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ORIGINAL ARTICLE

A Meta-analysis of the Short- and Long-Term Results of Randomized Controlled Trials That Compared Laparoscopy-Assisted and Conventional Open Surgery for Rectal 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 and open rectal surgery for the treatment of patients with rectal cancer.
Methods We searched MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register for relevant papers published between January 1990 and April 2011 by using the search terms “laparoscopy,” “laparoscopy assisted,” “surgery,” “rectal cancer,” and “randomized controlled trials.” We analyzed outcomes over short- and long-term periods.
Results We identified 12 papers reporting results from randomized controlled trials that compared laparoscopic surgery with open surgery for rectal cancer. Our meta-analysis included 2,095 patients with rectal cancer; 1,096 had undergone laparoscopic surgery, and 999 had undergone open surgery. In the short-term period, 13 outcome variables were examined. In the long-term period, eight oncologic variables, as well as late morbidity, urinary function, and sexual function were analyzed. Laparoscopic surgery for rectal cancer was associated with a reduction in intraoperative blood loss and the number of transfused patients, earlier resumption of oral intake, and a shorter duration of hospital stay over the short-term, but with similar short-term and long-term oncologic outcomes compared to conventional open surgery.
Conclusions Laparoscopic surgery may be an acceptable alternative treatment option to conventional open surgery for rectal cancer.

Keywords Meta-analysis · Laparoscopy-assisted rectal surgery · Rectal cancer

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Introduction

Laparoscopic surgery for rectal cancer has been reported to achieve superior short-term outcomes, including earlier postoperative recovery, less postoperative morbidity,[1,2] and better quality of life,[3] compared with conventional open surgery for rectal cancer. The use of laparoscopic surgery for rectal cancer has recently become more widespread, and several articles have described long-term outcomes associated with the procedure.[4–9] However, the curability of rectal cancer using laparoscopic surgery is controversial because the long-term oncologic outcomes of laparoscopic surgery, such as overall mortality, cancer-related mortality, and recurrence rate, remain uncertain. Laparoscopic surgery for rectal cancer is a technically demanding procedure because the surgical space of the rectum is a narrow pelvic cavity surrounded by solid bones, which prevents the manipulation of laparoscopic instruments.

A radical excision of rectal cancers includes high ligation of the inferior mesenteric artery for adequate lymphatic clearance and total mesorectal excision. It is difficult to assess the quality of total mesorectal excision in rectal cancer surgery; however, the rates of circumferential resection margin and distal resection margin involvement are the best direct measure of total mesorectal excision.[10] The conventional versus laparoscopic-assisted surgery in colorectal cancer (CLASICC) trial reported the importance of the circumferential resection margin.[8] The study showed that a conversion to an open from a laparoscopic surgery was associated with a significantly worse overall, but not disease-free, survival. To accurately evaluate the efficacy of laparoscopic surgery for rectal 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, followed by late morbidity and quality of life. Recently, several randomized controlled trials comparing laparoscopic surgery with open surgery for rectal cancer have been published.[11–18] We conducted a meta-analysis of the data from these randomized controlled trials to compare the short- and long-term outcomes of laparoscopic and open surgery for rectal cancer.

Materials and Methods

Literature Search

To identify papers relevant to our study, we searched the major medical databases MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register for studies published between January 1990 and April 2011. The following search terms were used: “laparoscopy,” “laparoscopy assisted,” “surgery,” “rectal cancer,” and “randomized controlled trials.” We treated studies that were part of a series as a single study.[7–9,11,19,20] Appropriate data from such study series were used for this meta-analysis. This meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses statement[21] (Fig. 1).

Inclusion Criteria

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

Exclusion Criteria

Studies were excluded from this analysis if (1) the outcomes of interest were not reported for the two surgical techniques and if (2) they reported on rectal surgery for benign lesions.

Data Extraction

Three researchers (H.O., Y.T., and K.H.) extracted data from each article by using a structured sheet and entered the data into a database. Because this analysis was performed on the principle of intention-to-treat,[22] all patients converted from the laparoscopic group to the open group remained in the laparoscopic group for analysis. We conducted separate meta-analyses for two different post-operative 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, hospital stay, time to oral diet, period of parenteral analgesic administration, overall complications, anastomotic leakage, perioperative mortality, circumferential resection margin, distal resection margin, and cost of surgery. The cost of surgery consisted of operating and hospitalization costs. We also examined the relationship between the conversion rate from laparoscopic to open surgery and

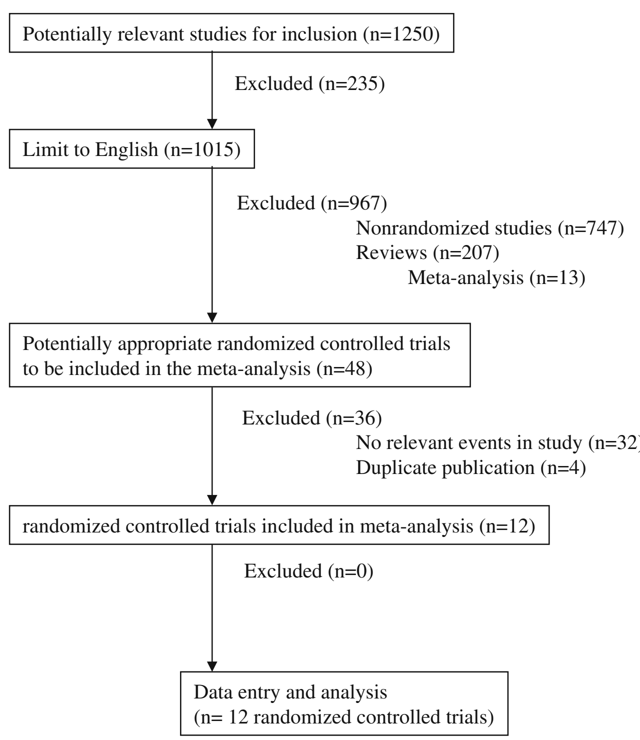


Fig. 1 Flow diagram of this meta-analysis in accordance with the QUOROM statement

Table 1 Characteristics of the randomized clinical trials

Authors	Year	Number of reference	Country	The type of institution	Study size (n) LR	Study size (n) OR	Conversion rate (%)	Follow-up period (months)	Randomization	Double blinding	Withdraws and dropouts	Jadad's score
Araujo et al.	2003	4	Brazil	Single institution	13	15	U	47.2 (mean)	1	0	1	2
Baik et al.	2011	5	United States of America	Single institution	54	108	11 (6/54)	59 (median)	1	0	1	2
Braga at al.	2007	6	Italy	Single institution	83	85	7.2 (6/83)	53.6 (mean) 54.2 (median)	2	0	1	3
CLASICC	2010 2007 2005	8 7 11	United Kingdom	Multicenter (27 centers)	253	128	34 (82/242)	56.3 (median)	2	2	1	5
Gonzalez et al.	2006	12	Spain	Single institution	20	20	10 (2/20)	U	1	0	1	2
Kan et al.	2010	3	Korea	Multicenter (3 centers)	170	170	1.2 (2/170)	U (short-term)	2	2	1	5
Lujan et al.	2009	13	Spain	Single institution	101	103	7.9 (8/101)	32.8±18.9 (laparoscopic surgery) (mean) 34.1±20.0 (open surgery) (mean)	2	2	1	5
Ng (low) et al.	2008	14	China	Single institution	51	48	9.8 (5/51)	87.2 (laparoscopic surgery) (median) 90.1 (open surgery) (median)	2	2	1	5
Ng (upper) et al.	2009	15	China	Single institution	76	77	30.3 (23/76)	112.5 (laparoscopic surgery) (median) 108.8 (open surgery) (median)	1	0	1	2
Park et al.	2009	16	Korea	Single institution	107	72	0 (0/170)	36 months (mean)	1	0	1	2
Quah et al.	2002	17	Singapore	Single institution	86	84	12 (10/86)	U	2	0	1	3
Zhou et al.	2004	18	China	Single institution	82	89	U	1–16 months	1	0	1	2

U unknown

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, wound site recurrence, cancer-related mortality, overall mortality, and disease-free survival at 3 and 5 years after surgery. For late morbidity in the long-term analysis, we used data on the rate of overall late morbidity, ileus, and incisional hernia. For quality of life in the long-term analysis, we used data on urinary and sexual dysfunction. Where necessary, we contacted the authors of the original papers to receive further information.

Assessment of Study Quality

The quality of the randomized controlled trials was assessed using Jadad's scoring system.[23] Two reviewers (H.O., Y.T.) assessed all studies that met the inclusion criteria (Table 1).

Statistical Analysis

Weighted mean differences and odds ratios were used for the analysis of continuous and dichotomous variables, respectively. Random effects models were used to identify heterogeneity between the studies,[24] and the degree of heterogeneity was assessed using the chi-square test. For the analysis of the conversion rate, the chi-square 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. As the cost data of one article[19] were precious and had neither a range nor any other measure of dispersion, the standard deviation was estimated by halving the mean.[25] One Euro and British pound were converted to US $1.4 and US $1.6, respectively. The statistical analyses were performed using the Review Manager (RevMan) software, version 5.1.1, provided by the Cochrane Collaboration, Copenhagen, Denmark.

Results

We identified 12 papers reporting results of randomized controlled trials that compared laparoscopic and open surgery for rectal cancer.[3–18] The characteristics of each randomized controlled trial are presented in Table 1. Our meta-analysis included 2,095 patients with rectal cancer; of these, 1,096 had undergone laparoscopic surgery, and 999 had undergone conventional open surgery. Short-term and long-term results are shown in Figs. 2 and 3, respectively. Late morbidity rate, urinary dysfunction, and sexual dysfunction are shown in Fig. 4.

Short-Term Outcomes

The operative time for laparoscopic surgery was significantly greater, by 40.96 min, than that for open surgery (weighted mean difference=40.96; 95% CI=25.53–56.38; $p<0.00001$). The intraoperative blood loss and the number of transfused patients in the laparoscopic group were significantly lower than in the open group. There was no significant difference in the number of harvested lymph nodes. The duration of hospital stay and the time to oral diet were significantly shorter with laparoscopic surgery than open surgery ($p=0.0001$ and 0.02, respectively). There was no significant difference in the period of parenteral analgesic administration. Overall complications and anastomotic leakage did not differ significantly between the two groups. We found no significant difference between patients who underwent laparoscopic surgery and those who underwent conventional open surgery for perioperative mortality.

Positive Circumferential Resection Margin

Seven articles reported data on the circumferential resection margin. Five of these compared data between laparoscopic and open groups. All five articles reported that there was no significant difference in the positive circumferential resection margin between the two groups. In an analysis of pooled data, we found that there was no significant difference in the positive circumferential resection margin between the two groups. There was no significant difference in the distal resection margin.

Cost of Surgery

In an analysis of the cost of surgery, there was no significant difference between the two groups. The cost of open surgery was similar among the three articles that assessed open surgery cost.

Conversion Rate

Ten articles reported data on the conversion rate from laparoscopic to open surgery, which ranged from 0% to 34% (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 ($p=0.51$).

Long-Term Outcomes

First, oncologic results of the long-term period were examined. Second, long-term morbidity and quality of life were evaluated.

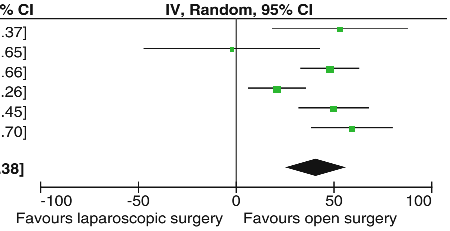
Fig. 2 Meta-analysis of the short-term period for rectal cancer ▶

Operation time

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Braga et al.	262	72	83	209	70	20	11.4%	53.00 [18.63, 87.37]
Gonzalez et al.	236.3	51.9	20	238.5	88.2	20	8.2%	-2.20 [-47.05, 42.65]
Kan et al.	244.9	75.4	170	197	62.9	170	21.3%	47.90 [33.14, 62.66]
Lujan et al.	193.7	45.1	101	172.9	59.4	103	21.5%	20.80 [6.34, 35.26]
Ng (low) et al.	213.5	46.2	51	163.7	43.4	48	19.6%	49.80 [32.15, 67.45]
Ng (upper) et al.	213.1	59.3	76	154	70.3	77	18.0%	59.10 [38.50, 79.70]
Total (95% CI)			**501**			**438**	**100.0%**	**40.96 [25.53, 56.38]**

Heterogeneity: Tau² = 234.06; Chi² = 16.29, df = 5 (P = 0.006); I² = 69%
Test for overall effect: Z = 5.20 (P < 0.00001)

Mean Difference IV, Random, 95% CI

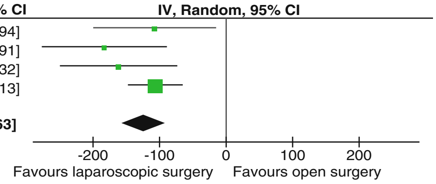


Blood loss

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baik et al.	313.2	260.9	54	420.6	314.7	108	12.9%	-107.40 [-198.86, -15.94]
Braga et al.	213	236	83	396	367	85	12.5%	-183.00 [-276.09, -89.91]
Gonzalez et al.	243.4	129.6	20	405	151.2	20	14.1%	-161.60 [-248.88, -74.32]
Lujan et al.	127.8	113.3	101	234.2	174.3	103	60.5%	-106.40 [-146.67, -66.13]
Total (95% CI)			**258**			**316**	**100.0%**	**-123.87 [-157.10, -90.63]**

Heterogeneity: Tau² = 52.99; Chi² = 3.11, df = 3 (P = 0.37); I² = 4%
Test for overall effect: Z = 7.30 (P < 0.00001)

Mean Difference IV, Random, 95% CI

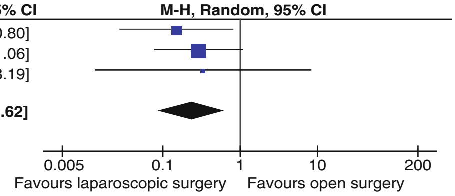


Number of transfused patients

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	3	13	10	15	34.0%	0.15 [0.03, 0.80]
Gonzalez et al.	7	20	13	20	56.7%	0.29 [0.08, 1.06]
Kan et al.	0	170	1	170	9.3%	0.33 [0.01, 8.19]
Total (95% CI)		**203**		**205**	**100.0%**	**0.23 [0.09, 0.62]**
Total events	10		24			

Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)

Odds Ratio M-H, Random, 95% CI

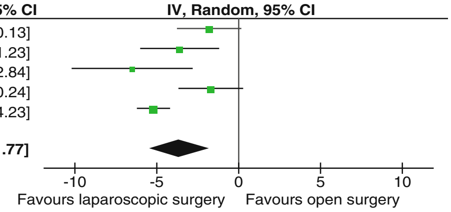


Hospital stay

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baik et al.	7	3.8	54	8.8	8.7	108	21.2%	-1.80 [-3.73, 0.13]
Braga et al.	10	4.9	83	13.6	10	85	18.9%	-3.60 [-5.97, -1.23]
Gonzalez et al.	9.1	5.7	20	15.6	6.1	20	13.2%	-6.50 [-10.16, -2.84]
Lujan et al.	8.2	7.3	101	9.9	6.8	103	21.1%	-1.70 [-3.64, 0.24]
Zhou et al.	8.1	3.1	82	13.3	3.4	89	25.6%	-5.20 [-6.17, -4.23]
Total (95% CI)			**340**			**405**	**100.0%**	**-3.61 [-5.45, -1.77]**

Heterogeneity: Tau² = 3.21; Chi² = 18.08, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 3.84 (P = 0.0001)

Mean Difference IV, Random, 95% CI

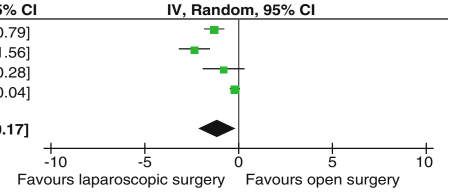


Time to oral diet

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Braga et al.	3.7	1.3	83	5	2	85	26.6%	-1.30 [-1.81, -0.79]
Gonzalez et al.	2.25	0.97	20	4.61	1.54	20	24.0%	-2.36 [-3.16, -1.56]
Lujan et al.	2.8	4.4	101	3.6	3.4	103	21.2%	-0.80 [-1.88, 0.28]
Zhou et al.	3.5	0.8	82	3.7	0.8	89	28.2%	-0.20 [-0.44, 0.04]
Total (95% CI)			**286**			**297**	**100.0%**	**-1.14 [-2.11, -0.17]**

Heterogeneity: Tau² = 0.86; Chi² = 36.50, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.29 (P = 0.02)

Mean Difference IV, Random, 95% CI

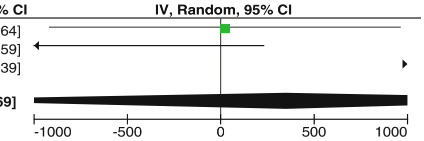


Costs for surgery

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CLASICC	8,279.5	4,139.7	222	8,257.6	4,128.8	112	34.3%	21.90 [-916.84, 960.64]
Gonzalez et al.	5,828.2	1,757.1	20	7,153	3,083.5	20	30.0%	-1324.80 [-2880.19, 230.59]
Ng (low) et al.	9,588	1,683	51	7,517	1,693	48	35.7%	2071.00 [1405.61, 2736.39]
Total (95% CI)			**293**			**180**	**100.0%**	**350.23 [-1570.23, 2270.69]**

Heterogeneity: Tau² = 2571595.80; Chi² = 22.58, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 0.36 (P = 0.72)

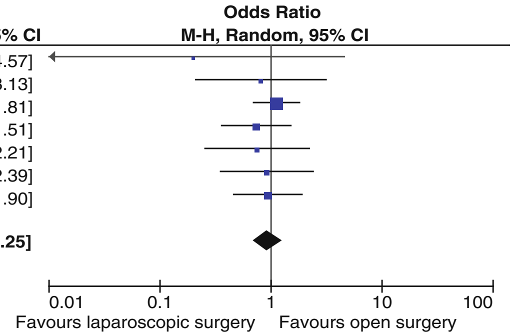
Mean Difference IV, Random, 95% CI



Overall recurrence

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	2	15	0.9%	0.20 [0.01, 4.57]
Braga et al.	4	83	5	85	5.0%	0.81 [0.21, 3.13]
CLASICC	73	253	34	128	40.2%	1.12 [0.70, 1.81]
Lujan et al.	16	101	21	103	17.8%	0.74 [0.36, 1.51]
Ng (low) et al.	8	40	9	36	7.8%	0.75 [0.25, 2.21]
Ng (upper) et al.	9	59	11	67	9.9%	0.92 [0.35, 2.39]
Park et al.	24	107	17	72	18.2%	0.94 [0.46, 1.90]
Total (95% CI)		**656**		**506**	**100.0%**	**0.93 [0.68, 1.25]**
Total events	134		99			

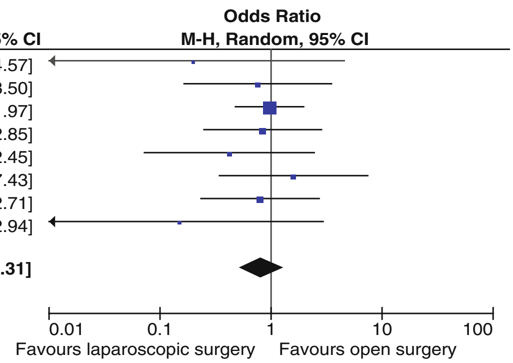
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 6 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.61)



Local recurrence

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	2	15	2.2%	0.20 [0.01, 4.57]
Braga et al.	3	83	4	85	9.1%	0.76 [0.16, 3.50]
CLASICC	25	253	13	128	42.4%	0.97 [0.48, 1.97]
Lujan et al.	5	101	6	103	14.2%	0.84 [0.25, 2.85]
Ng (low) et al.	2	40	4	36	6.8%	0.42 [0.07, 2.45]
Ng (upper) et al.	4	60	3	70	8.9%	1.60 [0.34, 7.43]
Park et al.	6	107	5	72	14.1%	0.80 [0.23, 2.71]
Zhou et al.	0	82	3	89	2.4%	0.15 [0.01, 2.94]
Total (95% CI)		**739**		**598**	**100.0%**	**0.83 [0.52, 1.31]**
Total events	45		40			

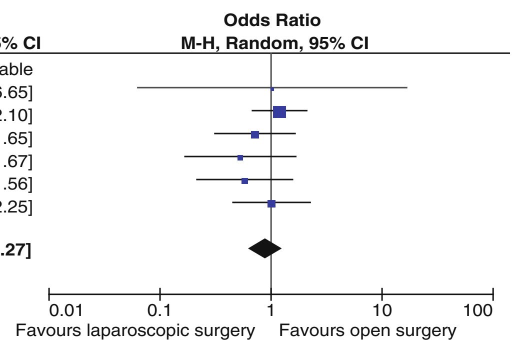
Heterogeneity: Tau² = 0.00; Chi² = 3.56, df = 7 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



Distant metastasis

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	0	15		Not estimable
Braga et al.	1	83	1	85	1.6%	1.02 [0.06, 16.65]
CLASICC	48	253	21	128	39.1%	1.19 [0.68, 2.10]
Lujan et al.	11	101	15	103	17.9%	0.72 [0.31, 1.65]
Ng (low) et al.	6	40	9	36	9.4%	0.53 [0.17, 1.67]
Ng (upper) et al.	7	60	13	70	12.6%	0.58 [0.21, 1.56]
Park et al.	18	107	12	72	19.4%	1.01 [0.45, 2.25]
Total (95% CI)		**657**		**509**	**100.0%**	**0.89 [0.63, 1.27]**
Total events	91		71			

Heterogeneity: Tau² = 0.00; Chi² = 2.91, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)



Wound-site recurrence

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	0	15		Not estimable
Baik et al.	0	54	0	108		Not estimable
Lujan et al.	0	101	0	103		Not estimable
Ng (low) et al.	0	40	1	36	48.3%	0.29 [0.01, 7.40]
Ng (upper) et al.	0	60	0	70		Not estimable
Zhou et al.	2	82	0	89	51.7%	5.56 [0.26, 117.53]
Total (95% CI)		**350**		**421**	**100.0%**	**1.34 [0.07, 24.10]**
Total events	2		1			

Heterogeneity: Tau² = 1.78; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.20 (P = 0.84)

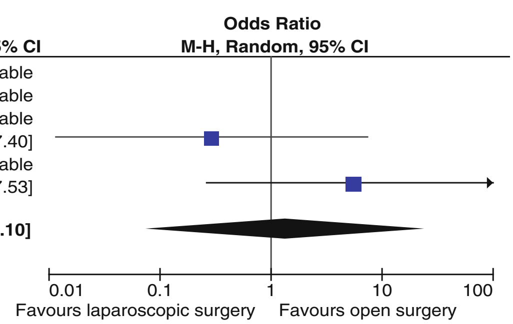


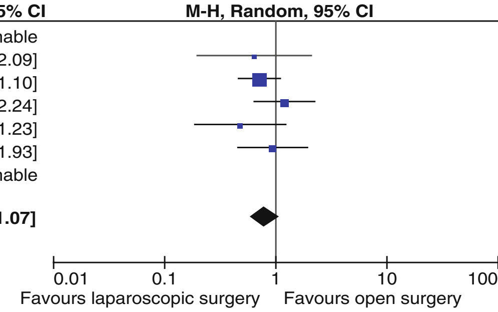
Fig. 3 Meta-analysis of the long-term oncologic results for rectal cancer

Overall mortality

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	0	15		Not estimable
Baik et al.	4	54	12	108	6.1%	0.64 [0.20, 2.09]
CLASICC	92	253	57	128	45.8%	0.71 [0.46, 1.10]
Lujan et al.	28	101	25	103	21.8%	1.20 [0.64, 2.24]
Ng (low) et al.	12	40	17	36	9.7%	0.48 [0.19, 1.23]
Ng (upper) et al.	22	59	26	67	16.5%	0.94 [0.46, 1.93]
Zhou et al.	0	82	0	89		Not estimable
Total (95% CI)		**602**		**546**	**100.0%**	**0.80 [0.60, 1.07]**
Total events	158		137			

Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 4 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

Odds Ratio M-H, Random, 95% CI

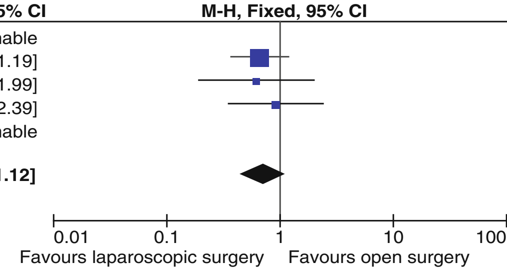


Cancer-related mortality

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Araujo et al.	0	13	0	15		Not estimable
CLASICC	32	253	23	128	62.7%	0.66 [0.37, 1.19]
Ng (low) et al.	6	40	8	36	16.8%	0.62 [0.19, 1.99]
Ng (upper) et al.	9	59	11	67	20.5%	0.92 [0.35, 2.39]
Zhou et al.	0	82	0	89		Not estimable
Total (95% CI)		**447**		**335**	**100.0%**	**0.71 [0.45, 1.12]**
Total events	47		42			

Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

Odds Ratio M-H, Fixed, 95% CI

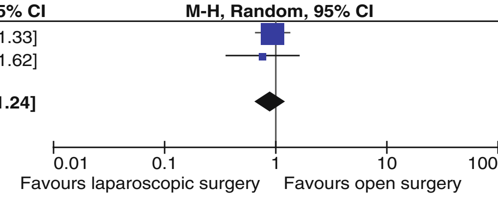


Disease-free survival at 3 years after surgery

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CLASICC	284	428	143	211	82.1%	0.94 [0.66, 1.33]
Park et al.	83	107	59	72	17.9%	0.76 [0.36, 1.62]
Total (95% CI)		**535**		**283**	**100.0%**	**0.90 [0.66, 1.24]**
Total events	367		202			

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)

Odds Ratio M-H, Random, 95% CI



Disease-free survival at 5 years after surgery

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Baik et al.	44	54	83	108	15.2%	1.33 [0.58, 3.01]
CLASICC	135	253	67	128	56.4%	1.04 [0.68, 1.59]
Lujan et al.	86	101	83	103	19.0%	1.38 [0.66, 2.88]
Ng (low) et al.	31	40	26	36	9.4%	1.32 [0.47, 3.75]
Total (95% CI)		**448**		**375**	**100.0%**	**1.17 [0.85, 1.61]**
Total events	296		259			

Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

Odds Ratio M-H, Random, 95% CI

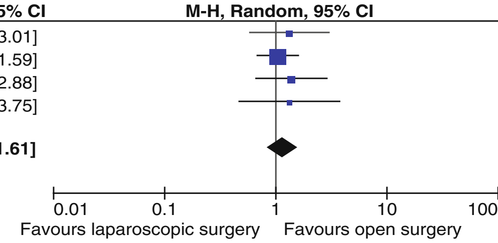


Fig. 3 (continued)

Tumor Recurrence

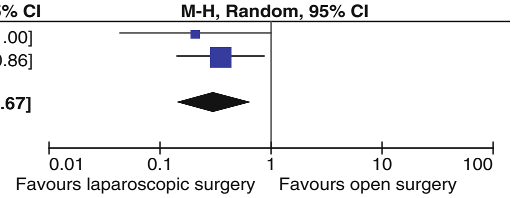
Eight, eight, and seven articles reported data on overall recurrence, local recurrence, and distant metastasis, respectively. Four, five, and four articles, respectively, compared these variables between laparoscopic and open surgery groups; none reported any significant difference. In an analysis of the pooled data, we found no significant difference in the overall recurrence, local recurrence, and distant metastasis between patients who underwent laparoscopic surgery and those who underwent open surgery. Further, no significant difference was found for wound site recurrence using the pooled data.

Overall late morbidity

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Braga et al.	2	83	9	85	24.9%	0.21 [0.04, 1.00]
Ng (upper) et al.	8	74	19	74	75.1%	0.35 [0.14, 0.86]
Total (95% CI)		**157**		**159**	**100.0%**	**0.31 [0.14, 0.67]**
Total events	10		28			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.96 (P = 0.003)

Odds Ratio M-H, Random, 95% CI

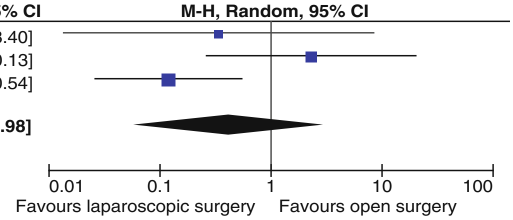


Ileus

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Braga et al.	0	83	1	85	22.8%	0.34 [0.01, 8.40]
CLASICC	5	129	1	58	34.1%	2.30 [0.26, 20.13]
Ng (upper) et al.	2	74	14	74	43.1%	0.12 [0.03, 0.54]
Total (95% CI)		**286**		**217**	**100.0%**	**0.41 [0.06, 2.98]**
Total events	7		16			

Heterogeneity: Tau² = 1.75; Chi² = 4.80, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.88 (P = 0.38)

Odds Ratio M-H, Random, 95% CI

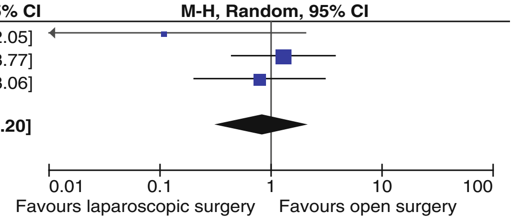


Incisional hernia

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Braga et al.	0	83	4	85	10.2%	0.11 [0.01, 2.05]
Gonzalez et al.	14	129	5	58	52.1%	1.29 [0.44, 3.77]
Ng (upper) et al.	4	74	5	74	37.7%	0.79 [0.20, 3.06]
Total (95% CI)		**286**		**217**	**100.0%**	**0.83 [0.32, 2.20]**
Total events	18		14			

Heterogeneity: Tau² = 0.17; Chi² = 2.55, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.37 (P = 0.71)

Odds Ratio M-H, Random, 95% CI

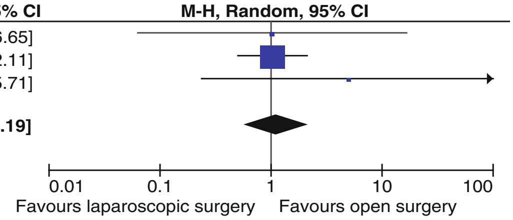


Urinary dysfunction

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
Braga et al.	1	83	1	85	5.9%	1.02 [0.06, 16.65]
CLASICC	34	98	17	50	89.2%	1.03 [0.50, 2.11]
Quah et al.	2	86	0	84	4.9%	5.00 [0.24, 105.71]
Total (95% CI)		**267**		**219**	**100.0%**	**1.11 [0.57, 2.19]**
Total events	37		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)

Odds Ratio M-H, Random, 95% CI



Sexual dysfunction (both male and female)

Study or Subgroup	laparoscopic surgery Events	laparoscopic surgery Total	open surgery Events	open surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
CLASICC	31	85	9	43	65.7%	2.17 [0.92, 5.11]
Quah et al.	7	21	1	28	34.3%	13.50 [1.51, 120.92]
Total (95% CI)		**106**		**71**	**100.0%**	**4.06 [0.73, 22.52]**
Total events	38		10			

Heterogeneity: Tau² = 0.97; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 1.60 (P = 0.11)

Odds Ratio M-H, Random, 95% CI

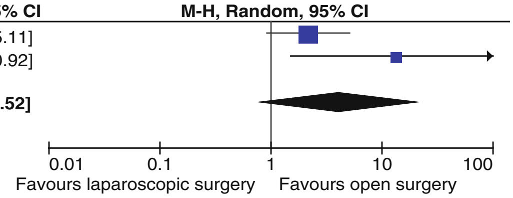


Fig. 4 Meta-analysis of the late morbidity and quality of life for rectal cancer

Mortality

Seven, five, two, and four articles reported data on overall mortality, cancer-related mortality, disease-free survival at 3 years after surgery, and that at 5 years, respectively. Five, two, one, and four articles, respectively, compared these variables between laparoscopic and open surgery groups; none reported any significant difference. In an analysis of the pooled data, we found no significant difference in the overall mortality, cancer-related mortality, and disease-free survival at 3 and 5 years after surgery between patients who underwent laparoscopic surgery and those who underwent conventional open surgery.

Long-Term Morbidity

Two, three, and three articles reported data on overall late morbidity, ileus, and incisional hernia, respectively. In an analysis of the pooled data, the rate of overall late morbidity in the laparoscopic group was significantly lower than that in the open group (odds ratio=0.31; 95% CI=0.14–0.67; p=0.003); however, we found no significant difference for ileus and incisional hernia between the two groups.

Long-Term Quality of Life

Three and two articles reported data on urinary and sexual dysfunction, respectively.

Urinary dysfunction did not differ significantly between the two groups (odds ratio=1.11; 95% CI=0.57–2.19; p=0.75). There was no significant difference in male, female, and both male and female sexual dysfunction between laparoscopic and open groups.

Heterogeneity

In the short-term period, a significant heterogeneity was found between studies with respect to operative time, duration of hospital stay, time to oral diet, and cost of surgery. In the long-term period, we found no significant heterogeneity between studies.

Discussion

In this meta-analysis, the examination of short-term outcomes showed that laparoscopic surgery for rectal cancer is associated with a significantly longer operative time, but significantly less intraoperative blood loss and the number of transfused patients compared with conventional open surgery. These results are consistent with those of recent randomized controlled trials.[3,6,12] Potential explanations for the abovementioned results include meticulous dissection facilitated by instruments for laparoscopic surgery and videoscopic magnification.[26–28] Patients who underwent laparoscopic surgery for rectal cancer resumed oral intake significantly earlier and had significantly shorter hospital stays than did patients who underwent conventional open surgery; this finding suggests that laparoscopic surgery for rectal cancer leads to faster recovery. In this meta-analysis, there was no significant difference in the period of parenteral analgesic administration between the two groups; however, Ng et al. reported that the number of postoperative analgesic requirements was significantly lower following laparoscopic surgery than conventional open surgery, both for upper and low rectal cancer.[14,15] The shorter surgical wound in laparoscopic surgery for rectal cancer may reduce the number of postoperative analgesic requirements, but not the duration of analgesic administration. No significant difference was found for overall perioperative complications, anastomotic leakage, and perioperative mortality between the two surgery groups; this finding suggests that the safety and feasibility of a laparoscopic surgery is similar to that of a conventional open surgery for rectal cancer. Further, the quality of laparoscopic surgery for rectal cancer appears to be similar to that of conventional open surgery, as shown by an insignificant difference in the number of dissected lymph nodes[16] and the rate of positive circumferential resection margin and distal resection margin[10] in this meta-analysis and previous studies.[5,13,15] In the analysis of the cost of surgery, we found no significant overall difference between laparoscopic and open surgery. The cost of open surgery for rectal cancer was similar among the three articles that assessed open surgery costs.[12,14,19] However, the operating costs were higher, and the hospitalization costs were lower for laparoscopic surgery compared with open surgery.

Several reports have shown that conversion from laparoscopic to open surgery is associated with inferior surgical outcomes.[11,29] In this analysis, the conversion rate was not significantly related to the type of study, i.e., single institution or multicenter. Both the CLASICC trial and Stohlein et al. reported that tumor infiltration/fixation and obesity were the most common reasons for conversion.[11,29]

In the long-term period, we found no significant difference in the overall recurrence, local recurrence, and distant metastasis between the two surgery groups. There was also no significant difference in wound site recurrence between the two groups, with the rate of wound site recurrence very small in the laparoscopic and open surgery groups. No significant difference was found in overall mortality, cancer-related mortality, and disease-free survival at 3 and 5 years after surgery. The abovementioned findings suggest that laparoscopic surgery for rectal cancer is comparable to conventional open surgery with respect to long-term oncologic results.

In the evaluation of long-term morbidity, the morbidity rate following laparoscopic surgery for rectal cancer was found to be significantly lower than that following conventional open surgery. Similarly, Ng et al. and Braga et al. described a high rate of adhesion-related bowel obstruction[15] and incisional hernia[6] in the conventional open surgery group, respectively, compared with the laparoscopic surgery group. No significant difference was found in the analysis of pooled data for the incidence of ileus between the two groups. There also was no significant difference in the analysis of pooled data for the rate of incisional hernia between the two surgery groups.

Urinary dysfunction and sexual dysfunction were examined in this analysis to evaluate long-term quality of life. Injury to the autonomic nervous system causes variable symptoms of bladder and sexual dysfunction.[30–32] The incidence of bladder and sexual dysfunction in patients with rectal cancer has diminished since total mesorectal excision was introduced and the need to preserve the autonomic nervous system was recognized.[32,33] However, few randomized controlled trials have reported data on urinary and sexual dysfunction in this patient population.[17,20] No significant difference was found in the analysis of pooled data for urinary dysfunction between laparoscopic and open surgery groups, which compares favorably with other reports. Further, in this meta-analysis, no significant differences were detected in the analysis of pooled data for male, female, and male and female sexual dysfunction, whereas Jayne et al. reported a trend towards worse male sexual dysfunction[20] and Quah et al. described a higher rate of male sexual dysfunction[17] in laparoscopic surgery compared with open surgery groups. In the CLASICC trial, total mesorectal excision was found to be more commonly performed in laparoscopic surgery than conventional open surgery, which was postulated to be the reason for the worse postoperative sexual function in men who underwent laparoscopic surgery for rectal cancer.[20] On the other hand, there is an idea that laparoscopic total mesorectal excision will allow for better preservation of the pelvic nervous system because the magnified view of the pelvis under the laparoscope allows for easier identification of pelvic nerves.[34,35] Because of the limited data, it is difficult to accurately quantify the influence of laparoscopic surgery on sexual function.

A significant heterogeneity between studies was observed only for short-term outcomes, including operative time, duration of hospital stay, time to oral diet, and cost of surgery. In the long-term period, we found no significant heterogeneity between studies. The reason for the observed heterogeneity in operative time 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 time to oral diet. Reasons for the heterogeneity in the cost of surgery may include variations in operative time and the cost of laparoscopic instruments.

In conclusion, this meta-analysis showed that laparoscopic surgery for rectal cancer is associated with a reduction in intraoperative blood loss and the number of transfused patients, earlier resumption of oral intake, and shorter duration of hospital stay over the short-term, but is associated with similar short-term and long-term oncologic outcomes compared to conventional open surgery. Therefore, laparoscopic surgery may be an acceptable alternative treatment option to conventional open surgery for rectal cancer.

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