

# Dissemination metastasis after laparoscopic colorectal surgery versus conventional open surgery for colorectal cancer: a metanalysis

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**Abstract. – PURPOSE:** The purpose of this systematic review is to evaluate and compare the risk of dissemination metastasis (wound, port-site metastases and peritoneal seeding) after laparoscopic colorectal surgery and conventional open surgery for colorectal cancer.

**MATERIALS AND METHODS:** The Authors searched relevant randomized controlled trials between January 1998 and July 2012.

**RESULTS:** Wound, port-site metastases and peritoneal seeding were rare and no significant differences occurred between the two groups. The port-site and extraction site recurrence were likely to be the results of suboptimal surgical techniques and occurred in the early phase of the learning curve. The authors also found no significant differences in overall, local and distant recurrences. No significant differences between laparoscopic and open surgery were found in cancer-related mortality during the follow up period of the study (7 RCTs, 3525 patients, 12.8% vs. 14.00%; OR (fixed) 0.83, 95% CI 0.68-1.02), with no significant heterogeneity ( $p = 0.35$ ).

**CONCLUSIONS:** The literature supports the implementation of laparoscopic surgery into daily practice. Laparoscopic surgery can be used for safe and radical resection of cancer in the right, left, sigmoid colon and rectum. However further studies should address whether laparoscopic surgery is superior to open surgery in this setting.

*Key Words:*

Laparoscopic colectomy, Colorectal cancer, Port-site metastases, Peritoneal seeding.

## Introduction

Since the first report of laparoscopic colon resection in 1991, there has been great enthusiasm in applying laparoscopy to oncologic colorectal

surgery, despite this surgical procedure is complicated and requires a long steep learning curve.

During the 1990s, appeared in literature early reports on port-site metastasis that challenged the oncological safety of the laparoscopic colectomy for colorectal cancer.

These concerns were subsequently proven to be unfounded. In recent years reports from randomized controlled trials (RCTs) confirmed the oncological safety and the long-term outcome of laparoscopic colectomy for cancer. The incidence of port-site recurrence and peritoneal carcinomatosis was low and increased incidence was not found in the laparoscopic group. The port-site and extraction site recurrence were likely to be the results of suboptimal surgical techniques and occurred in the early phase of the learning curve.

## Materials and Methods

### *Search Methods for Identification of Studies and Selection Criteria*

To identify all relevant papers, that evaluated laparoscopic surgery for colon and rectal cancer, we searched through the major medical databases MEDLINE, EMBASE, Science Citation Index and Cochrane library for studies published between January 1998 and July 2012.

The following search terms were used: “laparoscopy”, “surgery”, “colon”, “colectomy”, “rectal”, “cancer”. Moreover, we limited our search to those studies involving an adequate follow-up period. The reference lists of all relevant articles were searched.

Two researchers (A.Z. and G.P) extracted data from each article by using a structured excel sheet and entered the data into a database.

All non randomized studies were excluded. All patients converted from the laparoscopic group to the conventional open surgery group remained in the laparoscopic group for analysis. For the long term analysis we used data on the rate of local tumor recurrence, distant recurrences, wound, port site and peritoneal seeding, cancer related mortality, overall related mortality.

### Data Extraction

We identified 14 papers reporting randomized controlled studies that compared laparoscopic colorectal surgery and conventional colorectal surgery for colorectal cancer and that reported long-term outcome data (Figure 1).

Our meta analysis included 4.786 patients with colorectal cancer; of these 2.538 had undergone laparoscopic colorectal surgery and 2.248 had undergone conventional colorectal surgery.

The characteristic of each study are presented in Table I.

The goal of this meta-analysis is to compare laparoscopic surgery with open surgery for colorectal cancer in terms of oncologic adequacy of resection and long-term oncologic outcomes according to standard guideline.

### Assessment of Methodological Quality

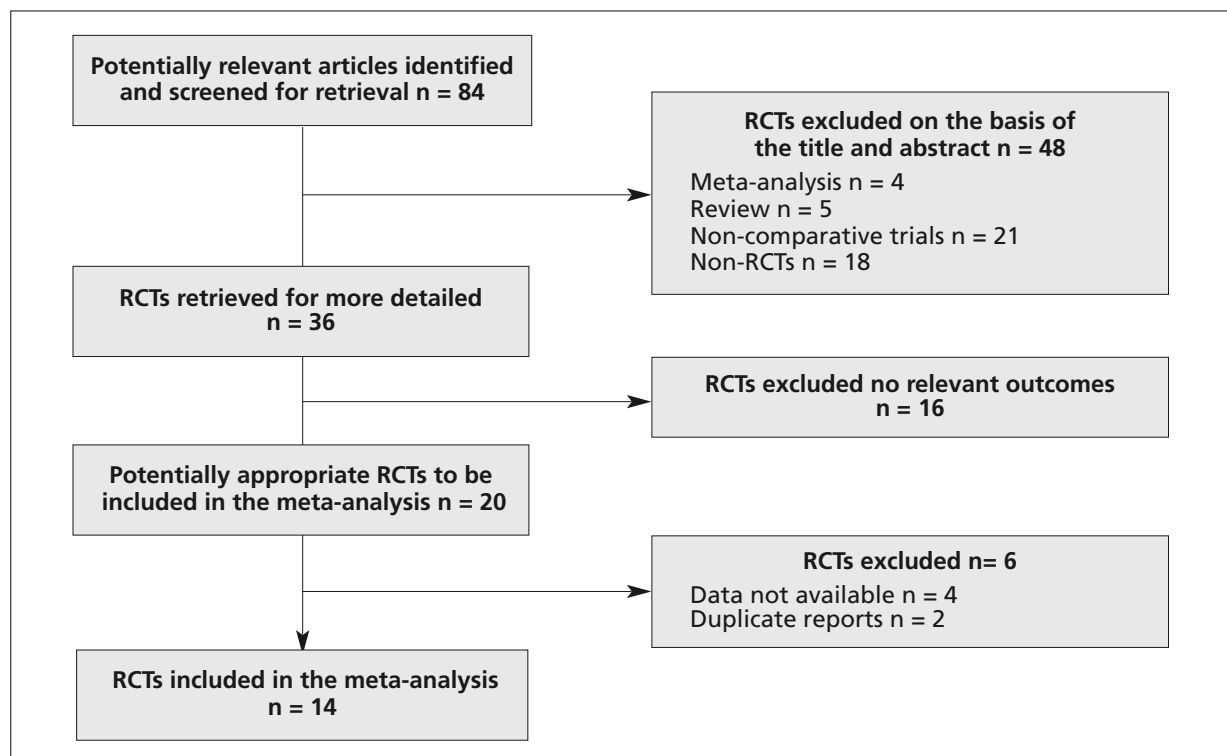
Three reviewers assessed all studies that met the selection criteria for methodological quality and details of the randomization process. Each included trial was read for the criteria: concealed randomization, time of randomization, and number of randomized patients. Blinding was not assessed after allocation because it was not possible to blind participants, surgeons, or assessor to the intervention.

### Statistical Analysis

Odds ratios (OR) were used for the analysis of dichotomous variables.

A fixed effect model was adopted when it was assumed that all studies came from a common population, and that the effect size (OR) was not significantly dissimilar among the different trials. This assumption was tested by the "Heterogeneity test". If this test yielded a low  $p$ -value ( $p < 0.05$ ), then the fixed effects model might have been invalid. In such case, the random effects model might have been more appropriate, in which both the random variation within the studies and the variation between the different studies were incorporated.

We used the Mantel-Haenszel method to calculate the weighted summary OR under the fixed



**Figure 1.** Diagram showing study methodology, number of abstracts and articles identified and evaluated during the review process.

**Table I.** Characteristics of included studies (RCTs) in this meta-analysis.

Authors	Year	Institutions of the study	Study size (n)		Localization of the tumor	Follow-up period (months)
			LCRS	OCRS		
Milsom JW <sup>2</sup>	1998	Single center	42	38	Colon	19 months (mean)
Araujo SE <sup>3</sup>	2003	Single center	13	15	Rectum	47 months (mean)
COST <sup>4,5</sup>	2004	Multicenter	435	428	Colon	4 years (median)
Leung KL <sup>6</sup>	2004	Two centers	167	170	Colon, rectum	51 months (median)
Zhou ZG <sup>7</sup>	2004	Single center	82	89	Rectum	1-16 months (range)
Liang JT <sup>8</sup>	2007	Single center	135	134	Colon	40 months (median)
NG SS <sup>9</sup>	2008	Single center	40	36	Low rectum	87 months (median)
Lacy AM <sup>10,11</sup>	2008	Single center	106	102	Colon	95 months (median)
Mirza MS <sup>12</sup>	2008	Single center	116	117	Colon, rectum	48 months (median)
Park IJ <sup>13</sup>	2009	Single center	107	72	Rectum	36 months (mean)
Lujan J <sup>14</sup>	2009	Single center	101	103	Rectum	33 months (mean)
COLOR I <sup>15</sup>	2009	Multicenter	534	542	Colon	53 months (median)
CLASICC <sup>16,17,18</sup>	2010	Multicenter	526	268	Colon, rectum	56 months (median)
Braga M <sup>19</sup>	2010	Single center	134	134	Colon	73 months (median)

RCTs = randomized controlled trials; LCRS = laparoscopic colorectal cancer surgery; OCRS = conventional open colorectal cancer surgery.

effects model. Next the heterogeneity statistic was incorporated to calculate the summary OR under the random effects model.

## Results

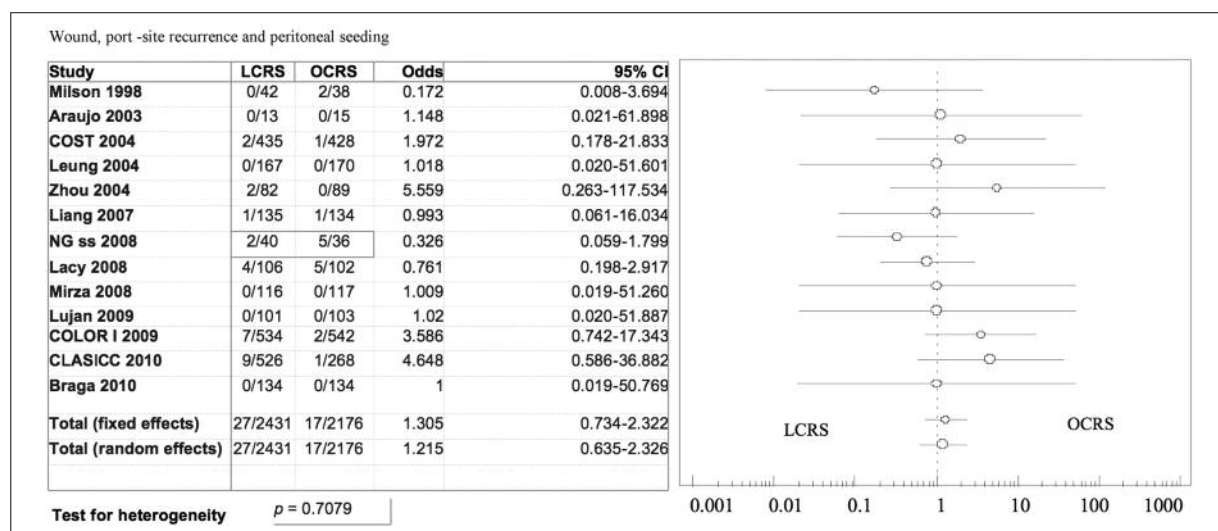
### Wound, Port-Side Metastasis and Peritoneal Seeding

Data on wound, port-site recurrence and peritoneal seeding were reported in 13 trials (4607 pa-

tients). The combined results of these studies showed no statistically significant difference in the OR between the laparoscopic colorectal surgery (LCRS) and conventional open surgery (OCRS) (13 RCTs; 4607 patients 1.11% vs. 0.78%; OR (fixed) 1.305, 95% CI, 0.73-2.322), with no significant heterogeneity ( $p = 0.707$ ) (Figure 2).

### Recurrences

Data on overall recurrence were reported in 12 trials (3843 patients). The number of patients



**Figure 2.** Wound, port-site recurrence and peritoneal seeding.

that developed an overall recurrence of the primary tumor during the follow up period of the study was similar after laparoscopic and open surgery (12 RCTs, 3843 patients, 19.60% vs. 19.36%; OR (fixed) 0.974, 95% CI 0.82-1.146), with no significant heterogeneity ( $p = 0.407$ ). No significant differences in the local recurrence were observed after laparoscopic and open surgery (13 RCTs, 4706 patients, 4.72% vs. 5.11%; OR (fixed) 0.84, 95% CI 0.64-1.10), with no significant heterogeneity ( $p = 0.62$ ). No significant difference in the development of distant metastases was found in colorectal cancer patients, when comparing laparoscopic and open surgery (13 RCTs, 4706 patients, 13.7% vs. 14.07%; OR (fixed) 0.95, 95% CI 0.80-1.12), with no significant heterogeneity ( $p = 0.94$ ). (Figure 3).

#### **Cancer-related and Overall Mortality**

The majority of the studies (7 out of 13) reported cancer-related mortality at maximum follow up. No significant differences between laparoscopic and open surgery were found in cancer-related mortality during the follow up period of the study (7 RCTs, 3525 patients, 12.8% vs. 14.00%; OR (fixed) 0.83, 95% CI 0.68-1.02), with no significant heterogeneity ( $p = 0.35$ ).

The meta-analysis on hazard ratios for overall mortality in colorectal cancer patients showed no significant difference between the laparoscopic and open arm (8 RCTs, 3793 patients, 26.53% vs. 25.94%; OR (fixed) 0.92, 95% CI 0.79-1.07), with no significant heterogeneity ( $p = 0.59$ ) (Figure 4).

## **Discussion**

#### **Short-Term Benefits of Laparoscopic Resection**

As proven in other laparoscopic procedures the short-term benefits of minimally invasive surgery can be demonstrated in laparoscopic colectomy. Laparoscopic colorectal resection compared with open resection offers the following advantages: earlier restoration of bowel function, earlier resumption of solid diet, small incision and less postoperative pain, lower analgesic consumption, shorter length of stay<sup>1</sup>.

All these short-term benefits were proven in the randomized trials comparing laparoscopic with open colorectal resection<sup>2-18</sup>.

#### **Long-term Oncological Outcome**

In all randomized trials comparing patients with laparoscopic and open surgery, with the exclusion of post-operative mortality, the survival was significantly equal between the two groups.

In the COST trial (Clinic Outcome of Surgical Therapy Study Group), 872 patients were randomized to either laparoscopic or open resection. In the initial report published in 2004, no difference in overall survival (OS) or recurrence rates could be demonstrated with a median follow-up of 4.5 years. Long-term results with a median follow-up of seven years confirmed that the OS, the disease free survival, overall recurrence rates and the patterns of recurrence were similar in the two groups<sup>4,5</sup>.

In the COLOR I trial (European multicenter Colon cancer Laparoscopic or Open Resection) between March 7, 1997 and March 6, 2003, 1248 patients from 29 European hospitals with a solitary cancer of the right or left colon and body-mass index up to 30 kg/m<sup>2</sup> were randomly assigned to either laparoscopic or open surgery in a randomized trial. Disease-free survival (DFS) at 3 years after surgery was the primary outcome.

OS and DFS survival in patients who had laparoscopic surgery did not differ from patients who underwent open colectomy. The 3 year DFS for all stages combined was 74.2% (95% CI 70.4-78.0) in the laparoscopic group and 76.2% (72.6-79.8) in the open-surgery group ( $p = 0.70$  by long-rank test).

The differences in DFS after 3 and 5 years were 2.0% (95% CI -3.2 to 7.2) and 1.4% (-4.6 to 7.5), respectively. The hazard ratio (HR) for DFS (open vs. laparoscopic surgery) was 0.92 (95% CI 0.74-1.15).

The overall 3 year survivals for all stages were 81.8% (78.4-85.1) in the laparoscopic group and 84.2% (81.1-87.3) in the open-surgery group ( $p = 0.45$  by log-rank test).

The corresponding differences in OS at 3 and 5 years were 2.4% (95% CI -2.1 to 7.0) and 0.4% (-5.3% to 6.1) respectively (HR 0.95 [0.74-1.22]). The p value regarding the primary endpoint of 3 year DFS was 0.030, which did not meet the predetermined significance level of 0.025.

Multivariable analysis of DFS and OS did not show differences between laparoscopic and open surgery ( $p = 0.49$  vs.  $p = 0.70$ ).

The COLOR I study concluded that the difference discovered in DFS and in OS between both groups (laparoscopic surgery versus open

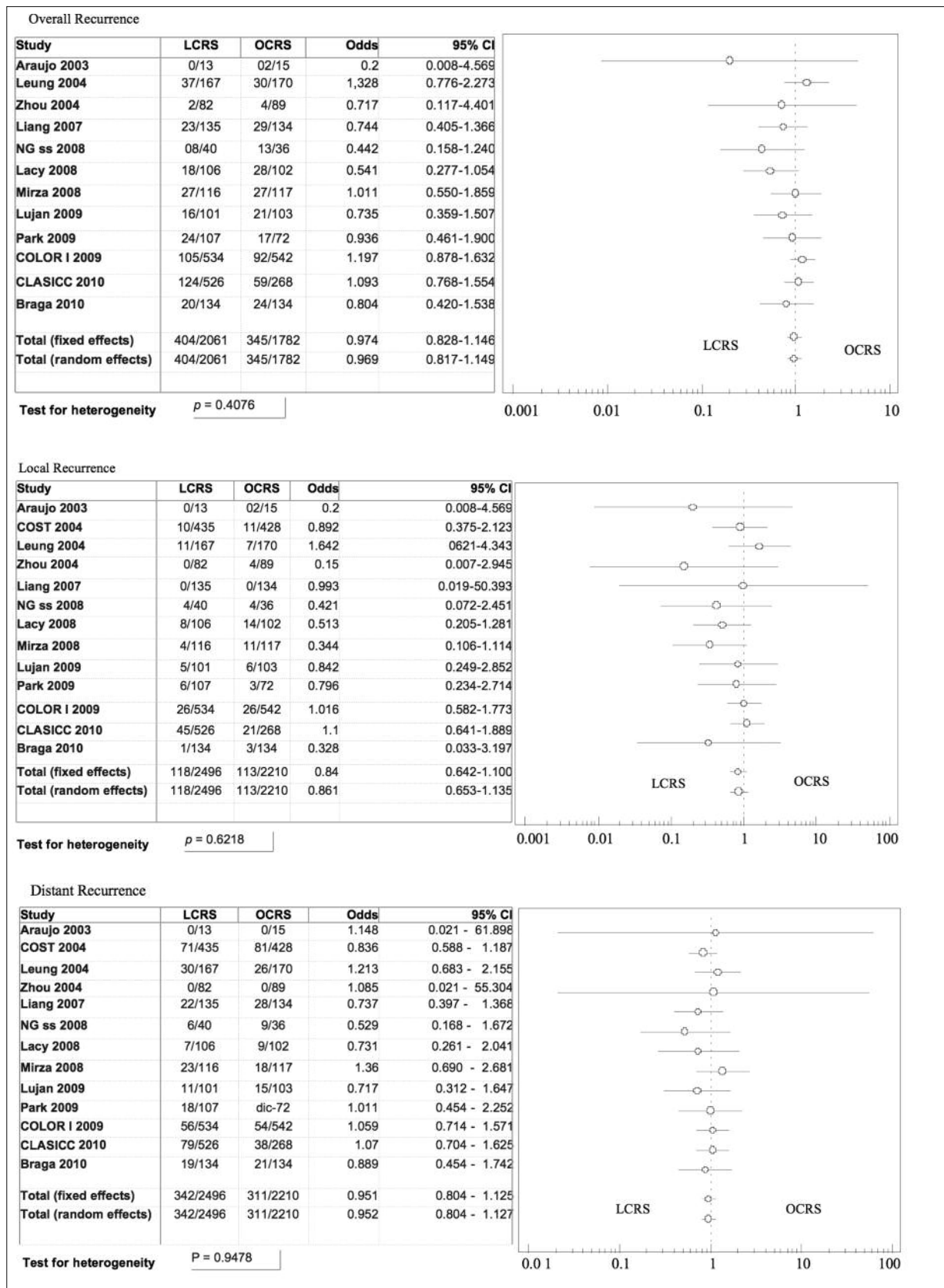


Figure 3. Recurrence.

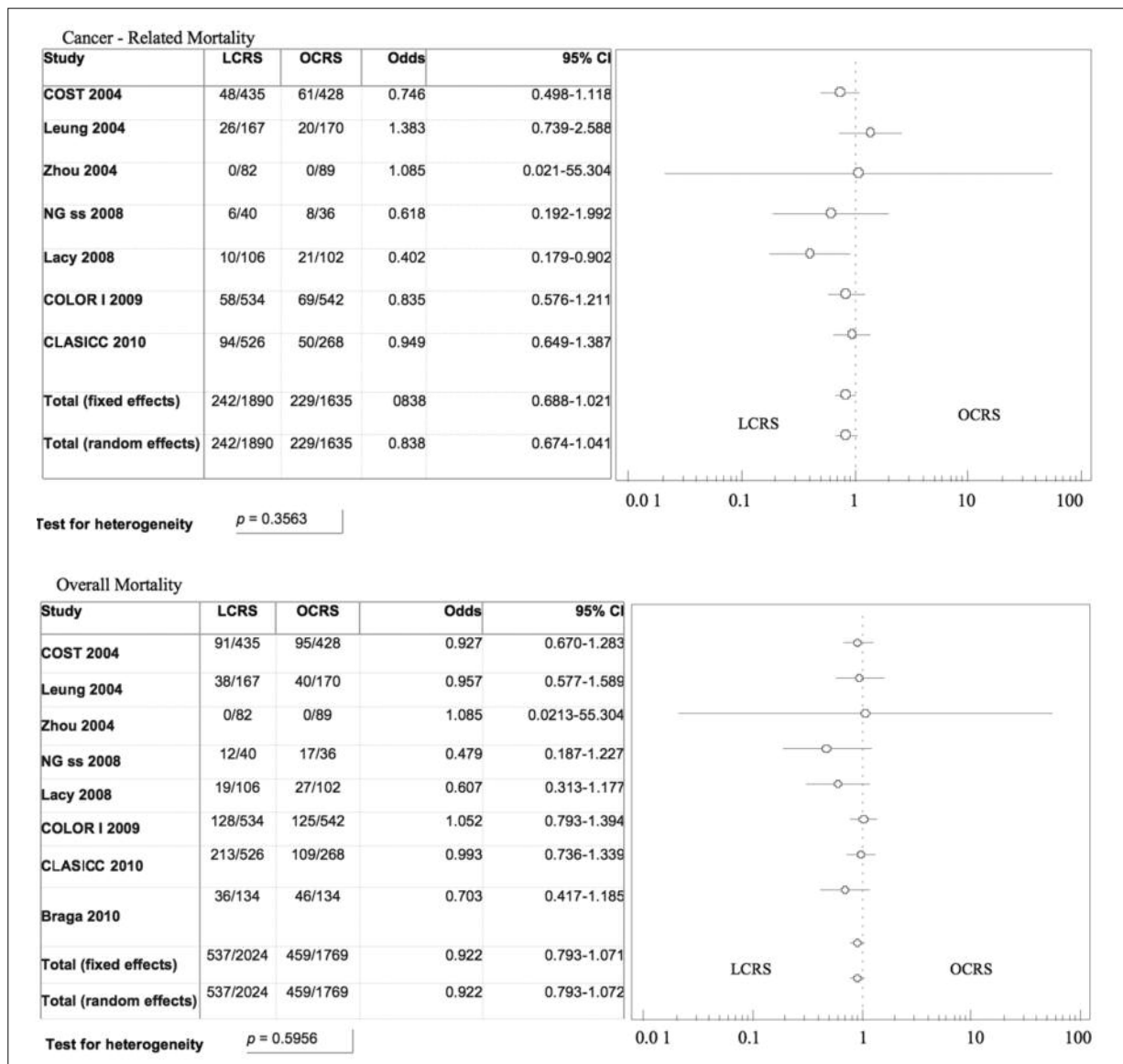


Figure 4. Mortality.

surgery) was so small and clinically acceptable, justifying the implementation of laparoscopic surgery into daily practice<sup>15</sup>.

The five year results from the MRC CLASICC trial (Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer) have been published recently. There were no differences in the five years DFS survival between the two groups 58.6% for open versus 55.3% for laparoscopic surgery (difference -3.4% (95% -11.8 to 5.0) log rank statistic = 0.492,  $p = 0.483$ ). The overall, local and distant recurrences did not show any difference between the two groups<sup>16</sup>.

Considering this aspect, this kind of surgical approach could be used in “frail” patients, e.g., elderly and HIV-positive patients<sup>20-33</sup>.

### Cancer Recurrences

In the COLOR I trial, regarding the end-point of the colon cancer recurrences, there were some difference in both groups (laparoscopic surgery versus open surgery) and only stage of disease was significantly related to recurrence and a worse prognosis.

In the laparoscopic group, the number of local recurrences, distant recurrences, and combined recurrences (defined as a local and dis-

tant recurrence at time of diagnosis) were 26, 56 and 23, respectively. In the open colectomy group these numbers were 26, 54 and 12, respectively.

These distributions of recurrences did not differ between the two groups ( $p = 0.24$ ).

Regarding the port-site or wound site recurrence there were any differences, tumor recurrence in the abdominal wall was noted in 1.3% of patients (seven of 534) who had been assigned to laparoscopic colectomy and in 0.4% of patients (two of 542) who had been assigned to open colectomy ( $p = 0.09$  by log-rank test). In the COLOR trial within the laparoscopic colorectal surgery group (LCRS), the number of trocar-site recurrences was higher than that of extraction-site recurrences, five of the seven tumor recurrences were at trocar sites whereas two tumor recurrences were at the extraction site<sup>15</sup>.

However, in the MRC CLASICC trial the number of extraction-site recurrences was higher than that of trocar-site recurrences in the LCRS group, only one was highlighted as being a true port-site rather than an extraction-site recurrence<sup>16</sup>.

The Cochrane systematic review including twelve trials (3346 patients) also demonstrated no differences in occurrence of port-site metastases and wound recurrences after laparoscopic and open surgery<sup>34</sup>.

The number of patients that developed a recurrence at the site of the primary tumor during the follow-up period of the study was similar after laparoscopic and open surgery (8 RCTs 1987 pts, 5.2% vs. 5.3%; OR (fixed) 0.81 (95% CI 0.54-1.22);  $p = 0.31$ ). Separate analyses for colon and rectal cancer showed no significant differences between laparoscopic and open procedures (for colon cancer: 4 RCTs, 938 pts, 5.2% vs. 5.6%; OR (fixed) 0.84 (95% CI 0.47-1.52);  $p = 0.57$ ; for rectal cancer: 4 RCTs, 714 pts, 7.2% vs. 7.7%; OR (fixed) 0.81 (95% CI 0.45-1.43);  $p = 0.46$ )<sup>34</sup>.

No significant differences in the occurrence of port-site/wound metastases or peritoneal metastases were observed ( $p = 0.16$ )<sup>34</sup>.

To support this, a large Japanese meta-analysis of the short and long term results of randomized controlled trials, that compared laparoscopy assisted and conventional open surgery for colorectal cancer, showed that there is no significant difference in the overall recurrence, local recurrence, or distant recurrence between the LCRS and OCRS for colorectal cancer groups<sup>35</sup>.

The rate of wound-site recurrence for the LCRS group was significantly higher than that for the OCRS group. Even if 5 of the 7 studies that reported data, the rates of wound-site recurrence for LCRS were similar to the rates for OCRS<sup>35</sup>.

Our metanalysis clearly indicated that the appearance of port-site metastases has decreased over time and no different from the prevalence of wound recurrences after open resections.

The prevalence of port-site recurrence rates in the laparoscopic arm remained stable at 1.11%, which was similar to the prevalence of wound recurrence 0.78% following open surgery for colorectal cancer.

With the improvement in instruments and strict adhesion to the no-touch techniques, the use a wound protector or an extraction bag, the wound/port site recurrence rate can be considered finally rare.

### **Rectal Cancer**

Laparoscopic rectal surgery has not developed as quickly as laparoscopic colon surgery because the techniques involved are more complex and technically demanding.

The correct surgical technique is important in the local control of the disease. The importance of circumferential margin and the need for meticulous mesorectal dissection, with its preserved integrity during resection, had been well recognized.

The MRC CLASICC trial is the only published randomized trial, which analyses mid and distal rectal cancer<sup>16-18</sup>.

Although the percentage of positive circumferential margin was higher in laparoscopic anterior resection (but not for laparoscopic abdominoperineal resection), the 5 year local recurrence rates for open and laparoscopic anterior resection were 7.6% and 9.4%, respectively (difference  $-1.8$  [95% c.i.  $-9.9$  to  $6.3$ ]; log rank statistic =  $0.110$ ,  $p = 0.740$ )<sup>16-18</sup>.

Similarly, there was no difference in local recurrence rates between the two techniques in patients undergoing abdominoperineal resection<sup>16-18</sup>.

Regarding the secondary long-term end point, the 5 year wound/port-site recurrence rates, overall, there were 10 (1.9%; 95% CI, 0.7% to 3.1%) wound/port-site recurrences: one wound/port-site recurrence in the open arm and nine wound/port-site recurrences in the laparoscopic arm (long-rank = 2.46;  $p = 0.12$ ; the open wound/port-site recurrences was 0.6%, and the laparoscopic wound/port-site recurrences was 2.5%, for a difference of  $-2.0$ %; 95% CI,  $-4.0$ % to  $0.02$ %)<sup>16-18</sup>.

Patients developing wound/port-site recurrences tended to have larger tumors compared with patients without wound/port-site recurrences, more advanced disease (seven of 10 patients had Dukes' C1 or C2 cancers), or evidence of intra-abdominal recurrence (seven of 10 patients). This emphasizes the need for adequate wound protection during specimen extraction<sup>16-18</sup>.

This data supports the continued use of the laparoscopic approach in the treatment of rectal cancer.

The effects of conversion to open surgery on morbidity and mortality remains unclear.

The conclusions of the studies examining the issue remain controversial for both colon and rectal carcinoma<sup>36-38</sup>.

Some studies have suggested that conversion does not influence outcome<sup>39,40</sup> but others<sup>41,42</sup> demonstrates a clear survival disadvantage associated with conversion. It is interesting that the sensitivity analysis of the survival data for surgeons with a lower than average conversion rate showed the same decreased survival as for the group as a whole, suggesting that the worse outcome in converted patients was not attributable to a surgeon-related factor. Thus, it would appear that conversion has a deleterious effect regardless of the experience of the surgeon. Conversion to open operation was associated with significantly worse overall but not disease-free survival, which was most marked in the early follow-up period (30 days)<sup>43</sup>.

## Conclusions

Many meta-analyses of the short and long term results of randomized controlled trials, that compared laparoscopy assisted and conventional open surgery for colorectal cancer, have been published over the last two decades. They clearly showed that there is no significant difference in the overall recurrence, local recurrence, or distant recurrence between the LCRS and OCRS for colorectal cancer groups.

Our meta-analysis clearly indicated that the incidence of port-site metastases has decreased over time and there is no significant difference from the incidence of wound recurrences after open resections. With the improvement in instruments, the strict adhesion to the no-touch techniques, the use a wound protector or an extraction bag, the desufflation of pneumoperitoneum before trocar extraction, the wound/port site recurrence rate has been limited.

According to our meta-analysis they can be considered finally rare.

Another aspect that could be investigated is the perioperative cancer-related fatigue<sup>45</sup>.

Moreover, video laparoscopy might be the best approach also for HIV-positive patients to avoid the risk of infection for health professionals<sup>43-57</sup>.

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## Conflict of Interest

None declared.

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