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ORIGINAL PAPER

A meta-analysis of laparoscopy compared with open colorectal resection for colorectal cancer

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Abstract The aim of this study was to compare the outcome of the overall complication, mortality, and recurrence rate between laparoscopic resection and open surgery for colorectal cancer. We searched the Medline, Embase, and Cochrane Library and systematically reviewed the randomized controlled trials by comparing the overall complication, mortality, and recurrence rate between laparoscopic resection and open surgery for colorectal cancer. Fifteen trials with 4,207 patients who reported long-term outcomes of the overall complication, mortality, and recurrence rate were included. The combined results of the individual trials showed no statistically significant difference in the odds ratio (OR) for overall recurrence (OR 0.92, 95% CI, 0.77–1.11, $P = 0.34$), local recurrence (OR 0.81, 95% CI, 0.59–1.12, $P = 0.20$), distant metastasis (OR 1.01, 95% CI, 0.78–1.30, $P = 0.95$), wound-site recurrence (OR 1.97, 95% CI, 0.77–5.02, $P = 0.16$), colorectal cancer-related mortality (OR 0.82, 95% CI, 0.66–1.02, $P = 0.07$), colon cancer-related mortality (OR 0.85, 95% CI, 0.66–1.09, $P = 0.20$), rectal cancer-related mortality (OR 0.76, 95% CI, 0.53–1.11, $P = 0.16$), and overall mortality (OR 0.87, 95% CI, 0.73–1.73, $P = 0.11$) between the laparoscopic surgery and open surgery groups. The overall complications in the laparoscopic surgery group were much lower than that in the open surgery group (OR 0.71, 95% CI, 0.58–0.87, $P = 0.001$). This meta-analysis showed that the successful laparoscopic colorectal resection for colorectal cancer was as effective as open surgery in terms of the oncological outcomes, thereby suggesting that laparoscopic surgery can be continued in patients with colorectal cancer.

Keywords Meta-analysis · Colorectal cancer · Surgery

Introduction

Minimally invasive surgery has revolutionized the way operations are performed. The widespread popularity and success of laparoscopic biliary tract surgery have persuaded surgeons to expand the application of this technology rapidly to the ever-increasing number of abdominal surgical procedures [1]. The possibility of laparoscopic resection for colorectal cancer (CRC) was first described in 1991 [2]; however, to date, this approach is still not common in surgical practice. The curability of colorectal cancer by using laparoscopic colorectal surgery (LCS) has remained controversial. The concerns about mortality, recurrence rate, and complications have prevented it from generally being accepted [3–6].

The indisputable physiological benefits of minimal invasive surgery, such as small incisions, decreased bleeding, less pain, decreased wound infection rate, less postoperative adhesions, and probably a better quality of life, are increasing the use of this technique in CRC surgery

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[7]. The techniques in minimal invasive surgery have also become refined, thereby reducing the operative times and improving patient recovery from surgery. However, there still exists a limitation in the long-term outcome data of recurrence rate and mortality to compare the effects of laparoscopic and open surgery for CRC [8–10].

As several randomized controlled trials (RCTs) have been published, the true assessment of the mortality and recurrence rate of LCS in CRC compared with open colorectal surgery (OCS) is best described in these reports [1, 3, 11–23]. Therefore, a meta-analysis of RCTs seems appropriate to determine whether LCS leads to different mortality and recurrence rates when compared with OCS.

Methods

The objectives, search strategy, study selection criteria, data elements, methods for extraction, and methods for assessing the study quality were defined. Two independent authors completed each step in this protocol and resolved disagreements by discussion.

Literature search

We followed MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines to identify appropriated studies (Fig. 1). A computerized search (Medline, Embase, and The Cochrane Library) was performed. The search terms were "laparoscopy," "surgery," "colon," "colectomy," "colonic neoplasms," or "colonic cancer," "rectal neoplasms," or "rectal cancer," "colorectal cancer," and "all related articles" functionality of Pubmed. In addition, the reference lists in selected articles were searched manually. There were no language and data restrictions. All literature searches of studies published from 1991 to 2008 were performed. All relevant RCTs that compared laparoscopic and open surgery for CRC were identified.

Study selection

Citations selected from this initial search were subsequently screened for eligibility. The criteria were as follows: contained patients with the CRC surgical technique as either "laparoscopic" or "open" for CRC; compared laparoscopic and open techniques in patients undergoing CRC resection; and RCT.

Data extraction

Data were extracted independently by two authors and cross-checked for research consensus. The following variables were recorded: first author, journal name, date of publication, study population characteristics, number of patients operated using each technique, duration of follow-up, and information on mortality and recurrence. If necessary, the primary authors were contacted to retrieve further information.

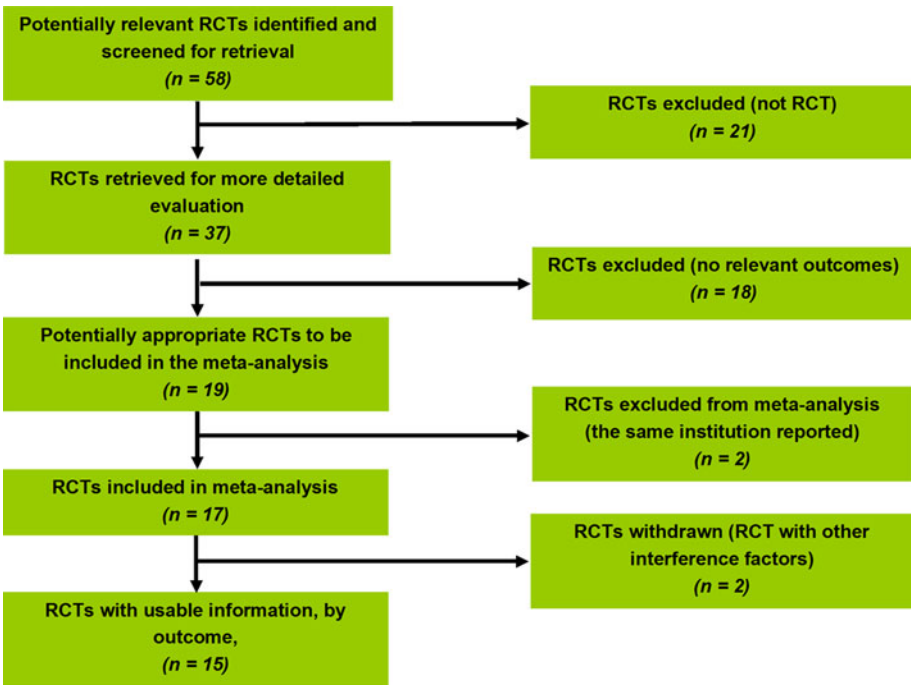

Fig. 1 QUOROM diagram showing study methodology. *RCT* randomized controlled trials

Assessment of study quality

Included trials were reviewed and appraised for methodological quality using the Jadad composite scale. Two reviewers assessed all studies that met the selection criteria for methodological quality and details of the randomization process. In case of differences in opinion, a third reviewer rechecked the assessment.

Statistical analysis

Dichotomous variables were analyzed using the odds ratio (OR) and a fixed-effect model, but a random-effect model was used according to heterogeneity. Sensitivity analysis was applied by removing individual studies from the data set and analyzing the effect on the overall results to identify sources of significant heterogeneity. Meta-analyses on hazard ratios for tumor recurrence and mortality were performed using Parmar's method. Data analyses were performed using the software Review Manager version 4.2.2 (Nordic Cochrane Centre, Copenhagen, Denmark). A P value less than 0.05 was considered statistically significant.

Results

Description of studies

A total of 15 RCTs that compared LCS and OCS for CRC were identified. Of 4,207 patients in 15 RCTs, 2,126 patients were allocated to the LCS group and 2,081 patients to the OCS group. The characteristics of these studies are listed in Table 1. All of the included studies were published as full articles. The quality of these RCTs varied greatly, and the mean Jadad score of the included studies was 3. There was no difference between the LCS and OCS groups regarding the mean age and the number of men and women. In 13 out of 15 studies, data on the cancer stage were provided. No significant difference in stage distribution was present between the LCS and OCS groups. Upon reviewing the data extraction, there was agreement among the reviewers.

Meta-analysis of the overall complication

Eleven studies compared the overall complication after laparoscopic and open surgery for CRC with 2,603 patients included in the meta-analysis. The overall complication rate was 16.1% in the laparoscopic group and 21.1% in the open surgery group. The combined result of these 11 studies showed that the overall complication in the open surgery group was significantly higher than that in the laparoscopic group for CRC; the OR was 0.71 (95% CI, 0.58–0.87, $P = 0.001$) (Fig. 2).

Meta-analysis of the overall recurrence

Thirteen studies reported the overall recurrence rate after laparoscopic and open surgery for CRC, with 3,494 patients included in the meta-analysis. The overall

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Reference	Year	Mean age (years)		Sex (Male/Female)		Study size (n)		Stage	Site	Follow-up (months)
		LCS	OCS	LCS	OCS	LCS	OCS			
Araujo et al.	2003	59.1	56.4	9/4	10/5	13	15	NR	Rectum	47
Braga et al.	2005	65	67	115/75	121/80	190	201	I–IV	Colon or rectum	36
COST	2004	70	69	223/212	208/220	435	428	I–IV	Colon	53
Curet et al.	2000	65.6	69.2	11/7	14/4	18	18	A–D	Colon	59
Jayne et al.	2007	NR	NR	NR	NR	526	268	A–C	Colon or rectum	36
Kaiser et al.	2004	59.0	60.5	9/11	7/8	20	15	I–III	Colon	35
Lacy et al.	2002	68	71	56/55	50/58	111	108	I–IV	Colon	43
Leung et al.	2004	67.1	66.5	104/99	114/86	203	200	AJCC I–IV	Colon or rectum	51
Liang et al.	2006	NR	NR	NR	NR	135	134	II, III	Colon	40
Milsom et al.	1998	69	69	26/29	36/18	55	54	I–IV	Colon or rectum	19
Mirza et al.	2008	72	71	59/56	62/65	116	117	I–III	Colon or rectum	49
Park et al.	2008	60.4	60.9	103/67	219/155	170	374	I–III	Rectum	36
Stage et al.	1997	72	73	8/7	5/9	15	14	A–D	Colon	14
Winslow et al.	2002	69.4	65.7	NR	NR	37	46	NR	Colon	30
Zhou et al.	2004	44	45	46/36	43/46	82	89	A–D	Rectum	1-16

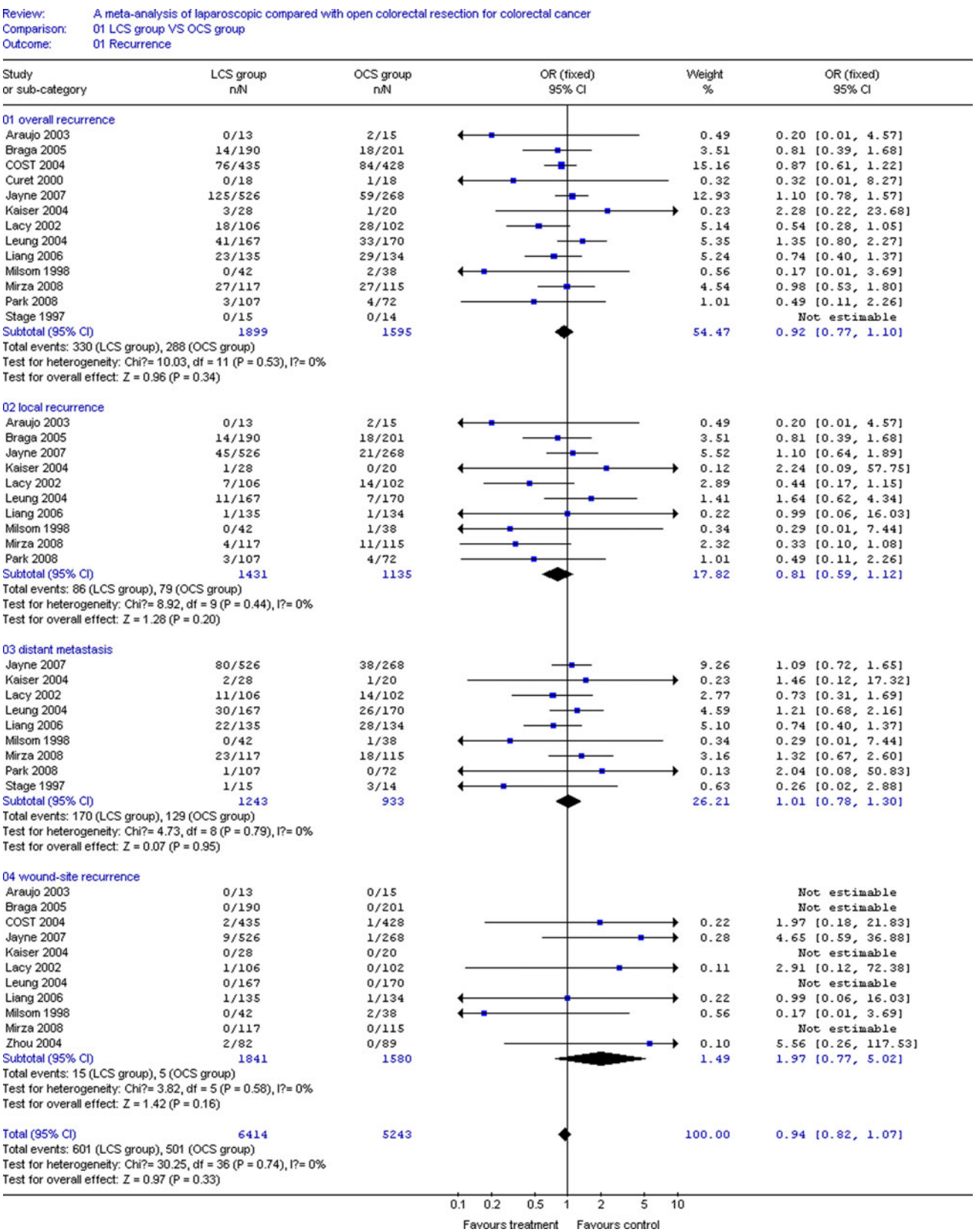

Fig. 2 Forest plot displaying the results of the meta-analysis of overall complications after laparoscopic surgery versus open surgery for colorectal cancer. *OR* odds ratio; *CI* confidence interval

recurrence rates were 17.4 and 18.1% in the laparoscopic group and open surgery group, respectively. The combined result of these 13 studies showed no significant difference in the OR for overall recurrence between the open surgery and laparoscopic groups for CRC; the OR was 0.92 (95% CI, 0.77–1.11, $P = 0.34$) (Fig. 3).

Meta-analysis of the local recurrence

Ten studies reported the rate of local recurrence after laparoscopic and open surgery for CRC, with 2,566 patients included in the meta-analysis. The local recurrence rates were 6.0 and 7.0% in the laparoscopic group and open

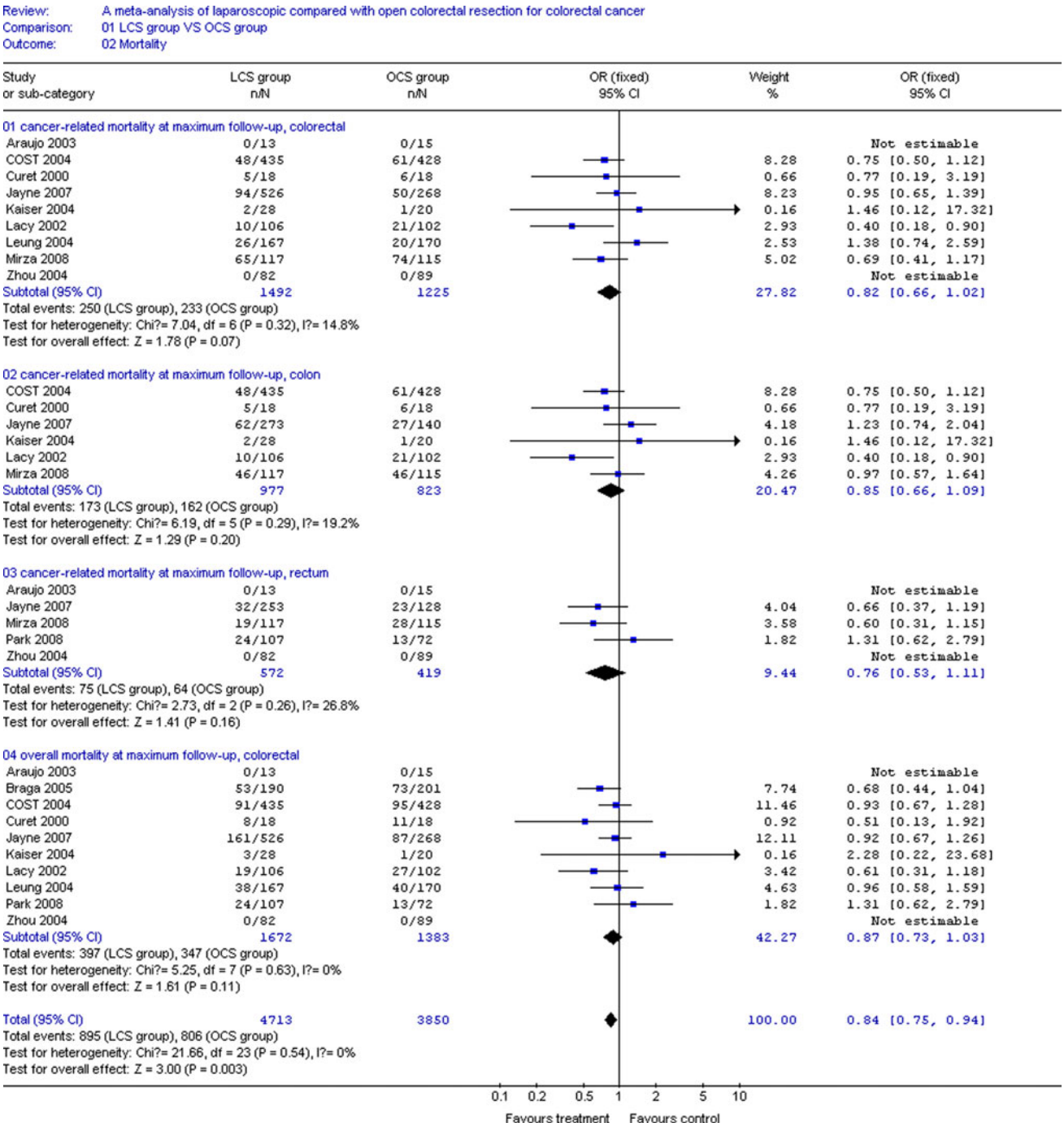

Fig. 3 Forest plot displaying the results of the meta-analysis of overall recurrence, local recurrence, distant metastasis, and wound-site recurrence after laparoscopic surgery versus open surgery for colorectal cancer. *OR* odds ratio; *CI* confidence interval

surgery group, respectively. The combined result of these 10 studies showed no significant difference in the OR for local recurrence between the open surgery and laparoscopic groups for CRC; the OR was 0.81 (95% CI, 0.59–1.12, $P = 0.20$) (Fig. 3).

Meta-analysis of distant metastasis

Nine studies reported the rate of distant metastasis after laparoscopic and open surgery for CRC, with 2,176 patients included in the meta-analysis. The distant metastasis rates were 13.7 and 13.8% in the laparoscopic group and open surgery group, respectively. The combined result of these nine studies showed no significant difference in the OR for the distant metastasis between the open surgery and laparoscopic groups for CRC; the OR was 1.01 (95% CI, 0.78–1.30, $P = 0.95$) (Fig. 3).

Meta-analysis of wound-site recurrence

Eleven studies reported the rate of wound-site recurrence after laparoscopic and open surgery for CRC, with 3,421 patients included in the meta-analysis. The wound-site recurrence rates in the laparoscopic group and open surgery group were 0.81 and 0.32%, respectively. The combined result of these 11 studies showed no significant difference in the OR for wound-site recurrence between the open surgery and laparoscopic groups for CRC; the OR was 1.97 (95% CI, 0.77–5.02, $P = 0.16$) (Fig. 3).

Meta-analysis of CRC-related mortality

Data from nine studies with 2,717 patients were available to calculate OR for CRC-related mortality after laparoscopic and open surgery for CRC. The CRC-related mortalities in the laparoscopic group and open surgery group were 16.8 and 19.0%, respectively. The combined result of these nine studies showed no significant difference in the OR for CRC-related mortality between the open surgery and laparoscopic groups; the OR was 0.82 (95% CI, 0.66–1.02, $P = 0.07$) (Fig. 4).

Meta-analysis of colon cancer-related mortality

Data from six studies with 1,800 patients were available to calculate the OR for colon cancer-related mortality after laparoscopic and open surgery. The colon cancer-related mortalities were 17.7 and 19.7% in the laparoscopic group and open surgery group, respectively. The combined result of these six studies showed no significant difference in the OR for the colon cancer-related mortality between the open surgery and laparoscopic groups; the OR was 0.85 (95% CI, 0.66–1.09, $P = 0.20$) (Fig. 4).

Meta-analysis of rectal cancer-related mortality

Data from five studies with 991 patients were available to calculate the OR for the rectal cancer-related mortality after laparoscopic and open surgery. The rectal cancer-related mortalities in the laparoscopic group the open surgery group were 13.1 and 15.3%, respectively. The

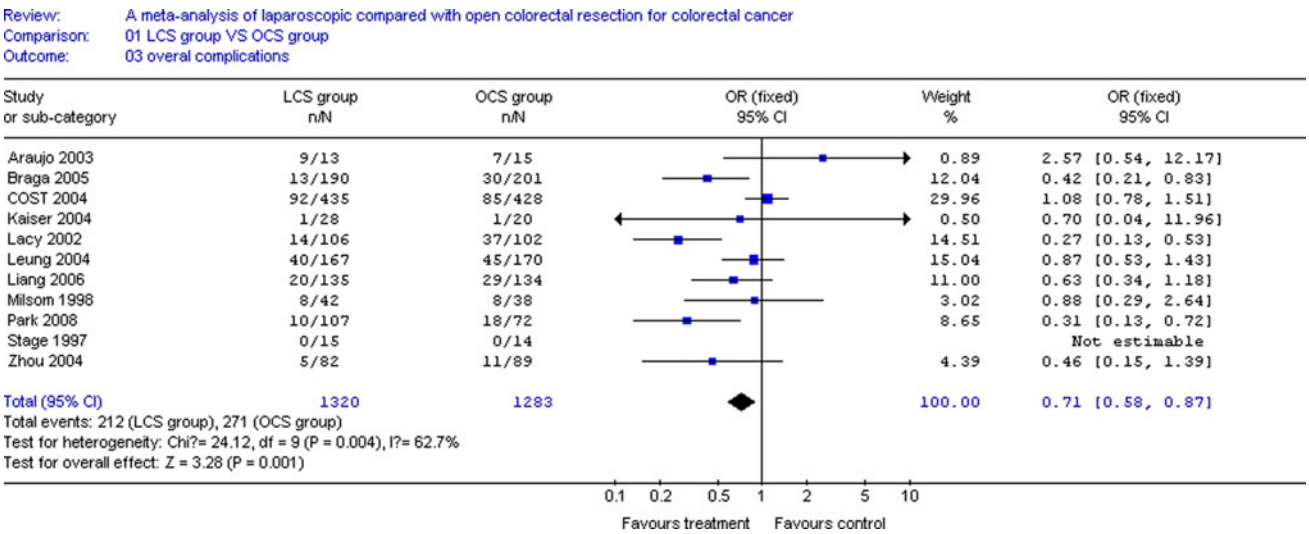

Fig. 4 Forest plot displaying the results of the meta-analysis of colorectal cancer-related mortality, colon cancer-related mortality, rectal cancer-related mortality, and overall mortality after laparoscopic surgery versus open surgery for colorectal cancer. *OR* odds ratio; *CI* confidence interval

combined result of these five studies showed no significant difference in the OR for rectal cancer-related mortality between the open surgery and laparoscopic groups; the OR was 0.76 (95% CI, 0.53–1.11, $P = 0.16$) (Fig. 4).

Meta-analysis of the overall mortality

Ten studies reported the overall mortality after laparoscopic and open surgery for CRC. The overall mortality was 23.7% in the laparoscopic group and 25.1% in the open surgery group. The combined result of these 10 studies showed no significant difference in the OR for the overall mortality between the open surgery and laparoscopic groups for CRC; the OR was 0.87 (95% CI, 0.73–1.73, $P = 0.11$) (Fig. 4).

Statistical analysis

Removing individual studies from the data set did not substantially change the Peto OR or the level of significance for the outcomes of complication, recurrence, and mortality between the laparoscopic and open surgery groups.

Publication bias

One funnel plot of the outcome recurrences in the included studies demonstrated symmetry, indicating no serious publication bias (Fig. 5).

Discussion

Laparoscopic technique has been enthusiastically applied to the resection of colorectal tumor for more than 10 years. Currently, many colorectal surgeons believe that the laparoscopic approach has quicker functional recovery and has achieved comparable and even better oncologic results for the treatment of patients with CRC [1, 24, 25]. Preliminary trials have reported many benefits of surgical excision by using the laparoscopic method, including reduction in stress and immunosuppression, less postoperative pain, early recovery of bowel function, few hospital stays, and faster recovery to perform normal activities [1, 7, 26, 27]. However, the mainstay of CRC treatment remained adequate for surgical resection. Controversy exists in several large prospective studies with regard to whether the laparoscopic method may even be more harmful to the patient than the conventional open surgery for CRC, because of a possible increase in the incidence of recurrence and mortality [3–6]. Therefore, a meta-analysis of disease recurrence, complication, and survival is necessary to evaluate the oncological efficacy of CRC treatment.

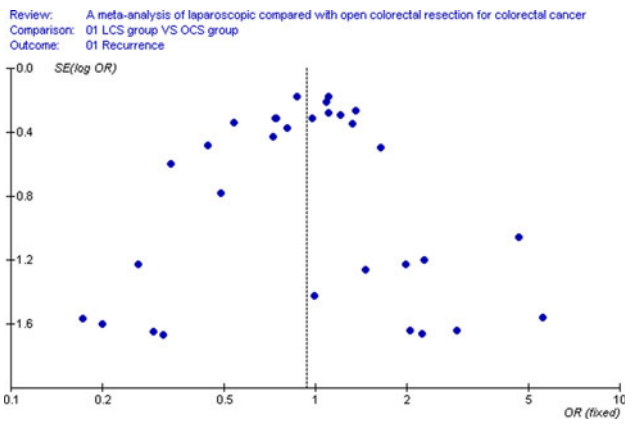

Fig. 5 Funnel plot of the outcome from all studies comparing overall recurrence in patients undergoing laparoscopic versus open surgery for colorectal cancer

The current meta-analysis focuses on the long-term outcome of randomized trials following laparoscopy when compared to open surgery for CRC. This is an evidence-based study including almost all reported RCTs. Although other systematic reviews comparing LCS and OCS for CRC have been performed [28, 29], the results of our study are more convincing because of its large sample size. The results of our study have shown that the overall complications in LCS group are less than that in the OCS group. There is no significant difference in the overall recurrence, local recurrence, distant metastasis, wound-site recurrence, CRC-related mortality, colon-related mortality, rectal-related mortality, and overall mortality. This is also an important confirmatory finding that provides support for the laparoscopic approach in terms of long-term survival by confirming from a surgical standpoint that the laparoscopic approach provides as good a resection as the open approach for treating CRC.

The present results are consistent with the COST study [1]. The COST study, with a median follow-up of 4.4 years, has shown no significant difference in the tumor recurrence rates between the two surgical techniques for treating potentially curable colon cancer. However, the analysis of 219 patients in a Spanish randomized trial has also shown favorable outcomes in the laparoscopic colectomy group [16]. As indicated in Liang's study, the range of recurrence following LCS relates to the fact that this approach is a surgeon- and instrument-dependent technique that is subjected to inadequate vascular dissection, poor establishment of laparoscopic anatomy, inadequate bleeding control, and also water irrigation during the operation [18]. In the early 1990s, several isolated cases of port-site recurrences after LCS for cancer were reported [30–34], and the incidence was estimated to be as high as 21%. However, recent studies have indicated that the incidence of port-site metastases was much lower and no different

from the incidence of wound recurrences after open resections [35]. Vukasin et al. [36] reported that the incidence of port-site recurrence was 1.1%, which is similar to the incidence of wound recurrence (1–1.5%) following OC for cancer. Additionally, significant differences in port-site or wound-site between the two groups are not shown in our present meta-analysis study.

In the meta-analysis of mortality after laparoscopy compared with that following open surgery for CRC, there is no statistically significant difference in the CRC-related, colon cancer-related, rectal cancer-related, and overall mortality between the laparoscopic and open surgery groups. A similar in-hospital and 30-day mortality in the two patient groups confirmed the clinical safety of the laparoscopic approach reported in earlier research [37]. However, the long-term outcome of mortality was indefinite between the LCS and OCS groups. The COST study [1], with a median follow-up of 4.4 years, demonstrated no difference in disease-free survival and overall survival rates between the two surgical techniques for treating potentially curable colon cancer. Mirza et al. [11] indicated that the laparoscopically assisted colectomy was independently associated with a reduced risk of disease recurrence and a reduced risk of cancer-related death when compared with the open colectomy. There is evidence that surgical stress impairs immunity and immunity has a critical role in tumor progression and metastatic spread. Previous studies investigating immune dysfunction after laparoscopic surgery have failed to show any difference in comparison with the open surgery [38–43]. This association could explain our findings that no difference in mortality exists between the LCS and OCS groups.

It should be noted that our current study has some limitations. Firstly, the analysis of mortality and recurrence rate was performed using the total number of events at the end of the follow-up period, and the time to events and duration of follow-up were not taken into account in the current meta-analysis since the data available in these RCTs were inadequate. As indicated by Kuhry et al. [28], this could cause a bias, since patients who are lost to follow-up are excluded, thereby lowering both the power and the validity of the studies. Secondly, we did not perform a separate analysis comparing converted procedures, completed laparoscopic procedures, and open surgery procedures for CRC, since this analysis would be biased.

In conclusion, our meta-analysis showed the benefits of laparoscopic resection in reducing overall complications. Laparoscopic resection did not increase overall disease recurrence rates, local recurrence rates, distant metastasis rates, wound-site recurrence rates, CRC-related mortality, colon or rectal cancer-related mortality, and overall mortality following surgery for CRC when comparing the open resection with laparoscopic surgery. Therefore, successful laparoscopic colorectal resection for CRC is as effective as open surgery in terms of oncological outcomes, and these results support the continued use of laparoscopic surgery in patients with CRC.

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