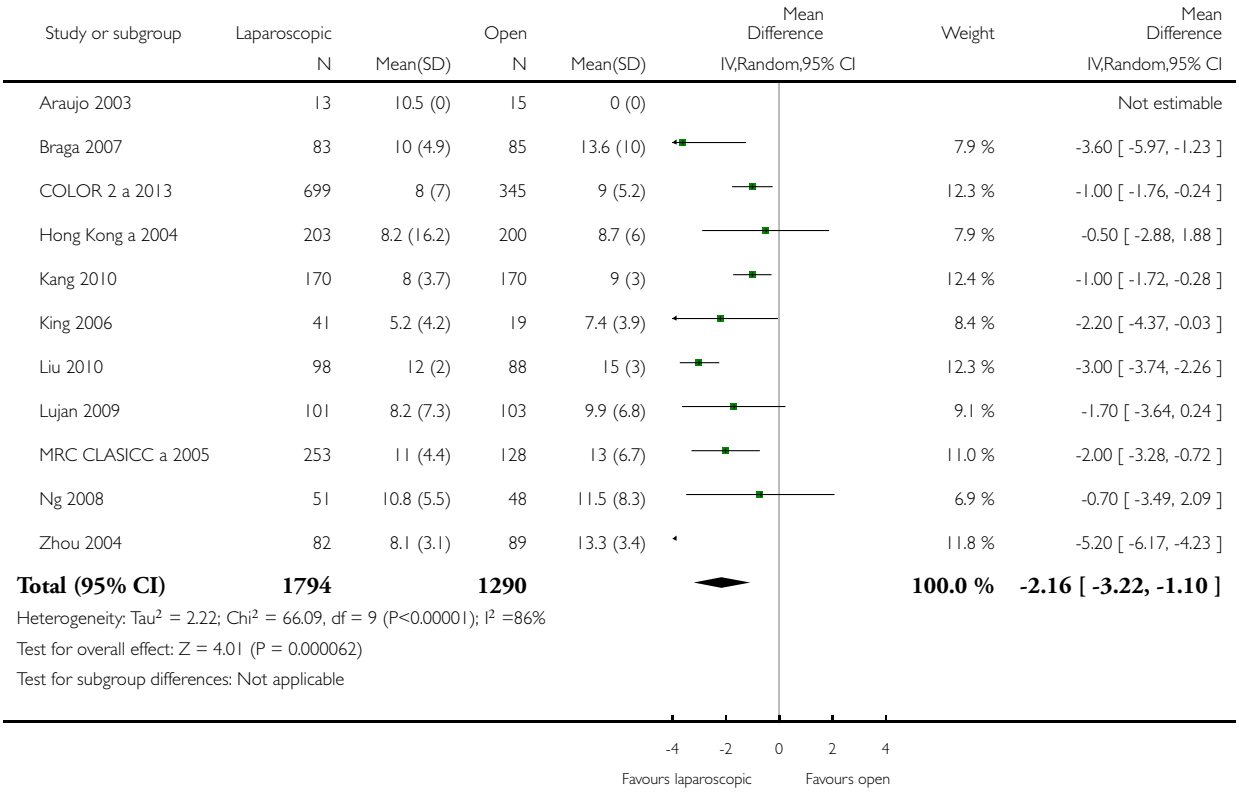
Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Postoperative recovery, Outcome 3 Hospital stay (days).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 4 Postoperative recovery

Outcome: 3 Hospital stay (days)



Analysis 4.4. Comparison 4 Postoperative recovery, Outcome 4 Time to normal diet (days).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 4 Postoperative recovery

Outcome: 4 Time to normal diet (days)

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Braga 2007	83	3.7 (1.3)	85	5 (2)		13.0 %	-1.30 [-1.81, -0.79]
Hong Kong a 2004	203	4.2 (3)	200	4.9 (2.2)		12.9 %	-0.70 [-1.21, -0.19]
Kang 2010	170	3.5 (0.9)	170	3.8 (1.1)		20.0 %	-0.30 [-0.51, -0.09]
Liang 2011	169	5.71 (1.716)	174	6.34 (1.618)		16.7 %	-0.63 [-0.98, -0.28]
Lujan 2009	101	2.8 (4.4)	103	3.6 (3.4)		5.2 %	-0.80 [-1.88, 0.28]
MRC CLASICC a 2005	253	6 (2.2)	128	6 (2.2)		13.9 %	0.0 [-0.47, 0.47]
Ng 2008	51	4.3 (5.8)	48	5.1 (3.3)		2.1 %	-0.80 [-2.65, 1.05]
Zhou 2004	82	4.3 (1.1)	89	4.5 (1.4)		16.1 %	-0.20 [-0.58, 0.18]
Total (95% CI)	**1112**		**997**			**100.0 %**	**-0.52 [-0.80, -0.23]**

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 20.23$, df = 7 (P = 0.01); $I^2 = 65\%$

Test for overall effect: Z = 3.58 (P = 0.00034)

Test for subgroup differences: Not applicable

Analysis 4.5. Comparison 4 Postoperative recovery, Outcome 5 Time to first defecation (days).

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 4 Postoperative recovery

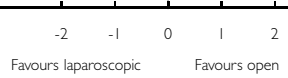
Outcome: 5 Time to first defecation (days)

Study or subgroup	Laparoscopic N	Mean(SD)	Open N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COLOR 2 a 2013	666	2 (1.5)	337	3 (1.5)		16.2 %	-1.00 [-1.20, -0.80]
Hong Kong a 2004	203	4 (2)	200	4.6 (2.5)		12.9 %	-0.60 [-1.04, -0.16]
Hong Kong b 2009	76	4.1 (1.5)	77	4.7 (1.8)		11.7 %	-0.60 [-1.12, -0.08]
Kang 2010	170	4 (1.7)	170	5.1 (1.9)		13.8 %	-1.10 [-1.48, -0.72]
Liang 2011	169	3.9 (0.85)	174	4.2 (0.79)		16.5 %	-0.30 [-0.47, -0.13]
MRC CLASICC a 2005	253	5 (2.2)	128	6 (2.2)		12.6 %	-1.00 [-1.47, -0.53]
Ng 2008	51	4.3 (5.3)	48	6.3 (2.8)		3.0 %	-2.00 [-3.66, -0.34]
Zhou 2004	82	1.5 (1.3)	89	2.7 (1.5)		13.3 %	-1.20 [-1.62, -0.78]
Total (95% CI)	**1670**		**1223**			**100.0 %**	**-0.86 [-1.17, -0.54]**

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 43.17$, df = 7 (P<0.00001); $I^2 = 84\%$

Test for overall effect: Z = 5.31 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Long term morbidity, Outcome 1 Incisional hernia.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 5 Long term morbidity

Outcome: 1 Incisional hernia

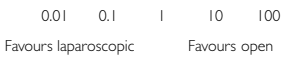
Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Braga 2007	0/83	4/85		10.1 %	0.11 [0.01, 2.05]
Hong Kong b 2009	4/76	5/77		37.8 %	0.80 [0.21, 3.10]
MRC CLASICC a 2005	14/129	5/58		52.1 %	1.29 [0.44, 3.77]
Total (95% CI)	**288**	**220**		**100.0 %**	**0.84 [0.32, 2.21]**

Total events: 18 (Laparoscopic), 14 (Open)

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 2.55$, df = 2 (P = 0.28); $I^2 = 21\%$

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5 Long term morbidity, Outcome 2 Intestinal obstruction.

Review: Laparoscopic versus open total mesorectal excision for rectal cancer

Comparison: 5 Long term morbidity

Outcome: 2 Intestinal obstruction

Study or subgroup	Laparoscopic n/N	Open n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2007	0/83	1/85		8.5 %	0.34 [0.01, 8.40]
Hong Kong b 2009	2/76	15/77		83.8 %	0.11 [0.02, 0.51]
MRC CLASICC a 2005	5/129	1/58		7.7 %	2.30 [0.26, 20.13]
Total (95% CI)	**288**	**220**		**100.0 %**	**0.30 [0.12, 0.75]**

Total events: 7 (Laparoscopic), 17 (Open)

Heterogeneity: $Chi^2 = 5.03$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 2.56 (P = 0.011)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Reported outcomes

Study ID	n	Long-term survival	30-day mortality	30-day morbidity	Long-term morbidity	Lymphnodes	Gastrointestinal recovery	Pain	Bleeding	Length of hospital stay	Immune response	Quality of life	Cost
Araujo 2003	28	-	-	+	-	+	-	-	+	+	-	-	-
Braga 2007	168	5y/3y	+	+	+	+	+	-	+	+	-	+	+
COLOR 2 a 2013	1044	-	+	+	-	+	+	+	+	+	-	-	-
COLOR 2 b 2011	40	-	+	+	-	+	-	-	+	+	+	-	-
Hong Kong a 2004	403	5y	+	+	-	+	+	+	+	+	-	-	+
Hong Kong b 2009	153	10y	-	-	+	-	+	-	-	-	-	-	-
Hong Kong c 2000	34	-	-	-	-	-	-	-	-	-	+	-	-
Hong Kong d 2003	40	-	-	-	-	-	-	-	-	-	+	-	-
Kang 2010	340	-	+	+	-	+	+	+	+	+	-	+	-
King 2006	19	-	+	+	-	-	-	-	+	+	-	+	+
Liang 2011	343	3y	+	+	-	+	+	-	+	-	-	-	-
Liu 2010	186	-	+	+	-	+	-	-	+	+	-	-	-

Table 1. Reported outcomes (*Continued*)

Lujan 2009	204	5y	+	+	-	+	+	-	+	+	-	-	-
MRC CLASICC a 2005	381	10y/ 5y/3y	+	+	-	+	+	-	-	+	-	+	-
MRC CLASICC b 2005	148	-	-	-	-	-	-	-	-	-	-	+	-
MRC CLASICC c 2001	236	-	-	-	-	-	-	-	-	-	+	-	-
Ng 2008	99	5y	+	+	-	+	+	+	+	+	-	-	+
Pechlivanides 2007	73	-	-	-	-	+	-	-	-	-	-	-	-
Zhou 2004	171	-	+	+	-	-	+	-	+	+	-	-	-
Zhou 2007	71	-	-	-	-	-	-	-	-	-	+	-	-

APPENDICES

Appendix 1. Cochrane Library (CENTRAL) search strategy

#	Search
1	MeSH descriptor: [Laparoscopy] explode all trees
2	MeSH descriptor: [Surgical Procedures, Minimally Invasive] explode all trees
3	laparoscopy OR laparoscop* OR minimally invasive surgery

(*Continued*)

4	(#1 or #2 or #3)
5	(anterior resecti*) OR (abdominoperineal resecti*) OR (total mesorectal excisi*)
6	((sexual* or gastrointestinal or urogenital or bladder) near/3 functi*):ti,ab,kw
7	(quality of life or QoL or survival or recurrence):ti,ab,kw
8	MeSH descriptor: [Erectile Dysfunction] explode all trees
9	MeSH descriptor: [Urinary Bladder] explode all trees
10	MeSH descriptor: [Quality of Life] explode all trees
11	MeSH descriptor: [Survival] explode all trees
12	MeSH descriptor: [Recurrence] explode all trees
13	(#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
14	MeSH descriptor: [Rectal Neoplasms] explode all trees
15	((rect* or anal* or anus*) near/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)):ti,ab,kw
16	(#14 or #15)
17	(#4 and #13 and #16)

Appendix 2. MEDLINE (Ovid) search strategy

#	Search
1	exp Laparoscopy/
2	exp Surgical Procedures, Minimally Invasive/
3	(laparoscop* or minimally invasive surgery).mp.
4	1 or 2 or 3
5	(anterior resecti* or abdominoperineal resecti* or total mesorectal excisi*).mp
6	((sexual* or gastrointestinal or urogenital or bladder) adj3 functi*).mp

(*Continued*)

7	(quality of life or QoL or survival or recurrence).mp.
8	exp sexual dysfunction, physiological/ or exp urinary bladder/ or exp quality of life/ or exp survival/ or exp recurrence/
9	5 or 6 or 7 or 8
10	exp Rectal Neoplasms/
11	((rect* or anal* or anus*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp
12	10 or 11
13	4 and 9 and 12
14	randomized controlled trial.pt.
15	controlled clinical trial.pt.
16	randomized.ab.
17	placebo.ab.
18	clinical trial.sh.
19	randomly.ab.
20	trial.ti.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	humans.sh.
23	21 and 22
24	13 and 23
25	limit 24 to yr="1990 -Current"

Appendix 3. EMBASE (Ovid) search strategy

#	Search
1	exp LAPAROSCOPY/
2	exp minimally invasive surgery/
3	(laparoscop* or minimally invasive surgery).mp.
4	1 or 2 or 3
5	exp rectum anterior resection/ or exp rectum abdominoperineal resection/ or exp sexual function/ or exp bladder/ or exp quality of life/ or exp survival/ or exp recurrent disease/
6	(anterior resecti* or abdominoperineal resecti* or total mesorectal excisi* or quality of life or QoL or survival or recurrence).mp
7	((sexual* or gastrointestinal or urogenital or bladder) adj3 functi*).mp
8	5 or 6 or 7
9	exp rectum tumor/
10	((rect* or anal* or anus*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp
11	9 or 10
12	4 and 8 and 11
13	randomized controlled trial/
14	randomization/
15	controlled study/
16	multicenter study/
17	phase 3 clinical trial/
18	phase 4 clinical trial/
19	double blind procedure/
20	single blind procedure/
21	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab
22	(random* or cross* over* or factorial* or placebo* or volunteer*).ti,ab

(*Continued*)

23	18 or 15 or 19 or 21 or 14 or 20 or 16 or 13 or 22 or 17
24	"human*".ti,ab.
25	(animal* or nonhuman*).ti,ab.
26	25 and 24
27	25 not 26
28	23 not 27
29	12 and 28
30	limit 29 to yr="1990 -Current"

WHAT'S NEW

Last assessed as up-to-date: 2 February 2013.

Date	Event	Description
2 February 2013	New citation required and conclusions have changed	New search, analysis and conclusion
2 February 2013	New search has been performed	In this updated review we included 14 trials (20 comparisons) ; 46 previously included studies from the first published version in 2006 were discarded and 12 new RCTs added

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 4, 2006

Date	Event	Description
5 August 2008	Amended	Converted to new review format.
10 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Sandra Vennix, MD: First reviewer to search literature, assess quality of trials and collect data, manage the data and write the review.

Loeki Pelzers, MD: Second reviewer to search literature, assess quality of trials and collect data.

Nicole Bouvy, MD, PhD: Providing general advice on the review, help write the review.

Geerard Beets, MD, PhD: Providing general advice on the review, help write the review.

Jean-Pierre Pierie, MD, PhD: Performing previous work that was the foundation of the current review, providing general advice on the review.

Theo Wiggers, MD, PhD: Performing previous work that was the foundation of the current review, providing general advice on the review.

Stephanie Breukink, MD, PhD: Writing the protocol, performing previous work that was the foundation of the current review, providing general advice on the review, co-ordinating the review.

DECLARATIONS OF INTEREST

No funding/conflicts of interest declared by all authors.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the published protocol and original review, in this version we only include randomised controlled trials (RCTs) which compared laparoscopic with open total mesorectal excision. This has resulted in discarding the 46 non-randomised studies of the 48 included studies in favour of 12 new RCTs not originally included.In addition to the outcome measures given in the protocol, we have included long-term morbidity, recurrences and overall survival. We have excluded the respiratory recovery rate, as the definition is unclear and only one trial reported on this outcome.

For methodological assessment, we have discarded the scale by Sackett 2000, because we now only include randomised controlled trials. We now assess the included trials according to the CONSORT Statement 2010 and using the Cochrane 'Risk of bias' tool.

INDEX TERMS

Medical Subject Headings (MeSH)

*Laparoscopy; Conversion to Open Surgery [statistics & numerical data]; Elective Surgical Procedures; Rectal Neoplasms [*surgery]; Rectum [*surgery]; Treatment Outcome

MeSH check words

Humans