

Research Paper

# A Meta-Analysis of the Short- And Long-Term Results of Randomized Controlled Trials That Compared Laparoscopy-Assisted and Open Colectomy for Colon Cancer

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## Abstract

**Purpose:** We conducted a meta-analysis to evaluate and compare the short- and long-term results of laparoscopy-assisted colectomy (LAC) and open colectomy (OC) for colon cancer.

**Methods:** We searched MEDLINE, EMBASE, Science Citation Index, and Cochrane Controlled Trial Register for relevant papers published between January 1990 and October 2011 by using the search terms “laparoscopy,” “laparoscopy-assisted,” “surgery,” “colectomy,” “colon cancer,” and “randomized clinical trials (RCTs)”. We analyzed the outcomes of each type of surgery over short- and long-term periods.

**Results:** We selected 12 papers reporting RCTs that compared LAC with OC for colon cancer. Our meta-analysis included 4614 patients with colon cancer; of these, 2444 had undergone LAC and 2170 had undergone OC. In the short-term period, we found that the rates of overall postoperative complications and ileus in LAC were lower than in OC groups. LAC was associated with a reduction in intraoperative blood loss, a shorter duration of time to resumption and hospital stay, and lower rates of overall complication and ileus over the short-term, but with similar long-term oncologic outcomes such as overall and cancer-related mortality, overall recurrence, local recurrence, distant metastasis, and wound-site recurrence, compared to OC.

**Conclusions:** It is suggested that LAC may be preferred to OC for colon cancer.

**Key words:** meta-analysis, laparoscopy-assisted colectomy, colon cancer

## Introduction

Colon cancer is one of the most common types of cancer in developed countries, and surgery is the only curative treatment. Successful laparoscopy-assisted sigmoidectomy for colon cancer was first described in 1991<sup>1</sup> and has since then been widely applied by surgeons to treat patients with colon cancer.

Several articles have reported the short-term advantages of laparoscopy-assisted colectomy (LAC) over conventional open colectomy (OC) and have

concluded that laparoscopic surgery causes less pain, results in better pulmonary function, shortens the duration of postoperative ileus, reduces fatigue, and offers a better quality of life<sup>2-5</sup>. However, the benefits of LAC have remained controversial because the long-term outcomes have not yet been clarified. To accurately evaluate the efficacy of laparoscopic surgery for colon cancer, the short- and long-term outcomes of laparoscopic surgery must be compared to

those of open surgery. For short-term outcomes, perioperative variables, pathologic factors, and the cost of surgery should be examined. For long-term outcomes, long-term oncologic results are the primary endpoint of interest. The long-term oncologic outcomes of LAC, such as tumor recurrence rate and mortality rate, have been published over time<sup>6-9</sup>. Several randomized control trials (RCTs) that compare LAC with OC have been reported<sup>6-25</sup>. Therefore, we conducted a meta-analysis of the data obtained from these RCTs and compared the short- and long-term outcomes of LAC and OC by considering several factors.

**Materials and methods**

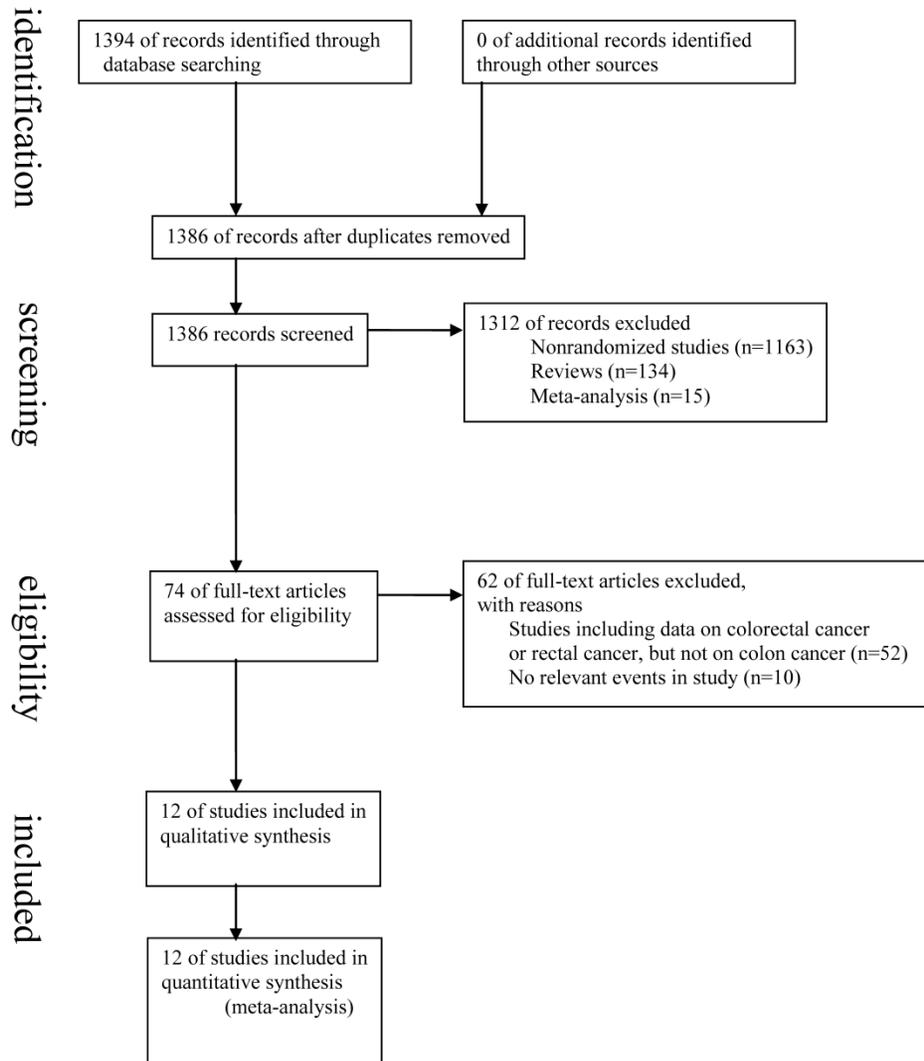
**Literature search**

To identify papers relevant to our study, we searched through the major medical databases such as MEDLINE, EMBASE, Science Citation Index, and

Cochrane Controlled Trial Register for studies published between January 1990 and October 2011. The following search terms were used: “laparoscopy,” “laparoscopy-assisted,” “surgery,” “colectomy,” and “colon cancer.” Furthermore, we limited our literature search to randomized controlled trials. We treated studies that were part of a series as a single study. The appropriate data from such study series were used for this meta-analysis. This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>26</sup> (Fig.1).

**Inclusion criteria**

To enter this meta-analysis, studies had to: (1) be described in English (2) be randomized controlled trials (3) compare laparoscopic and open conventional surgery for colon cancer (4) report on at least one of the outcome measures mentioned below.



**Fig.1** Flow diagram of this meta-analysis in accordance with PRISMA Statement.

## Data extraction

Three researchers (H.O., Y.T., and Y.A.) extracted data from each article by using a structured sheet and entered the data into a database. Because this analysis was based on the intention-to-treat principle<sup>27</sup>, all patients converted from the laparoscopic group to the conventional open surgery group remained in the laparoscopic group for analysis. We conducted separate meta-analyses for 2 different postoperative time periods: short-term and long-term. For the short-term analysis, we collected data on operation time, estimated blood loss, number of transfused patients, number of dissected lymph nodes, time to resumption, hospital stay, incision length, overall postoperative complications, ileus, anastomotic leakage, perioperative mortality, circumferential resection margin, oral resection margin, distal resection margin, and cost of surgery. We also examined the relationship between the conversion rate from laparoscopic to open surgery and single-institution versus multicenter trials. For the oncologic results in the long-term analysis, we used data on the rate of overall recurrence, local recurrence,

distant metastasis, peritoneal dissemination, wound-site recurrence, overall mortality, and cancer-related mortality. If necessary, we contacted the authors of the original article to collect further information.

## Assessment of study quality

The quality of the randomized controlled trials was assessed using Jadad's scoring system<sup>28</sup>. Two reviewers (H.O., Y.T.) assessed all studies that met the inclusion criteria (Table 1).

## Statistical analysis

Weighted mean differences (WMDs) and odds ratios (ORs) were used for the analysis of continuous and dichotomous variables, respectively. Random-effects models were used to identify heterogeneity between the studies<sup>29</sup>, and the degree of heterogeneity was assessed using the  $\chi^2$  test. For the analysis of the conversion rate, the  $\chi^2$  test was used. The confidence interval (CI) was established at 95%, and p values of less than 0.05 were considered to indicate statistical significance.

**Table 1.** Characteristics of randomized controlled trials.

authors	Year	country	number of reference	institutions of the study	Conversion rate (%)	Study size (n)		follow-up period (months)	Randomization	Double Blinding	Withdrawals and dropouts	Jadad's score
						LC	OC					
Braga et al.	2010	Italy	10	single center	5.2(7/134)	134	134	73 months (median)	2	2	1	5
CLASICC trial	2010, 2007, 2005	UK	6, 7, 13, 21	multicenter (27)	25(61/246)	526	268	56.3 months (median)	2	2	1	5
COLOR trial	2009, 2005	Sweden, Netherlands, Spain, Italy, France, UK, Germany	14, 15	multicenter (29)	19(102/534)	534	542	53 months (median)	2	2	1	5
COST trial	2004	USA and Canada	16, 18	multicenter (48)	21(90/435)	435	428	7 years (median)	2	2	1	5
Curet et al.	2000	USA	17	single center	28(7/25)	25	18	4.9 years (mean)	2	2	1	5
ALCCaS trial (Hewett et al.)	2008	Australia and New Zealand	24	multicenter (31)	14.6(43/294)	294	298	unknown	2	0	1	3
Kaiser et al.	2004	USA	22	single center	46.4(13/28)	28	20	35 months (median)	2	0	1	3
Barcelona trial (Lacy et al.)	2008	Spain	8, 9	single center	11(12/111)	111	108	95 months (median)	2	2	1	5
Liang et al.	2006	Taiwan	19	single center	3(4/135)	135	134	40 months (median)	2	2	1	5
Mirza et al.	2008	UK	20	single center	17 (19/113) concluding rectal cancer	116	117	48 months (median)	1	0	0	1
Pascual et al.	2011	Spain	23	single center	12(7/60)	60	60	41 months (median)	2	2	1	5
Winslow et al	2002	USA	25	single center	15(7/46)	46	43	30.1 months (mean)	2	0	1	3

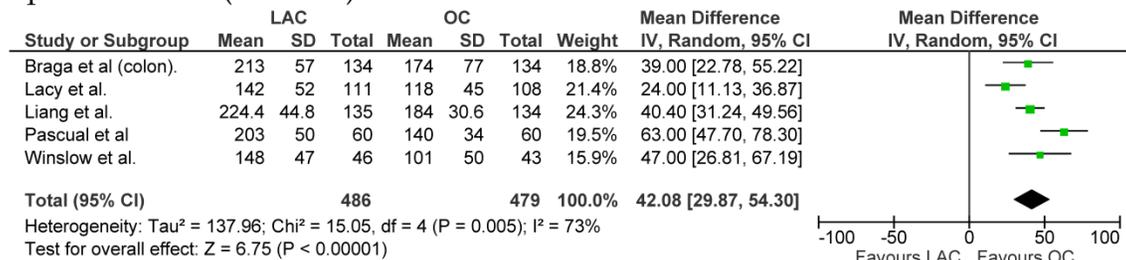
UK: United Kingdom, US: United States of America

As the cost data of 1 article<sup>21</sup> were precious and had neither a range nor any other measure of dispersion, the standard deviation (SD) was estimated by halving the mean<sup>30</sup>. One Euro and British pound were converted to 1.4 and 1.6 US dollars, respectively. Statistical analyses were performed using the Review Manager (RevMan) software version 5.1.4 provided by the Cochrane Collaboration, Copenhagen, Denmark.

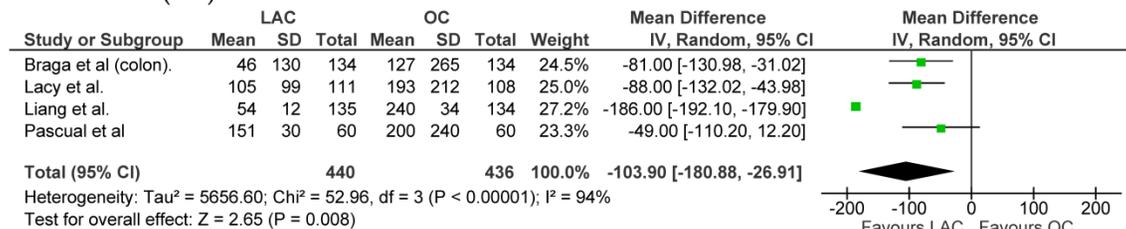
## Results

We identified 12 RCTs that compared LAC and OC for colon cancer<sup>6-25</sup>. The characteristics of each RCT are presented in Table 1. Our meta-analysis included 4614 patients with colon cancer; of these, 2444 had undergone LAC, and 2170, OC. The results of the outcomes over short- and long-term periods are shown in Fig. 2 and Fig. 3, respectively.

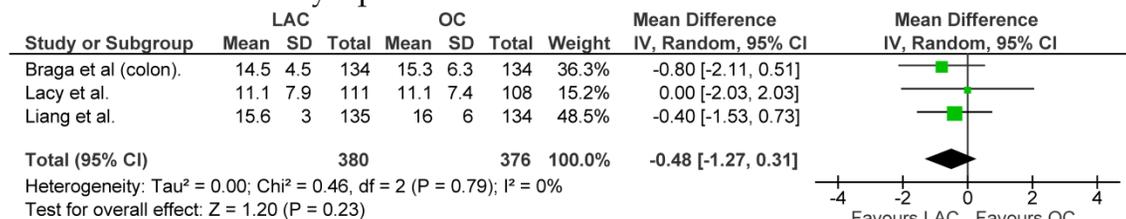
### operative time (minutes)



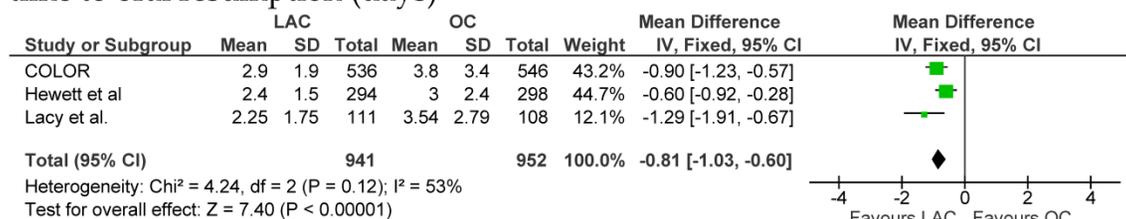
### blood loss (ml)



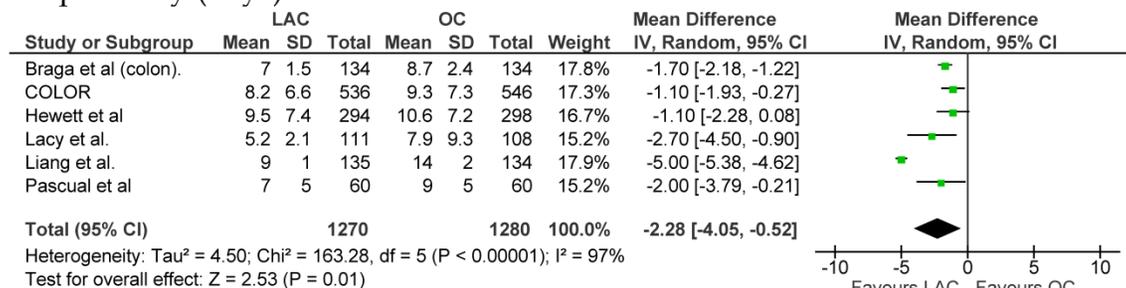
### number of dissected lymph nodes



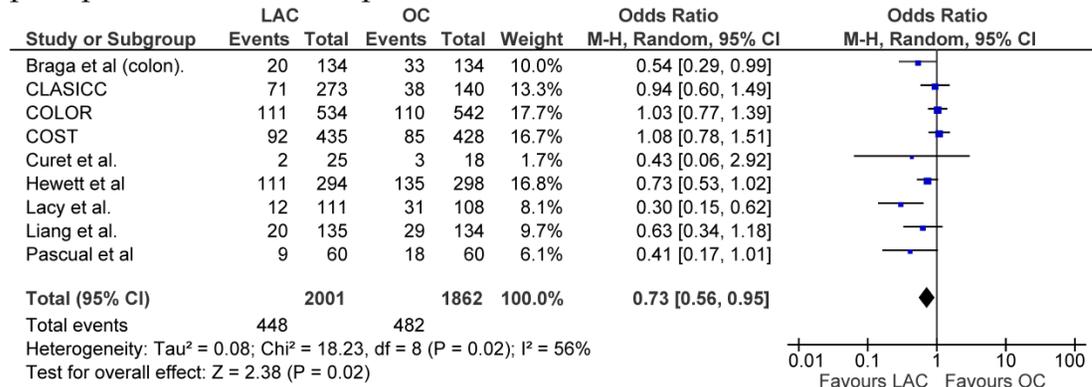
### time to oral resumption (days)



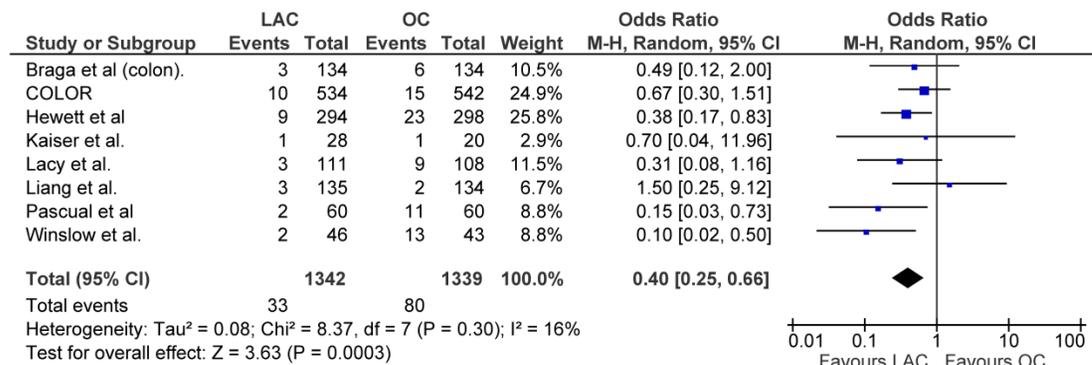
### hospital stay (days)



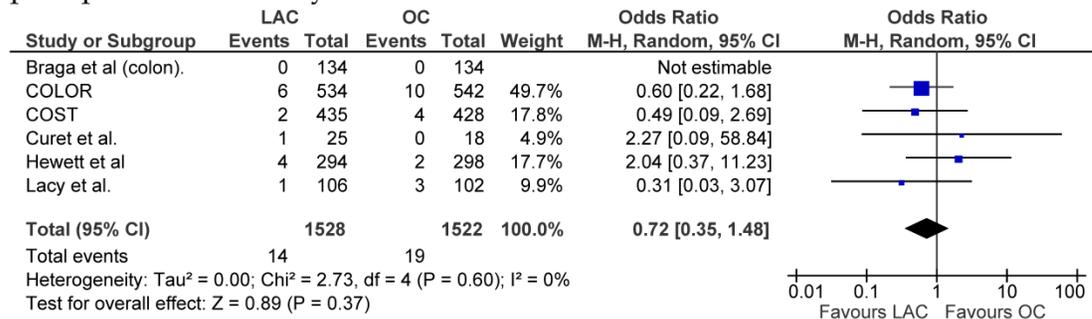
perioperative overall complications



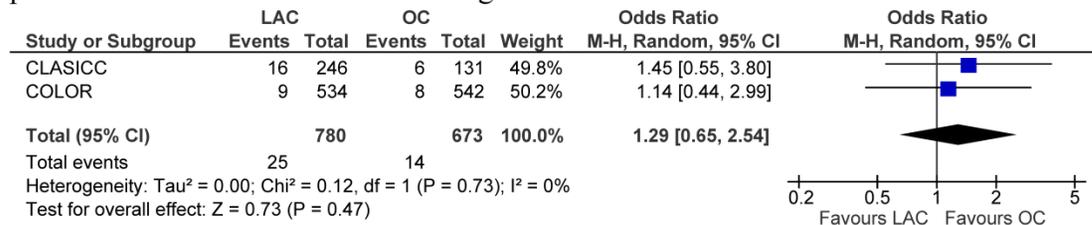
ileus



perioperative mortality



positive circumferential resection margin



cost of surgery (USD)

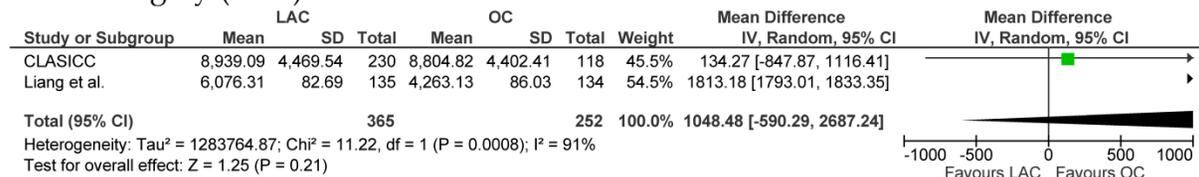
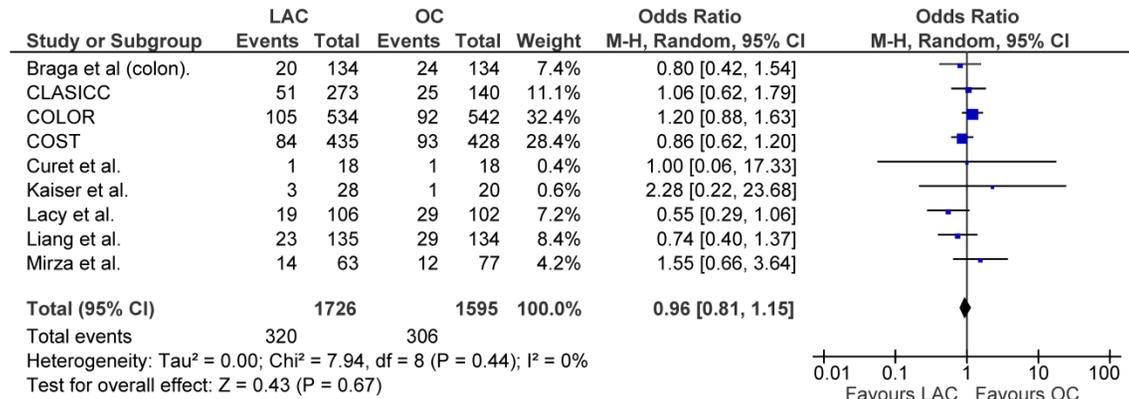
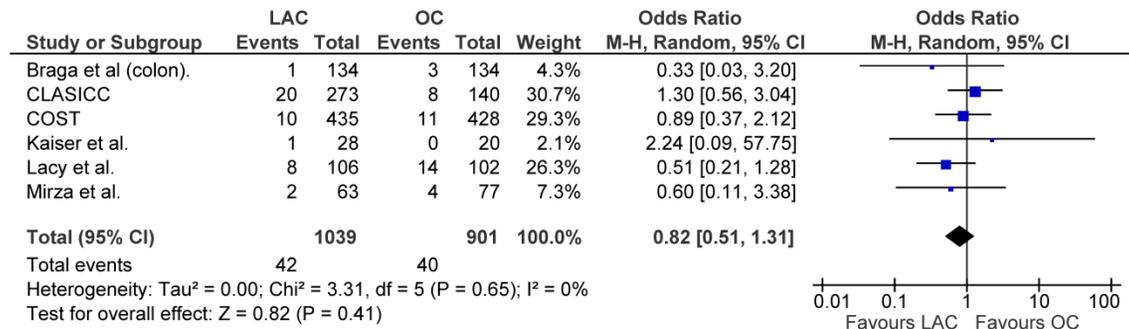


Fig. 2 Meta-analysis of the short-term period for colon cancer

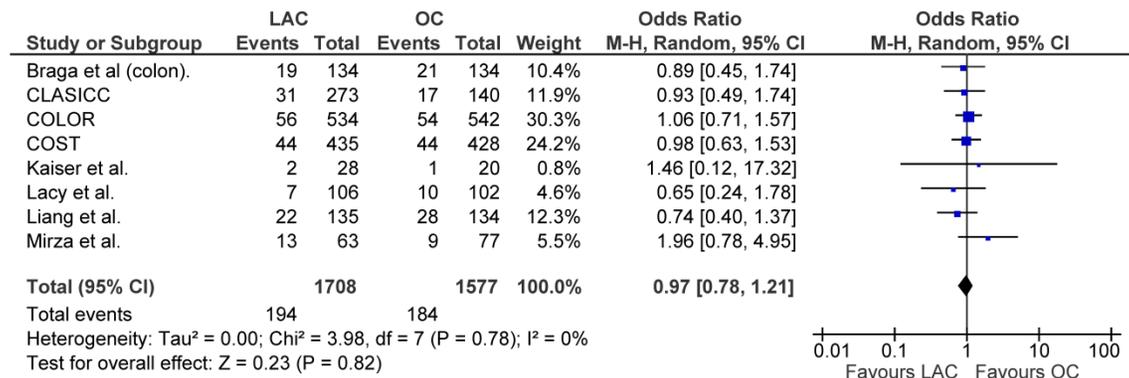
overall recurrence



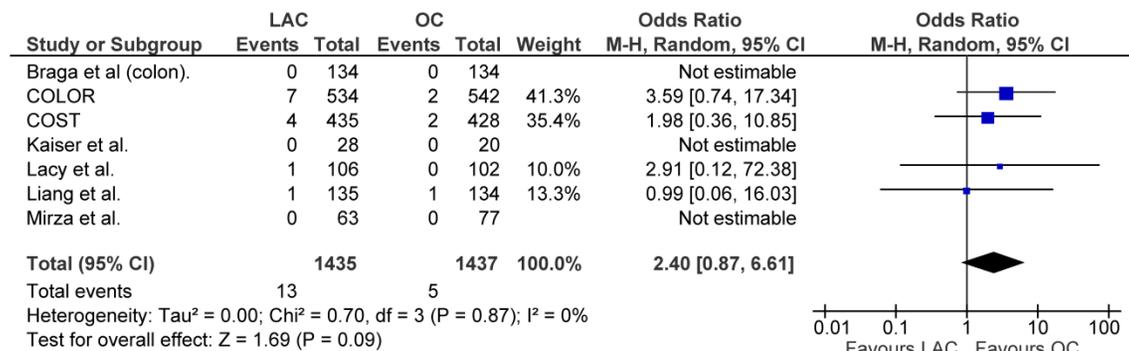
local recurrence



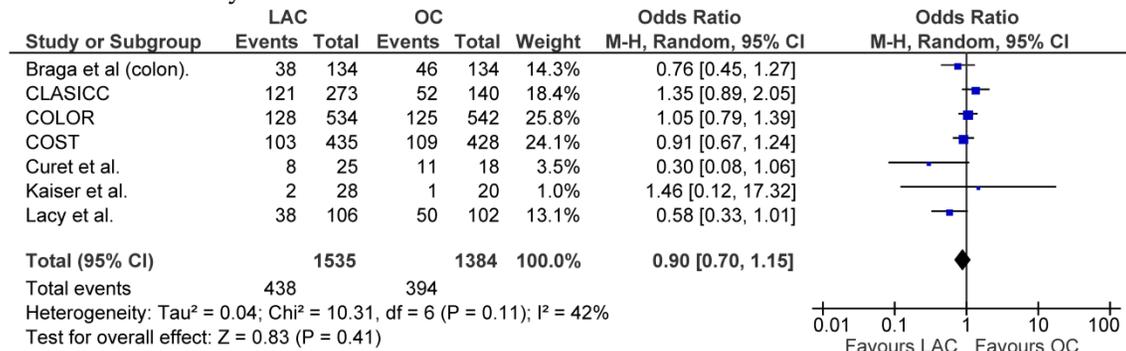
distant metastasis



wound-site recurrence



overall mortality



cancer-related mortality

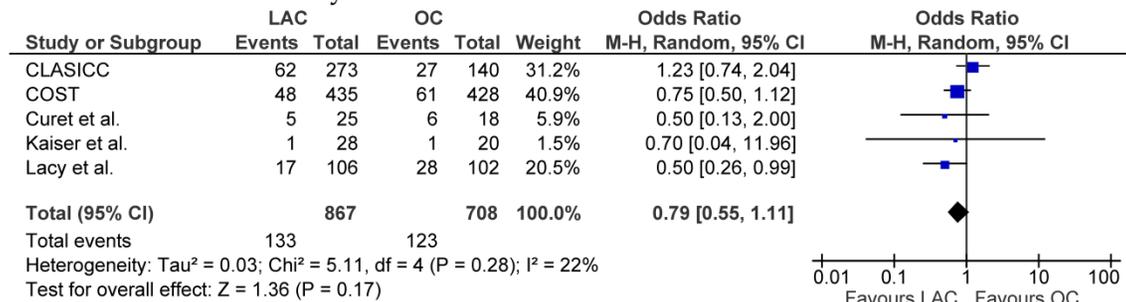


Fig. 3 Meta-analysis of the long-term oncologic results for colon cancer

Short-term outcomes

Of the 12 RCTs, 5 reported the operative duration; in all 5 reports, the operative duration was significantly longer for LAC than for OC. Our analysis showed that the operative duration for LAC was significantly longer than that for OC by 42.08 min (WMD = 42.08; 95% CI = 29.87 to 54.30; p < 0.00001). Blood loss in patients who underwent LAC was significantly lesser than that in patients who underwent OC, by an average volume of 103.9 ml (WMD = -103.90; 95% CI = -180.88 to -26.91; p = 0.008). There was no significant difference in the number of transfused patients. We found no significant difference in the number of dissected lymph nodes between LAC and OC groups. The duration of hospital stay and the time to oral diet were significantly shorter with LAC than with OC (p = 0.01 and < 0.00001, respectively). The incision length was significantly shorter by 11.77 cm in LAC than in OC. The rate of the overall postoperative complications was significantly lower in LAC than in OC (OR = 0.73; 95% CI = 0.56 to 0.95; p = 0.02). In examining the details of them, we found that the rate of ileus was significantly lower in LAC than in OC (OR = 0.40; 95% CI = 0.25 to 0.66; p = 0.0003). The rate of anastomotic leakage between the 2 groups was insignificant. We also found no significant differences in perioperative

mortality between the 2 groups when we pooled the data for LAC and OC for colon cancer.

Pathological factors

In an analysis of pooled data, we found that there was no significant difference in the circumferential resection margin between the 2 groups. There was no significant difference in the oral and distal resection margin.

Cost of surgery

In an analysis of the total cost of surgery, there was no significant difference between the 2 groups.

Conversion rate

Twelve articles reported data on the conversion rate from laparoscopic to open surgery, which ranged from 3 to 46.4% (Table 1). In an analysis of the conversion rate, there was no significant difference between the trials performed by a single institution and those performed on a multicenter basis (p = 0.31).

Long-term outcomes

With respect to overall recurrence, local recurrence, distant metastasis, and peritoneal dissemination, the differences between the 2 groups were insignificant. Our analysis of the wound-site recurrence between the LAC and OC groups indicated no signif-

icant difference. There was also no significant difference in the overall and cancer-related mortality between the 2 groups.

### Heterogeneity

In the short-term period, significant heterogeneity was detected between studies for the following 6 factors: operative time, intraoperative blood loss, duration of hospital stay, incision length, overall postoperative complications, and cost of surgery. In the long-term periods, no significant heterogeneity was detected between studies.

### Discussion

In short-term periods, laparoscopic surgery for colon cancer is associated with a significantly longer operative time, but significantly less intraoperative blood loss compared with conventional open surgery. These results are consistent with those of recent randomized controlled trials<sup>8,13,15</sup>. Potential explanations for the abovementioned results include meticulous dissection facilitated by instruments for laparoscopic surgery and videoscopic magnification. The similarity of oncological outcomes such as circumferential, oral, and distal resection margin and the number of harvested lymph nodes between the 2 groups indicates identical quality of the operative techniques. Patients who underwent LAC resumed oral intake significantly earlier and had significantly shorter hospital stays than did patients who underwent OC; this finding suggests that LAC leads to faster recovery. The rate of postoperative complications was significantly lower in LAC than on OC. In examining the details, we found the rate of ileus significantly lower in LAC than in OC. Gutt et al. describe that laparoscopic surgery reduces adhesion formation compared with open surgery. Because laparoscopic procedures reduce the overall degree of trauma to the abdominal wall, intraabdominal operative site, and distant intraabdominal organs, they potentially have an advantage in reducing the formation of postoperative adhesion<sup>31</sup>. The abovementioned suggests that LAC may be safer and more feasible than OC.

In the analysis of the total cost of surgery, we found no significant overall difference between LAC and OC. However, the operating costs were higher and the hospitalization costs were lower for LAC compared with OC.

Several reports have shown that conversion from laparoscopic to open surgery is associated with inferior surgical outcomes<sup>6</sup>. In this analysis, the conversion rate was not significantly related to the type of study, i.e., single-institution or multicenter. The CLASICC trial reported that tumor infiltra-

tion/fixation and obesity were the most common reason for conversion<sup>13</sup>.

In the long-term period, we found no significant difference in overall recurrence, local recurrence, distant metastasis, and peritoneal dissemination between the 2 surgery groups. There was also no significant difference in wound-site recurrence between the 2 groups. No significant difference was found in overall and cancer-related mortality. The abovementioned findings suggest that LAC is comparable to OC with respect to long-term oncologic results. Lacy et al. reported that there was a tendency of higher cancer-related and overall survival for LAC<sup>9</sup>, but our meta-analysis of the pooled data did not show this difference.

Significant heterogeneity was observed for operative time, intraoperative blood loss, duration of hospital stay, incision length, overall postoperative complications, and cost of surgery in the short-term period. The reason for the observed heterogeneity in operative time, intraoperative blood loss, and overall postoperative complications may be variations in the skill of the surgeon and the condition of the tumor. Differences in the clinical approach at different institutions may have caused the heterogeneity in the duration of hospital stay and incision length. Significant heterogeneity for cost of surgery may be caused by differences in medical fees among countries.

In conclusion, this meta-analysis showed that laparoscopic surgery for colon cancer is associated with a reduction in intraoperative blood loss, earlier resumption of oral intake, shorter duration of hospital stay, and rate of postoperative complications concluding ileus over the short-term, but is associated with similar short-term and long-term oncologic outcomes compared to conventional open surgery. Therefore, it is suggested that laparoscopic surgery may be preferred to conventional open surgery for colon cancer.

### Conflict of Interest

The authors have declared that no conflict of interest exists.

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