

Title: Long term survival following laparoscopic and open colectomy for colon cancer: A meta-analysis of RCTs

Short Title: Laparoscopic vs. Open Colectomy: Survival.

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## ABSTRACT

### **Background and Objective**

Large randomised clinical trials comparing long term survival in patients undergoing laparoscopic and open colectomy show equivalence, however meaningful analysis of data by stage has not been possible due to small numbers within individual trials. The aim of this meta-analysis is to improve the power by combining data to enable assessment of survival for individual stages.

### **Methods**

A formal systematic review and meta-analysis was conducted. A computerised search of all Randomised Controlled Trials (RCTs) was performed. Overall survival data was analysed and subgroup analysis performed for cancer stages I-III.

### **Results**

Five trials (n = 3152 patients) were included. Overall survival was equivalent (HR: 0.93, 95 CI: 0.80-1.07). With each of the cancer stages I-III there was no difference in outcomes for 5 year survival. There was however a non-significant trend in favour of open surgery in the sub-group analysis of Stage II patients.

### **Conclusions**

Laparoscopic assisted surgery for colon cancer is equivalent to open surgery with respect to long term survival.

### WHAT DOES THIS PAPER ADDS TO THE LITERATURE?

This paper includes long term data from all large RCTs on long term survival following laparoscopic and open colon cancer surgery. It is the only such meta-analysis to exclude all rectal cancers from the analysis to ensure accuracy. The increased numbers enabled subgroup analyses by cancer stage.

## INTRODUCTION

Surgery is the mainstay for cure for colorectal cancer and until the introduction of laparoscopic colectomy in 1991<sup>6,9</sup>, laparotomy was the main surgical approach utilised. Short term benefits of laparoscopic colectomy over open colon resection such as decreased length of stay, shorter return to function and better cosmesis have now been proven<sup>22</sup>. Subsequently, the debate has moved to the possibility of differences in oncological outcomes between the two techniques.

Evidence to date regarding long-term survival comparing laparoscopic versus open resection for colon cancer has been mainly from the results of large scale Randomised Controlled Clinical Trials (RCTs) and some case series. Although there have been meta-analyses looking at some of these trials, showing equivalence, these did not include the long term data from all of them and did not exclude the rectal cancers in the UK MRC CLASICC trial<sup>4</sup>. More recently, the Australasian Laparoscopic Colon Cancer Study (ALCCaS)<sup>1</sup> have released their 5 year survival outcomes that can now be included. In addition, there has been no subgroup analysis by cancer stage within the published meta-analyses.

The aim of this study was to undertake a meta-analysis of the overall survival results for clinical trials comparing laparoscopic versus open surgery in only patients with colon cancer. In addition, the study aimed to undertake a sub-group analysis of overall survival by cancer stage.

## METHODS

In compliance with Quality of Reporting of Meta-analyses (QUORUM) guidelines<sup>16</sup>, an initial systematic literature review was undertaken.

### **Search strategy**

A computerised search was undertaken using the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines<sup>23</sup>. The Cochrane developed Highly Sensitive Search Strategy (HSSS) was employed when searching Medline (Ovid and Pubmed) (figure 1). The Cochrane Library and Embase were also searched for studies that met the inclusion criteria within the years 1990-2010. MeSh terms included ‘laparoscopic’, ‘surgery’, ‘colon’ and ‘cancer’. Reference lists of suitable retrieved articles and of prior meta-analyses were also searched. There were no language restrictions. Most recent data from established trials were sought from the trial investigators and statisticians.

### **Study Selection**

Published Randomised Controlled Trials (RCTs) comparing laparoscopic with open colectomy for colon cancer from 1990-2010 were selected. Updated, unpublished data received directly from the statisticians for these trials was also included. In order to be included, studies had to have at-least 3 year survival data and have outcome measures that primarily included overall survival.

Rectal cancers were excluded. Studies that included benign pathology in analyses were excluded in addition to those that did not meet the inclusion criteria above. A flow diagram summarising the selection of suitable studies is shown in figure 2.

## **Analysis**

Log hazard ratios and their variance were used as the summary outcome measure from all trials in the meta-analysis. Published hazard ratios were used then available, or estimated from log rank p-values or from a combination of number of deaths, numbers at risk and Kaplan-Meier survival curves. Formulae from Parmar et al<sup>19</sup> were utilised to enable extraction and estimation of the log hazard ratios. Analysis of aggregated data was performed using metan in STATA 12.0. The log hazard ratios were graphed on Forest plots using Inverse-Variance weighted fixed effect methods (I-V pooled) and DerSimonian and Laird random effects methods (D+L pooled). Heterogeneity was assessed using the  $I^2$  statistic, which is the percentage of between-study heterogeneity that is attributable to variability in the true treatment effect rather than sampling variation. Only fixed effects estimates are reported in the absence of evidence of heterogeneity. The presence of bias was assessed using funnel plots (metafunnel in STATA 12.0) and the Cochrane risk of bias tool<sup>5</sup>.

## RESULTS

### **Study Characteristics**

Five Trials were identified and included in this meta-analysis: Barcelona Trial<sup>12</sup>, Clinical Outcomes of Surgical Therapy (COST)<sup>7</sup>, Colon Cancer Laparoscopic or Open Resection (COLOR)<sup>3</sup>, Conventional vs. Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASICC)<sup>10</sup> and the Australasian Laparoscopic Colon Cancer Study (ALCCaS)<sup>1</sup>.

Of these, four were multicentre and one<sup>12</sup> was from a single institution; overall, procedures were carried out in 136 centres. Only the CLASICC study included rectal cancers, but these were excluded from analysis. All studies excluded transverse colon cancers and emergency presentations with bowel obstruction. Basic study characteristics are summarised in Table 1. All of the trials had ethics approval. Surgeons in the COST, CLASICC and COLOR trials required credentialing with at least 20 laparoscopic colectomies to be eligible. Within the Barcelona and ALCCAS trials, surgeons were noted to be experienced, with the former having one surgical team performing all procedures. Randomisation was 1:1 in all except the CLASICC trial which undertook a 2:1 randomisation in favour of laparoscopic procedures. None of the studies were blinded and all were powered to show non-inferiority of the laparoscopic technique.

### **Analysis**

Final analysis was carried out on information from the five studies previously described. With the CLASICC trial, which included surgery on rectal cancers, colon-only data was obtained directly from the study statistician to enable inclusion. All studies had 5 year survival data available for extraction from either published figures or from correspondence with the authors and respective statisticians. For those studies reporting conversions from the

laparoscopic to the open approach, the intention to treat figures were used. Overall survival figures for all trial patients include those with Stage IV disease. Although most studies excluded these patients, some were diagnosed at operation and included in the final analysis as part of the intention to treat analysis.

Overall survival (all-cause mortality) as estimated from the total number of deaths that occurred in the follow up period, was used as the primary outcome measure for analysis. Only overall survival figures were used from the studies. Most studies did not define overall survival but reported total patients in each study arm and total number of deaths in each arm. Start time was either from the date of randomisation (COST, CLASICC) or from date of surgery (Barcelona), but not mentioned in two trials (ALCCaS, COLOR).

Information for sub-group analysis by Stage for overall survival, was available for the COLOR, COST and Barcelona trials by extraction of estimated log hazard ratios from Kaplan-Meier survival curves in the published material. Similar information for the CLASICC and ALCCaS trials were obtained via correspondence with the statisticians of the respective studies. The CLASICC trial reported Duke staging. For the purposes of inclusion in the final analysis by stage Dukes A, B and combined C1 and C2 were treated as Stages I, II and III respectively. Allowance was made for the 2:1 randomisation of laparoscopic to open with this study<sup>19</sup>.

### **Meta-analysis findings**

This meta-analysis included five trials with information on long-term survival, with a total of 3152 patients (n=1510 open, n= 1642 laparoscopic). The vast majority of patients were in the Stage II group (1318 patients, 42%), with the least number of patients in Stage I (n=714,

23%). There were a small number of patients (n=155) who were discovered to have more advanced disease at the time of operation and were included in the final results of all stages as part of the intention to treat analysis in all studies.

Overall there was some evidence of heterogeneity between the studies ( $I^2 = 32\%$ ) but this did not reach significance ( $p=0.206$ ) on the combined data. With respect to subgroup analysis, there was no significant heterogeneity in Stage I ( $p = 0.853$ ) and Stage II ( $p=0.872$ ) studies. With Stage III there was evidence of heterogeneity amongst the studies with an  $I^2$  of 60% ( $p=0.039$ ). The presence of between-study heterogeneity means that the fixed-effect assumption (that the true treatment effect is the same in each study) may be incorrect. Therefore, random-effects models were also generated for Stage III studies and the overall data and are shown on the Forest plot (Figure 3). There were no obvious asymmetries observed when bias was assessed using Funnel plots with little evidence of small study effects and publication bias (data not shown). A summary of the potential risks of study biases are also included in Table 1.

In the combined results, there was no statistical difference in long term overall survival between the laparoscopic and open surgery groups (HR: 0.93, 95 CI: 0.80-1.07). The subgroup analysis showed no significant difference in overall survival at 5 years between laparoscopic and open groups for individual stages. Although Stage I (HR: 1.04, 95 CI 0.68-1.56) and Stage III (fixed effects HR: 0.99, 95 CI 0.81-1.20; random effects HR: 0.97, 95 CI: 0.70-1.35) were completely equivalent, there was a non-significant survival trend with the Stage II group (HR: 1.21 CI 0.96-1.51) that favoured open surgery (figure 3).



## DISCUSSION

Whilst the uptake of laparoscopic colectomy has been slower over the last three decades than other minimally invasive techniques, its use has become prevalent, and up to 25% of surgery for elective colorectal cancer in Australia is now performed laparoscopically<sup>24</sup>. Laparoscopic colectomy has even been proposed as the new gold standard for colectomy by some advocates<sup>20</sup>. As with many new techniques, the initial focus has been on short term outcomes, but with the results of several large randomised controlled trials being published attention has been redirected to the long term oncological results.

This is the first meta-analysis to look at long term survival outcomes using time to event outcomes, the log hazard ratio, across all the major randomised controlled trials that have assessed laparoscopic versus open surgery for colon cancer and therefore has the largest number of patients (n=3152) compared to previous meta-analyses<sup>8, 11, 13, 15</sup>. Moreover, this large data collection allows analysis by stage to be more meaningful by increasing the power. Stage specific analysis was performed using data from all included studies at five years and showed equivalence in overall survival for each stage. Prior to this study, only the meta-analysis by Bonjer et al<sup>4</sup>, which reported similar overall survival by Stage at three years across four RCTs (n=1536 patients) had looked at stage specific data.

This study is unique because most systemic reviews and meta-analyses in the past have included non-randomised data and looked at a variety of parameters including short term outcomes<sup>21, 11</sup> and recurrence<sup>14</sup>. None have looked at colon-only data across all major trials. Overall numbers in previous studies are small. A recent meta-analysis with large numbers by Ma<sup>15</sup>, showed similar results (OR =0.87, CI 0.73-1.73) when looking at ten studies with

results on overall survival without excluding rectal cancers. In addition time to events had not been accounted for in the combined results of that study.

The results for all patients, in our study, are in keeping with those from previous meta-analyses<sup>2, 8, 11, 15</sup> and the study results themselves, as expected. There was also no significant difference in overall survival when looking at individual stages. The Barcelona trial<sup>12</sup>, which had the lightest weighting in this meta-analysis, showed a survival benefit for laparoscopic surgery in the Stage III subgroup. The COST trial<sup>7</sup> however showed a survival benefit for those Stage I patients undergoing open colectomy. Neither of these results are supported when looking at aggregate stage data as in this study.

Interestingly, when looking at Stage II in this meta-analysis, there was a non-significant trend for survival benefit in favour of open surgery (fig. 1). Outcomes for Stage II colon cancer may be a better marker for the contribution of surgical technique to survival. Few of these patients receive chemotherapy<sup>17</sup> and so differences in survival outcomes can be attributable to surgical technique and quality. Furthermore, there is evidence that compared to Stage I colon cancers, there is a significant recurrence rate amongst Stage II<sup>17</sup> cohorts and so analysis of the influence of different surgical techniques on such outcomes is possible with a fewer number of patients<sup>18</sup>.

This meta-analysis is limited by the studies included which are all large scale RCTs with strict inclusion criteria. For instance, transverse colon cancers were excluded in all, and these results therefore cannot necessarily be extrapolated to such patients. In addition, it is possible that this meta-analysis is still underpowered to show significant differences and more work is required to validate laparoscopic surgery, especially in patients with Stage II disease. Trials

are unlikely to be able to provide the power for this type of analysis that would probably be better served by studying larger population based datasets, which also overcomes the problems with applicability of results at the community level.

## CONCLUSION

A meta-analysis of five clinical trials involving a large series of patients with colon cancer in whom there is now long term follow-up confirms equivalence of long term survival outcomes for laparoscopic assisted versus open colon surgery. It is indicative of the oncological safety of laparoscopic colectomy. This result is independent of stage. Whether these outcomes can be reproduced in the community setting where there are no strict inclusion criteria as with trials, is yet to be determined. More work on population studies looking at morbidity and mortality outcomes must now be performed to assess this fully.

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## Figure Legends

Figure 1: Highly sensitive search strategy (HSSS) terms

Figure 2: CONSORT diagram demonstrating study selection process

Figure 3: Forest plots for Stages I-III and overall

I-V pooled effects = Inverse-variance weighted fixed effects model. D+L pooled effects = DerSimonian and Laird random effects method

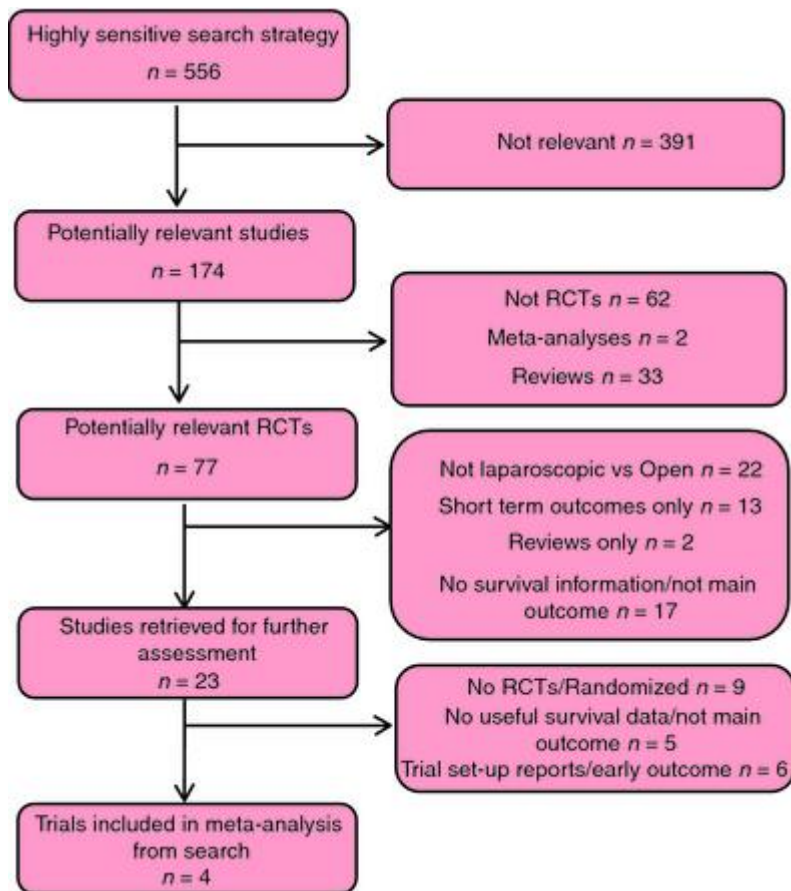
Table 1: Characteristics of included studies and risk of bias assessment



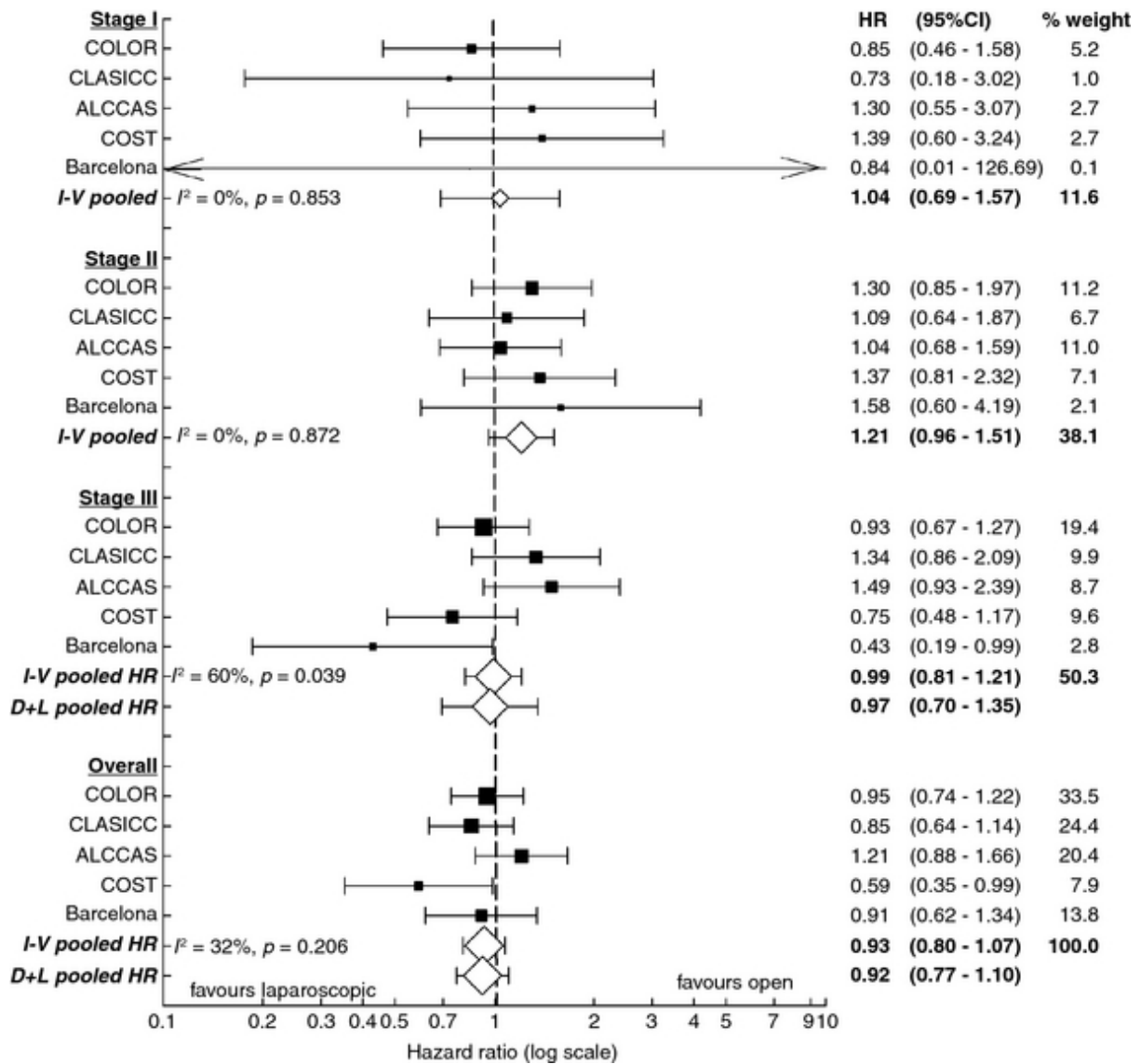
**Figure 1.** Highly sensitive search strategy (HSS) terms

- | HSSS terms   |
|--|
| 1. randomized controlled trial.pt.   |
| 2. controlled clinical trial.pt.   |
| 3. randomized.ab.  |
| 4. randomly.ab.  |
| 5. trial.ab.   |
| 6. groups.ab.  |
| 7. 1 or 2 or 3 or 4 or 5 or 6  |
| 8. exp animals/ not humans.sh.   |
| 9. 7 not 8   |
| 10. Aged/ or Laparoscopy/ or<br>middle aged/ or postoperative<br>complications/ or<br>laparoscopic.mp. or adult/     |
| 11. surgery.mp. or general<br>surgery  |
| 12. colon.mp. or colon, sigmoid/<br>or colon, descending/ or colon/ or<br>colon, ascending/ or colon,<br>transverse/ |
| 13. cancer.mp. or neoplasms/   |
| 14. 10 and 11 and 12 and 13  |
| 15. 9 and 14   |
| 16. limit 15 to yr="1990 - 2012"   |

**Figure 2.** CONSORT diagram demonstrating study selection process



**Figure 3.** Forest plots for Stages I–III and overall I-V pooled effects = Inverse-variance weighted fixed effects model; D + L pooled effects = DerSimonian and Laird random effects method



**Table 1. Characteristics of included studies and risk of bias assessment.**

Trial name	COST	COLOR	CLASICC	Barcelona	ALCCAS
Region	US	Europe	UK	Spain	Australia
Recruitment period	August 1994 to August 2001	March 1997 to March 2003	July 1998 to July 2002	November 1993 to July 1998	January 1998 to April 2005
Single/multicentre (no. of centres)	Multicentre (48)	Multicentre (29)	Multicentre (27)	Single centre	Multicentre (31)
Number of patients					
Laparoscopy	435	534	273 <sup>a</sup>	106	294
Open	428	542	140 <sup>a</sup>	102	298
Mean (median) age (years)					
Laparoscopy	70	71	(69)	(68)	(71)
Open	69	71	(69)	(71)	(69)
Number of male patients (%)					
Laparoscopy	51	52	56	50	47
Open	49	53	54	45	48
Stages	I–III	I–III	A–C2	I–III	I–III
Median follow-up (months)	84	54	70	95	62
Risk of bias assessment					
Selection bias					
Random allocation	Unclear	Yes	Yes	Yes	Yes
Concealment	Unclear	Unclear	Unclear	Yes	Unclear
Performance bias					
Blinding	No	No	No	No	No
Detection bias					
Outcome reporting	Yes	Yes	Yes	Yes	Yes
Blinding	No	No	No	No	No
Completeness	Yes	Yes	Yes	Yes	Yes

<sup>a</sup> Colon only figures for CLASICC obtained directly from the study statistician.