This article was published in Surgical Endoscopy and the original publication is available at http://www.springerlink.com/.
The link to the original article is:
http://www.springerlink.com/content/jw235m3452727g23/?p=0cce66fcdfa24ef4ae5a8daf3cd637df&pi=1

Laparoscopic surgery for colorectal cancer: safe and effective? – A systematic review

Tania Lourenco, MSc,[1] Alison Murray, PhD,[1] Adrian Grant, DM,[1] Aileen McKinley, MBChB FRCS (Ed),[2] Zygmunt Krukowski (PhD),[2] Luke Vale, PhD,[1,3]

[1] Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, United Kingdom.

[2] NHS Grampian, United Kingdom.

[3] Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, United Kingdom.

Corresponding author: Tania Lourenco

Research Fellow
Health Services Research Unit
University of Aberdeen
Health Sciences Building, 3rd Floor
Foresterhill
Aberdeen
AB25 2ZD
UK
Tel: +44 (0) 1224 559265
Fax: +44 (0) 1224 554580

Requests for reprints:

Requests for reprints should be addressed to the corresponding author.

Sources of support:

This study was supported by the NHS R&D HTA Programme. The Health Services Research Unit and the Health Economics Research Unit are funded by the Chief Scientist Office of the Scottish Executive Health Department. The views expressed here are those of the authors.

ABSTRACT
Laparoscopic surgery

Objective: To determine the clinical effectiveness of laparoscopic and laparoscopically assisted surgery in comparison with open surgery for the treatment of colorectal cancer.

Background: Open resection is the standard method for surgical removal of primary colorectal tumours. However, there is significant morbidity associated with this procedure. Laparoscopic resection (LR) is technically more difficult but may overcome problems associated with open resections (OR).

Methods: Systematic review and meta-analysis of short and long-term data from randomised controlled trials (RCTs) comparing LS with OR.

Results: Highly sensitive searches of nine databases identified 19 primary RCTs describing data from over 4500 participants. Length of hospital stay is shorter, blood loss and pain are less, and return to usual activities is likely to be faster after LR than after OR, but duration of operation is longer. Lymph node retrieval, completeness of resection and quality of life do not appear to differ. No statistically significant differences were observed in rates of anastomotic leakage, abdominal wound breakdown, incisional hernia, wound and urinary tract infections, operative and 30-day mortality, and recurrences, nor in overall and disease-free survival up to three years.

Conclusions: LR is associated with a quicker recovery in terms of return to usual activities and length of hospital stay with no evidence of a difference in complications or long-term outcomes in comparison to OR, up to three years post-operatively.

INTRODUCTION

Colorectal cancer is one of the most common malignancies. In England and Wales it is the second most common in terms both of incidence and mortality[1] with approximately 36,000 new cases diagnosed in 2002 and 17,000 people dying from colorectal cancer in the same year.[2] In the USA it is the third most common cancer with an estimated 149,000 new cases in 2006 and approximately 55,000 deaths.[3]

About 80% of all patients diagnosed with colorectal cancer (including some with advanced disease) undergo surgery.[4] Open resection is the standard method for surgical removal of primary colorectal tumours in the UK;[5] it results in significant morbidity. Over the past 15 years, laparoscopic resection has been considered as an alternative to open surgery although there are concerns about both its safety and effectiveness compared with open resections. There are three types of laparoscopic surgery: totally laparoscopic, laparoscopic-assisted and hand-assisted laparoscopic surgery (HALS).

In response to these concerns, the National Institute for Health and Clinical Excellence (NICE) issued guidance in 2000 on the use of laparoscopic surgery for colorectal cancer. This guidance stated that open rather that laparoscopic surgery was the preferred procedure and that laparoscopic surgery should only be undertaken as part of a randomised controlled trial (RCT).[5] New data have since become available, particularly from three large RCTs[6-8] (each with around 800 participants) and an individual patient data (IPD) meta-analysis of these three

trials[9] plus a further moderate sized trial.[10] The aim of this systematic review was to assess the clinical effectiveness of laparoscopic, laparoscopically assisted (hereafter together described as laparoscopic surgery) and HALS in comparison with open resection in the context of a reassessment by NICE.

METHODS

Searching for the evidence

Published and unpublished reports of RCTs and systematic reviews evaluating the effectiveness of laparoscopic and HAL surgery for colorectal cancer were identified by the electronic searches. Searches were restricted to the years 2000 onwards (as earlier trials had been identified by the previous systematic review)[11] without language restriction and included abstracts from recent conference proceedings. Full details of the search strategy are reported elsewhere.[12] Additional data and relevant studies were identified from the reference lists of included studies and systematic reviews as well as by contacting lead authors of all included RCTs.

Inclusion and exclusion criteria

Individual RCTs and individual patient data meta-analyses of RCTs of laparoscopic surgery compared to open surgery for colorectal cancer were included. Studies including patients undergoing palliative treatment were excluded. The pre-specified subgroups considered were defined by: location of cancer; stage of cancer; and mean age at diagnosis. The pre-specified outcomes are listed in Table 1.

Quality assessment strategy

Two reviewers, working independently, assessed the methodological quality of included studies. Disagreements were resolved by consensus or arbitration. Primary

RCTs were assessed using the Delphi criteria list[13] and the meta-analyses were assessed using the Oxman and colleagues checklist.[14, 15]

Data extraction strategy

The titles and abstracts of all papers identified by the search strategy were screened. Two reviewers independently assessed full-text copies of all potentially relevant studies and extracted data from the included studies. Reviewers were not blinded to the names of studies' authors, institutions or sources of the reports. Any differences that could not be resolved through discussion were referred to an arbiter.

Data synthesis

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

Due to the lack of uniformity of the data presented by many studies, a qualitative review looking for consistency between studies was also performed. This was supplemented, where appropriate by considering the consistency in the direction of effects using the Sign-test.[16]

RESULTS

Forty four reports describing 20 studies (19 RCTs and one individual patient data (IPD) meta-analysis[9] met the inclusion criteria for the review (Figure 1).

Quality and characteristics of available evidence

All RCTs were generally of a similar good quality (Table 2). The IPD meta-analysis[9] was not fully comprehensive in terms of the search methods employed and failed to report the selection criteria for including studies. No details were given about how the quality of included studies was assessed. However, the findings of the included studies were combined appropriately relative to the primary question the review addressed and the conclusions were supported by the data and the analysis reported.

In the 19 eligible RCTs, there were 19 relevant comparisons, none of which involved a comparison with HALS. Studies included varied in relation to settings, age and gender of participants, types of outcomes measured, and site and stage of cancer (Table 3). In general, studies reported the participants' stage of cancer using either Dukes' or TNM classification. One study failed to report the stage of cancer at which participants were enrolled[17] and in another the stage was not clearly reported.[7] Where specified, the majority of participants receiving either laparoscopic or conventional open interventions had either Dukes' B (TNM stage II) or Dukes' C (TNM stage III) cancer.

The IPD meta-analysis[9] included patients from four of the included trials: CLASICC,[7] COLOR[8], COST[6] and Lacy and colleagues.[10] A total of 1765 patients who were randomised before 1 April 2000 and had three years follow-up were included in this IPD meta-analysis.

Description of surgery received

'Opposite method initiated'

The 'opposite' method to the one that the patient was randomised to was initiated in 46/1173 (3.9%) of those randomised to laparoscopic resections[7, 8, 10] and 4/268 (1.5%) of patients randomized to open surgery. Rates varied between the trials. In the IPD meta-analysis,[9] the rates were similar in both groups (<1%).

Number of ports

The number of port-sites used for laparoscopic resection varied between three and five across the studies reporting this outcome.[18-24]

Conversion

Overall, 421 of 2027 (21%; range 0%-46%) laparoscopic procedures were converted to open surgery.[6-8, 18-20, 23-28] A similar result was reported in the IPD meta-analysis.[9]

Surgeons' prior experience

Ten RCTs reported that surgeons performing the procedures were experienced in laparoscopic colorectal surgery.[6-8, 10, 19, 21, 23, 25, 26, 29] However, only three[6-8] reported a minimum level of experience required, which in each was that surgeons

had undertaken at least 20 laparoscopic colorectal operations before participating in the trial.

Assessment of effectiveness

Duration of operation

Sixteen studies (n=4125) provided information on the duration of operation (Table 4). In all but one study[18] the duration of operation was longer in the laparoscopic group (Sign-test, $p<0.001$) and this difference was statistically significant ($p<0.05$) in 12 studies. Only three studies[10, 22, 26] presented data in a form sufficiently similar to allow meta-analysis, which showed that laparoscopic surgery took 40 minutes longer than open surgery (95% CI 32 to 48, $p<0.001$). This finding is consistent with the data not amenable to meta-analysis (Table 4). There was evidence of statistical heterogeneity, but the direction of effect was consistent across the studies. Using a random effects model did not change this pattern.

Blood loss

Nine studies[8, 10, 19, 20, 23, 25, 26, 28, 30] provided information on blood loss but the data were not reported in a form sufficiently similar to allow for a quantitative synthesis (Table 4). Eight studies reported less blood loss following laparoscopic surgery,[8, 10, 19, 20, 23, 26, 28, 30] and this was statistically significant in six[8, 10, 19, 20, 28, 30] (Sign-test, $p=0.039$).

Lymph node retrieval

Seven[7, 18, 20, 23, 25-27] of the 12 studies providing data (Table 4) reported more lymph nodes retrieved in the open compared with the laparoscopic group, two[19, 29] reported more in the laparoscopic group and three studies reported no differences[6, 8, 10] (Sign-test, $p=0.289$). Meta-analysis of the three trials[10, 26, 29]

reporting data suitable for synthesis showed no statistically significant difference between groups (WMD -0.41; 95%CI -1.42 to 0.59, p=0.42). The mean number of lymph nodes retrieved reported in the IPD meta-analysis[9] was 11.8 and 12.2 in the laparoscopic and open groups respectively.

Length of hospital stay

All 14 studies[6-8, 10, 18-23, 25, 26, 28, 30] that provided information on length of hospital stay reported lower mean or median stay in the laparoscopic group, which was statistically significant in 11 studies[6, 8, 10, 19, 20, 22, 23, 25, 26, 28, 30] (Table 4) (Sign-test ($p<0.001$)). Four studies reported data suitable for synthesis[8, 10, 22, 30] and the average length of stay was significantly shorter following laparoscopic surgery (WMD -2.58 days, 95% CI -3.12 to -2.03, $p<0.001$). This result was consistent with the data from those trials that reported data not amenable to meta-analysis (Table 4). There was marked heterogeneity observed in this meta-analysis, but there was consistency in the direction of effect. Using a random effects model did not change this pattern. The main source of heterogeneity appears to be from the study by Zhou and colleagues,[30] where the average age of participants was lower than in the other studies reviewed. Additionally, all participants in the Zhou study had rectal cancer.

Adverse events

Eight[7, 8, 10, 20, 24, 26, 28, 30], three,[8, 18, 28] seven[8, 10, 19, 22, 24-26] and nine studies[7, 8, 10, 19, 20, 24, 26, 28, 31] reported data on anastomotic leakages, abdominal wound breakdown, wound infection and urinary tract infections, respectively. There was no statistical significant differences between the two groups,

but clinically important differences could not be ruled out as the size and direction of effect varied across studies and the confidence intervals were wide (Figure 2).

Seven RCTs[6-8, 10, 19, 26, 28] provided information on operative and 30-day mortality. In terms of operative mortality, the difference was not statistically significant and the confidence interval was wide (Figure 2). 30-day mortality was less in the laparoscopic group than in the open group but again this was not statistically significant and no difference was detected (Figure 2; RR 0.92, 95% CI 0.74 to 1.14).

Seven RCTs[6, 10, 18, 19, 23, 25, 26] provided information on recurrence (n=1528). Recurrences appeared less frequently in the laparoscopic group than in the open resection group (Figure 2), but the difference was not statistically significant. The results of this meta-analysis should be treated with caution as the follow-ups of the RCTs ranged from three to 108 months. The recurrence rate reported in the IPD meta-analysis was 14% in the laparoscopic group and 16% in the open group at three years (p=0.43).[9] There were only three reported cases of wound recurrences across the four RCTs[6, 21, 22, 28] that reported this outcome (laparoscopic=2; open=1).[6] Eight studies[10, 20, 23, 25-27, 30, 32] provided information on port-site recurrence (3/483, 0.6%).

Only two studies reported incidence of incisional and port site hernia.[26, 31] The average follow-up in one was 2.5 years[31] and in the other 4.2 years.[26] Hernias were reported in 17 (one of which was a port-site hernia) out of 249 (7%) participants in the laparoscopic group and 13 out of 243 (5%) in the open group, but this difference was not statistically significant (Figure 2).

Postoperative pain

Five studies included a measure of postoperative pain.[7, 23, 26, 33, 34] Between the first day and two weeks post-operation, four studies favoured the laparoscopic group[7, 23, 26, 33] and one did not show any difference[34] (Sign-test p=0.125). Three studies measured pain at one to three months postoperatively but this did not differ significantly between the two interventions.[7, 23, 34] Four studies report that patients in the laparoscopic group required fewer days of postoperative analgesia than in the open group,[6, 20, 25, 30] (Sign-test p=0.031). Other data on analgesic use was consistent with this.[21, 28]

Time to return to usual activities

Only one study reported data on time to return to usual activities.[26] The average time to resume household activities in the laparoscopic group (mean 32 days, range 4 to 365) was lower than that in the open group for patients with rectosigmoid cancer (mean 44 days, range 7 to 198, p=0.002).

Health related quality of life (QoL)

Four studies, using a variety of instruments, reported the QoL of people undergoing laparoscopic or open resections.[7, 28, 34, 35] Three studies reported higher QoL following laparoscopic surgery[7, 34, 35] and one reported similar scores,[28] but this was a randomised study embedded within an enhanced recovery program.

Overall survival

Six RCTs[6, 10, 19, 25, 26, 30] provided information on overall survival. Length of follow-up of the RCTs ranged from one to 108 months. In the 'time to event' IPD

meta-analysis[9] of four trials, no evidence of a statistically significant difference in overall survival was found (hazard ratio 1.07; 95% CI 0.83 to 1.37, p=0.61). As the IPD meta-analyis did not include all relevant studies, the data from all six RCTs reporting survival data were included in a meta-analysis (Figure 3; RR 1.03, 95% CI 0.98 to 1.09). The results of this meta-analysis should be treated with caution as the length of follow-up of the RCTs varied and the analysis only considered the proportion of deaths and not time to death.

Disease-free survival

Four RCTs[6, 10, 25, 26] provided information on disease-free survival (Figure 3: RR 1.01 95% CI 0.95 to 1.07, p=0.83). This result is consistent with the IPD meta-analysis[9] where disease-free survival up to three years was found to be greater (by 0.5%) in the laparoscopic group although this was not statistically significant (hazard ratio 0.99; 95% CI 0.80 to 1.22; p=0.92).[9]

Important subgroup differences for laparoscopic versus open techniques

Patients undergoing conversions

Three studies reported separate outcome data for patients undergoing conversions.[7, 19, 25] The pattern observed in converted patients, for duration of operation, urinary tract and wound infection, and overall survival was similar to that reported above. Converted patients however, displayed higher blood loss and longer length of hospital stay. In addition, tumour recurrence appeared to be greater than that observed for patients who were successfully managed according to their treatment allocation although lymph node retrieval was higher. Converted patients

showed poorer QoL at baseline and at every follow-up assessment than patients who underwent laparoscopic resection.[34]

Effect of surgeon experience

Three trials reported the effect of surgeon experience on outcomes.[6-8] The COST trial found no experience-based trends for conversion, length of stay or QoL measures.[6, 34] However, the CLASICC trial reported a decline in number of conversions by year of recruitment from 38% in the first year to 16% in the sixth year.[7] The COLOR trial also found that the duration of surgery for laparoscopic procedures became shorter with increasing numbers of patients per centre ($p=0.03$), although number of lymph-nodes harvested and length of hospital stay did not differ significantly.[8]

Location of cancer

Subgroup analysis showed no evidence that the treatment effect size for anastomotic leakages was different for colon compared with rectal cancer (Figure 4). However, the evidence is limited as only two RCTs reported anastomotic leakages in rectal patients[7, 30] and hence confidence intervals are wide. A similar result was observed for wound infections and urinary tract infections (Figure 4).

Stage of cancer

Two RCTs provided subgroup analysis by stage of cancer for overall survival.[6, 26] In both of these trials there was no significant difference in overall survival of patients undergoing laparoscopic resection compared to open resection for cancer stages I, II or III ($p>0.05$). The IPD meta-analysis compared overall and disease-free survival for patients undergoing laparoscopic with open resection by stage of

cancer.[9] These analyses were based upon data from 426 (stage I), 612 (stage II) and 480 (stage III) patients, although data were not available from all of these for the whole three year follow-up period. Using the log-rank test, the authors found no evidence of a statistically significant difference at three years in overall and disease-free survival between the randomised groups by stage of disease. They reported p-values of 0.92, 0.44, and 0.53 for stages I, II, and III respectively for disease-free survival.[9]

DISCUSSION

This paper reports an update of the review[14] that underpinned NICE's guidance in 2000. Other reviews have been published since this guidance was issued, with the most recent being the one by Reza and colleagues.[36] We considered data from over 4500 randomised participants across 19 RCTs of generally good quality. Our review includes nine more RCTs than included in the review by Reza and colleagues[36] plus an additional IPD meta-analysis[9] which included unpublished data. In summary, we found that convalescence is more rapid after laparoscopic surgery (reflected in less postoperative pain and blood loss, shorter hospital stay, and more rapid return to usual activities). The duration of operation for laparoscopic resection is longer. Lymph node retrieval, completeness of resection and QoL do not appear to differ between the two approaches, although clinically important differences could not be ruled out. The occurrence of complications such as anastomotic leakage, abdominal wound breakdown, incisional hernia, wound and urinary tract infections are similar, again with wide confidence intervals. Operative and 30-day mortality, were also similar in both groups.

The major development since the 2000 review[11] has been in the evidence on recurrence, disease-free survival and overall survival. We found no evidence of a difference in the number of recurrences (including wound recurrences), disease-free survival and overall survival. Furthermore, after laparoscopic resection, port-site recurrences were found in less than 1% of patients. This updated review also attempted to assess relative effectiveness in terms of differences in wound related morbidities such as incisional and port-site hernias, and persisting pain. Few data were identified for hernia.

Although there were marked differences in study populations and setting for duration of operation and length of hospital stay, resulting in significant heterogeneity, consistency on the direction of effect was observed.

There were relatively few data for any of the subgroups. The data that were available suggest that there may be important differences between colon and rectal cancer as well as between patients undergoing conversions. However, this is tentative, and it was impossible to judge whether or not there are potentially important differences between treatments within clinical subgroups of colorectal cancer patients. In addition, there is emerging experience in the literature in support of considering colon and rectal cancer as separate entities as rectal cancer has unique technical and pelvic dissection issues. Moreover, the systematic review was conducted on an intention to treat basis. Therefore, any reduction in the rate at which patients undergoing laparoscopic surgery are converted to open surgery might be expected to increase the difference observed between laparoscopic and open surgery.

Several limitations must be noted when interpreting the results of this review. An extensive literature search was conducted and both published and unpublished data were sought. Despite these efforts, it is possible that some unpublished studies may have been missed. Moreover, some trials excluded patients with advanced disease while others included only patients with colon cancer, thus limiting subgroup analyses and making results not generalisable to all groups of patients.

For many of the review outcomes the data were sparse. Nonetheless, the direction and magnitude of effect of these data appeared to be consistent.

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

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

In conclusion, with the supplement of new high quality data that have become available and the IPD meta-analysis, this review supports the use of laparoscopic surgery for the treatment of colorectal cancer beyond an RCT setting provided that is

carried out by surgeons with appropriate experience and competence. Based on this review and other considerations, NICE changed its guidance in 2006 and laparoscopic resection is now an accepted alterative to open resection in the UK. Nevertheless, there is insufficient evidence to judge whether the procedures differed in respect to long-term outcomes as the best data relates to a three-year follow-up. However, three of the largest trials[6-8] are still to be concluded which will provide more reliable data on long-term outcomes. In addition, a multicentre trial involving over 800 patients has started in Japan to evaluate whether laparoscopic surgery is the optimal treatment for colorectal cancer in which the primary outcome of interest in the study is overall survival.[37] As these data become available, they should be used to update systematic reviews. Also, the authors of the IPD meta-analysis should be encouraged to extend their data in terms of both follow-up and inclusion of other relevant studies by involving other groups. Lastly, there is very limited data available on HALS and if this technique is to be adopted widely, methodological sound RCTs comparing HALS with both laparoscopic and open surgery are necessary.

ACKNOWLEDGEMENTS

The authors are thankful to information officer Cynthia Fraser for undertaking the searches and secretarial support from Bronwyn Davidson.

Work on the review was supported by a grant from the National Institute for Health and Clinical Excellence.

The Health Services Research Unit is core funded by the Chief Scientist Office of the Scottish Executive Health Department. The views expressed in this paper are those of the authors not the institutions providing funding.

REFERENCES

1. Wanebo HJ editor (1993) Colorectal cancer Mosby, St Louis

2. Rowan S, Wood H, Cooper N, Quinn M (2005) Update to Cancer Trends for England & Wales 1950-1999 Available at: http://www.statistics.gov.uk/downloads/theme_health/CancerTrendsUpdates.pdf. Accessed June 2005.

3. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ (2006) Cancer statistics, 2006. CA Cancer J Clin 56(2): 106-130

4. Fazio VW, Lopez-Kostner F (2000) Role of laparoscopic surgery for treatment of early colorectal carcinoma. World J Surg 24(9): 1056-1060

5. National Institute for Clinical Excellence Guidance on the use of laparoscopic surgery for colorectal surgery. Technology appraisal guidance no 17 Available at: http://www.nice.org.uk/pdf/guidancelapcolcanc.pdf Accessed June 2005.

6. Clinical Outcomes of Surgical Therapy Study Group (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 350(20): 2050-2059

7. Guillou P.J, Quirke P, Thorpe H, Walker J, Jayne D, Smith AM, Brown JM (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 3651718-1726

8. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM, COlon cancer Laparoscopic or Open Resection Study Group (2005) Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 6(7): 477-484

9. Trans Atlantic Laparoscopically-Assisted versus Open Colectomy Trials Study Group (2007) Laparoscopically assisted vs open colectomy for colon cancer - a meta-analysis. Arch Surg 142: 298-303

10. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 359(9325): 2224-2229

11. Vardulaki K, Bennett-Lloyd B, Parfitt J, Normond C, Paisley S, Darzi A, Reeves B A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer. Available at: http://www.nice.org.uk/pdf/HTAreportonlapsurgcoloreccanc.pdf. Accessed June 2005

12. Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, Krukowski Z, Vale L, Grant A (2006) Clincal effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. Health Technol Assess 10(45)

13. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG (1998) The Delphi list: a criteria list for quality assessment of

randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 51(12): 1235-1241

14. Oxman AD, Guyatt GH (1993) The science of reviewing research. Ann NY Acad Sci 703125-133

15. Oxman AD, Cook DJ, Guyatt GH (1994) Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA 272(17): 1367-1371

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

17. Neudecker J, Junghans T, Ziemer S, Raue W, Schwenk W (2003) Prospective randomized trial to determine the influence of laparoscopic and conventional colorectal resection on intravasal fibrinolytic capacity. Surg Endosc 17(1): 73-77

18. Araujo SE, da Silva eSousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, Nahas SC, da Silva J, Kiss DR, Gama-Rodrigues JJ (2003) Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. Rev Hosp Clin Fac Med Sao Paulo 58(3): 133-140

19. Curet MJ, Putrakul K, Pitcher DE, Josloff RKZucker KA (2000) Laparoscopically assisted colon resection for colon carcinoma: perioperative results and long-term outcome. Surg Endosc 14(11): 1062-1066

20. Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M (2003) Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. Surg Endosc 17(4): 636-640

21. Hewitt PM, Ip SM, Kwok SP, Somers SS, Li K, Leung KL, Lau WY, Li AK (1998) Laparoscopic-assisted vs. open surgery for colorectal cancer: comparative study of immune effects. Dis Colon Rectum 41(7): 901-909

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

23. Stage JG, Schulze S, Moller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, Nielsen HJ (1997) Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. Br J Surg 84(3): 391-396

24. Tang C-, Eu K-, Tai B-, Soh JGS, MacHin D, Seow-Choen F (2001) Randomized clinical trial of the effect of open versus laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer. Br J Surg 88(6): 801-807

25. Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW,Jr (2004) Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. J Laparoendosc Adv Surg Tech A 14(6): 329-334

26. Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY (2004) Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet 363(9416): 1187-1192

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

28. King PM (2006) Open versus laparoscopic surgery for colorectal cancer: a randomised study embedded within an enhanced recovery programme. Br J Surg

29. Vignali A, Braga M, Zuliani W, Frasson M, Radaelli G, Di C,V. (2004) Laparoscopic colorectal surgery modifies risk factors for postoperative morbidity. Dis Colon Rectum 47(10): 1686-1693

30. Zhou ZG, Hu M, Li Y, Lei WZ, Yu YY, Cheng Z, Li L, Shu Y, Wang TC (2004) Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer. Surg Endosc 18(8): 1211-1215

31. Winslow ER, Fleshman JW, Birnbaum EH, Brunt LM (2002) Wound complications of laparoscopic vs open colectomy. Surg Endosc 16(10): 1420-1425

32. Kim SH, Milsom JW, Gramlich TL, Toddy SM, Shore GI, Okuda J, Fazio VW (1998) Does laparoscopic vs. conventional surgery increase exfoliated cancer cells in the peritoneal cavity during resection of colorectal cancer? Dis Colon Rectum 41(8): 971-978

33. Schwenk W, Bohm B, Muller JM (1998) Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial. Surg Endosc 12(9): 1131-1136

34. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G, Clinical Outcomes of Surgical Therapy (COST) Study Group (2002) Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 287(3): 321-328

35. Schwenk W, Bohm B, Muller JM (1998) Influence of laparoscopic or conventional colorectal resection on postoperative quality of life. Zentralbl Chir 123(5): 483-490

36. Reza MM, Blasco JA, Andradas E, Cantero R, Mayol J (2006) Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg 93: 921-928

37. Kitano S, Inomata M, Sato A, Yoshimura K, Moriya Y, Japan Clinical Oncology Group Study (2005) Randomized controlled trial to evaluate laparoscopic surgery for colorectal cancer: Japan Clinical Oncology Group Study JCOG 0404. Jpn J Clin Oncol 35: 475-477

Tables and Figures:

Table 1 Summary of outcomes reported in the included studies

	SHORT-TERM OUTCOMES																		LONG-TERM OUTCOMES						
Study id	Duration of operation	Blood loss	Anastomotic leakage	Abdominal wound breakdown	Lymph node retrieval	Number ports used	Opposite method initiated	Completeness of resection/ margins of tumour clearence	Conversion	Seroma	Infection	Port site hernia	Vascular injury	Visceral injury	30 day mortality	Length hospital stay	Post-operative pain	Time to return to usual activities	Survival	Disease-free survival	Quality of life	Recurrence	Time to recurrence	Incisional hernia	Long term pain
Araujo 2003[18]	✓			✓	✓	✓			✓							✓						✓			
CLASICC 2005[7]	✓		✓		✓		✓	✓	✓		✓				✓	✓	✓				✓				
COLOR 2005[8]	✓	✓	✓	✓	✓		✓	✓	✓		✓				✓	✓									
COST 2004[6]	✓				✓			✓	✓						✓	✓	✓		✓	✓		✓			
Winslow 2002[31]						✓					✓													✓	
Weeks 2002[34]																	✓				✓				
Curet 2000[19]	✓	✓			✓	✓			✓		✓				✓	✓			✓			✓			
Hasegawa 2003[20]	✓	✓	✓		✓	✓			✓		✓					✓	✓					✓			
Hewitt 1998[21]	✓					✓										✓	✓								
Kaiser, 2004[25]	✓	✓			✓				✓		✓					✓	✓		✓	✓		✓			
Kim 1998[32]																						✓			
King 2005[28]	✓	✓	✓	✓					✓		✓				✓	✓	✓				✓				
Lacy 2002[10]	✓	✓	✓		✓		✓				✓				✓	✓	✓		✓	✓		✓	✓		
Leung 2004[26]	✓	✓	✓		✓			✓	✓		✓				✓	✓		✓	✓	✓		✓	✓	✓	
Milsom 1998[27]					✓			✓														✓			
Neudecker 2003[17]	✓																								
Schwenk 1998a[22]	✓										✓														
Schwenk 1998b						✓										✓	✓								
Schwenk 1998c																					✓				
Stage 1997[23]	✓	✓			✓	✓		✓	✓							✓	✓					✓			
Tang 2001[24]	✓		✓			✓			✓		✓														
Vignali 2004[29]					✓																				
Zhou 2004[30]	✓	✓	✓					✓								✓	✓		✓			✓			

Table 2 Summary of the quality assessment of the included RCTs

Criteria	Yes	No	Unknown
1. Was a method of randomisation performed?	**18** [6-8, 10, 17-21, 23-29, 32, 35]	**0**	**1** [30]
2. Was the treatment allocation concealed?	**6** [6-8, 17, 26, 28]	**5** [10, 19, 24, 29, 32]	**8** [18, 20, 21, 23, 25, 27, 30, 35]
3. Were the groups similar at baseline regarding the most important prognostic indicators?	**14** [6-8, 10, 17-20, 24, 26-28, 30, 35]	**5** [21, 23, 25, 29, 32]	**0**
4. Were the eligibility criteria specified?	**19**[6-8, 10, 17-21, 23-30, 32, 35]	**0**	**0**
5. Was the outcome assessor blinded?	**1** [6]	**2** [8, 27]	**16** [7, 10, 17-21, 23-26, 28-30, 32, 35]
6. Was the care provider blinded?	**0**	**19** [6-8, 10, 17-21, 23-30, 32, 35]	**0**
7. Was the patient blinded?	**0**	**3**[8, 17, 27]	**16** [6, 7, 10, 18-21, 23-26, 28-30, 32, 35]
8. Were point estimates and measures of variability presented for the primary outcome measures?	**18** [6-8, 10, 17, 19-21, 23-30, 32, 35]	**1** [18]	**0**
9. Did the analysis include an intention-to-treat analysis?	**7** [6-8, 24, 28, 29, 35]	**7** [19-21, 23, 25-27]	**5** [10, 17, 18, 30, 32]

Table 3 Summary of the baseline characteristics

Study id	Comparators	Number of participants	Age (years) *	Male/Female	Colon/Rectum
Araujo 2003[18]	Laparoscopic	13	59	9/4	0/13
	Open	15	56	10/5	0/15
CLASICC 2005[7]	Laparoscopic	526	69	296/230	273/253
	Open	268	69	145/123	140/128
COLOR 2005[8]	Laparoscopic	536	71†	326/301	536/0
	Open	546	71†	336/285	546/0
COST 2004[6]	Laparoscopic	435	70†	223/212	435/0
	Open	428	69†	208/220	428/0
Curet 2000[19]	Laparoscopic	25	66	15/10	25/0
	Open	18	69	14/4	18/0
Hasegawa 2003[20]	Laparoscopic	24	61	14/10	22/2
	Open	26	61	18/8	24/2
Hewitt 1998[21]	Laparoscopic	8	54†	4/4	8/0
	Open	8	70†	3/5	8/0
Kaiser 2004[25]	Laparoscopic	28	59	12/16	28/0
	Open	20	60	9/11	20/0
Kim 1998{[32]	Laparoscopic	19	70†	8/11	19/0
	Open	19	65†	10/8	18/0
King 2005[28]	Laparoscopic	41	72	23/18	27/14
	Open	19	70	8/11	14/5
Lacy 2002[10]	Lap-assisted	111	68	56/55	111/0
	Open	108	71	50/58	108/0
Leung 2004[26]	Laparoscopic	203	67	104/99	0/203
	Open	200	66	114/86	0/200
Milsom 1998[27]	Laparoscopic	55	69†	26/29	48/7 §
	Open	54	69†	36/18	50/4 §
Neudecker 2003[17]	Laparoscopic	14	62†	7/7	14/0
	Open	16	64†	10/6	16/0
Schwenk 1998a[22]	Laparoscopic	30	64	14/16	23/7
	Open	30	65	16/14	23/7
Stage 1997[23]	Laparoscopic	15	72†	8/7	15/0
	Open	14	73†	5/9	14/0
Tang 2001[24]	Laparoscopic	118	64†	61/57	118/0
	Open	118	62†	70/48	118/0
Vignali 2004[29]	Laparoscopic	146	NR	NR	98/48
	Open	143	NR	NR	94/49
Zhou 2004[30]	Laparoscopic	82	45	46/36	0/82
	Open	89	44	43/46	0/89

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

Table 4 Continuous outcomes for laparoscopic versus open resection

Study id	Duration of operation (minutes)			Blood loss (ml)			Lymph node retrieval (number)			Length of hospital stay (days)		
	LR	OR	*p value*	LR	OR	*p value*	LR	OR	*p value*	LR	OR	*p value*
Araujo 2003[18]	228	284	0.04				5.5	11.9	0.04	10.5	NR*	0.42
CLASICC 2005[7]	180† (135-220) ††	135† (100-180) ††					12† (8-17) ††	13.5† (8-19) ††		9† (7-14) ††	11† (8-15) ††	
COLOR 2005[8]	145† (45-420)	115† (40-355)	<0.001	100† (0-2700)	175† (0-2000)	<0.001	10† (0-41)	10† (0-42)	0.35	8.2 SD 6.6	9.3 SD 7.3	<0.001
COST 2004[6]	150† (35-450)	95† (27-435)	<0.001				12†	12†		5† (4-6) ††	6† (5-7) ††	<0.001
Curet 2000[19]	210* (128-275)*	138* (95-240)*	<0.05	284* (100-700)*	407* (100-1000)*	<0.05	11* (2-23)*	10* (1-21)*		5.2*	7.3*	<0.05
Hasegawa 2003[20]	275 (184-410)	188 (127-272)	<0.001	58 (1-350)	137 (32-355)	0.0034	23 (7-50)	26 (15-56)	0.25	7.1 (4-15)	12.7 (6-57)	0.016
Hewitt 1998[21]	165† (130-300)	107.5 † (90-150)	0.02							6† (5-7)	7† (4-9)	
Kaiser 2004[25]	125 (70-270)	65 (45-125)	<0.05	146.4 (100-1000)	100 (100-800)		13.3 (1-32)	14 (3-27)		5.9 (3-13)	6 (5-9)	<0.05
King 2005[28]	187** (95% CI 168-207)	140** (95% CI 121-163)	0.001	11‡ (27%)	18‡ (95%)	<0.001				5.2** (95% CI 4.2-6.5)	7.4** (95% CI 6.0-9.2)	0.018
Lacy 2002[10]	142 SD 52	118 SD 45	0.001	105 SD 99	193 SD 212	0.001	11.1 SD 7.9	11.1 SD 7.4		5.2 SD 2.1	7.9 SD 9.3	0.005
Leung 2004[26]	190 SD 55	144 SD 58	<0.001	169 (0-3000)	238 (0-5836)	0.06	11.1 (7.9)	12.1 (7.1)		8.2 (2-99)	8.7 (3-39)	<0.001
Milsom1998[27]							19† (5-59)	25† (4-74)				
Neudecker 2003[17]	205† (120-260)	165† (100-285)	<0.05									
Schwenk 1998a[22]	219 SD 64	146 SD 41	<0.01							10.1 SD 3.0	11.6 SD 2.0	<0.05
Stage 1997[23]	150† (60-275)	95† (40-195)	0.05	275† (50-2100)	300† (50-2150)		7† (3-14)	8† (4-15)		5 (3-12)	8 (5-30)	0.01
Tang 2001[24]	88† (15-220)	70† (20-195)										
Vignali 2004[29]							15.2 SD 8.6	15.0 SD 7.7	0.9			
Zhou 2004[30]	120 (110-220)	106 (80-230)	0.051	20 (5-120)	92 (50-200)	0.025				8.1 SD 3.1	13.3 SD 3.4	0.001

Values given as mean values (range), unless otherwise specified; LR: laparoscopic resection; OR: open resectionSD: standard deviation; CI: confidence interval; † Median; †† Interquartile range; *Not reported ** geometric mean; ‡ number with blood loss>100ml (%)

Figure 1 **Study selection process**

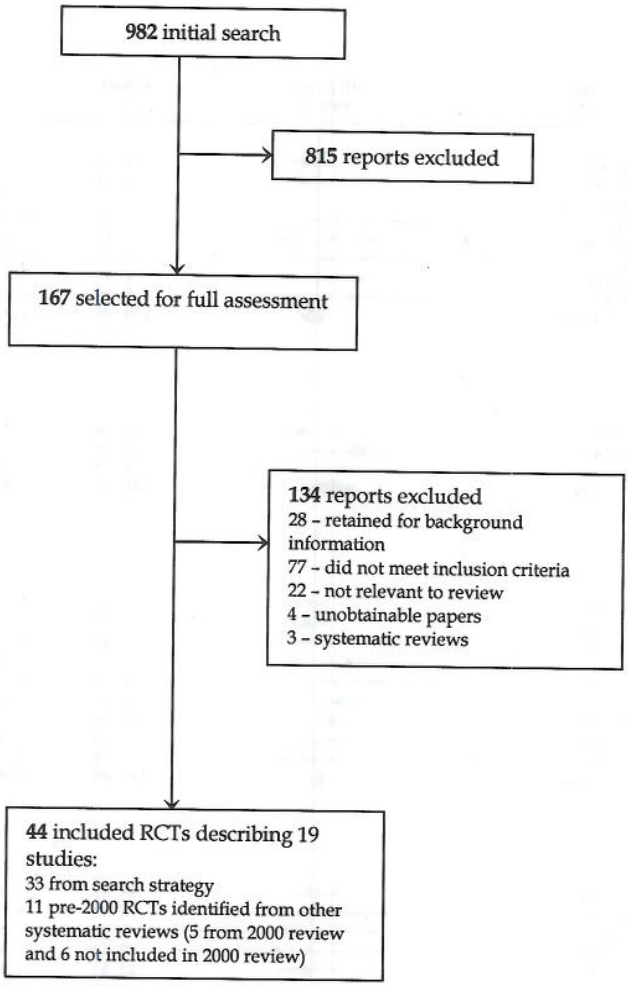

Figure 2 **Adverse events for laparoscopic versus open surgery**

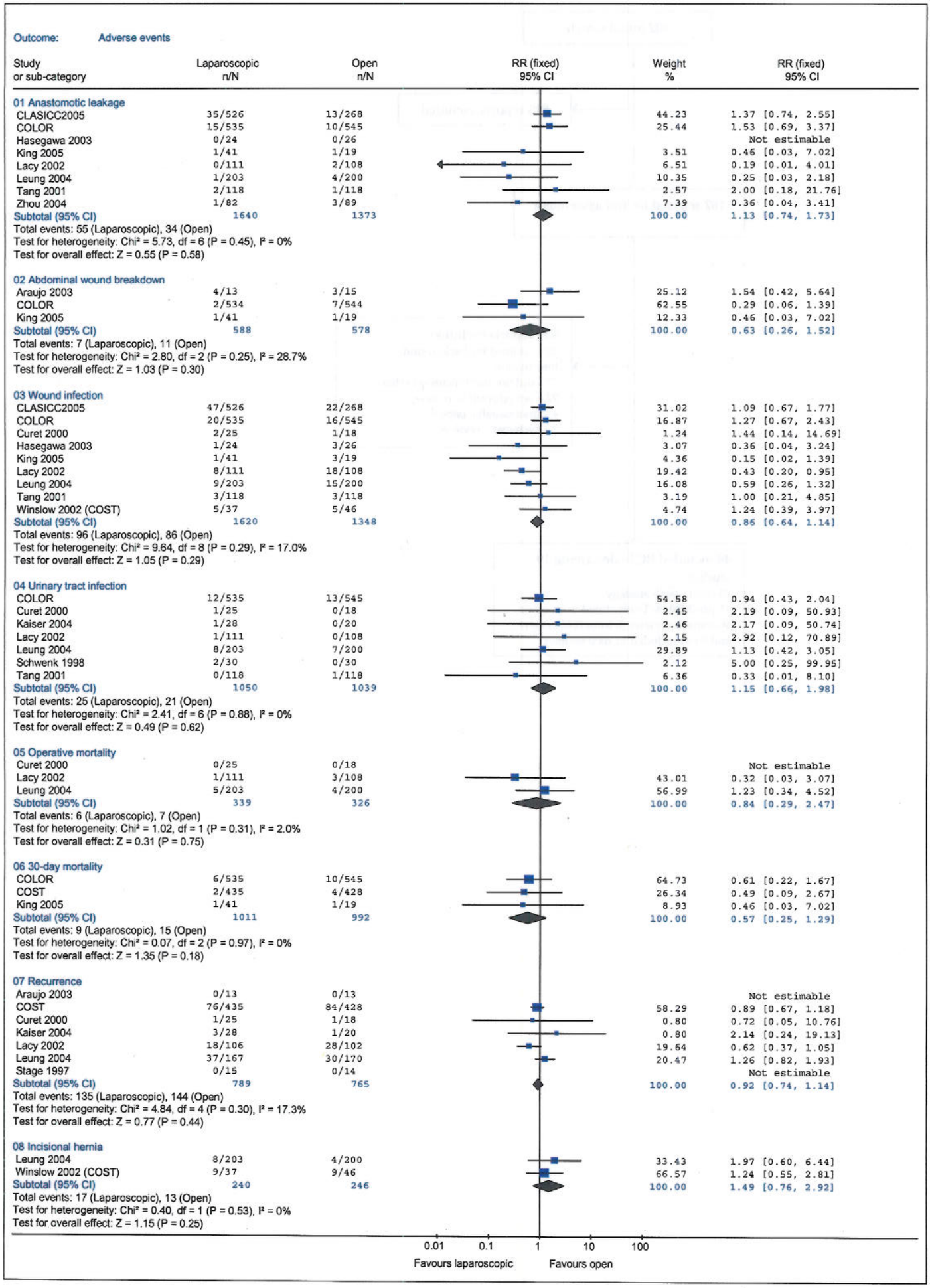

Figure 3 **Overall survival and disease-free survival for laparoscopic versus open surgery**

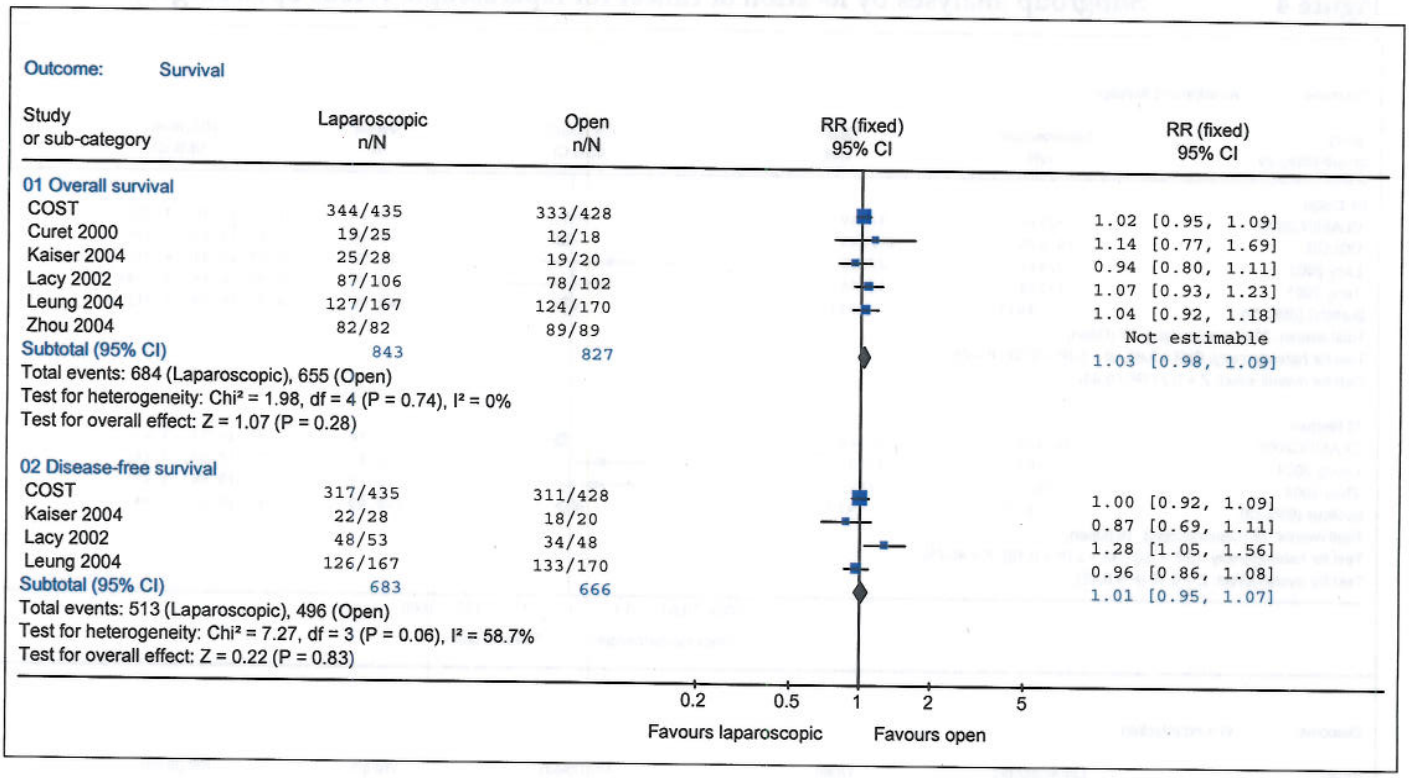

Figure 4 **Subgroup analyses by location of cancer for laparoscopic versus open surgery**