# Is the laparoscopic approach for rectal cancer superior to open surgery? A systematic review and meta-analysis on short-term surgical outcomes

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#### Abstract

**Introduction:** Over the past years the incidence of colorectal cancers has increased worldwide. Currently it is the most common gastrointestinal malignancy worldwide. The laparoscopic approach has become the gold standard for surgical treatment. However, a recently published meta-analysis showed no difference in short- and long-term oncological outcomes of laparoscopy for treating rectal cancer.

**Aim:** To assess current literature on short-term outcomes of rectal cancer treatment using laparoscopic surgery in comparison to the open approach.

**Material and methods:** We performed a systematic review and meta-analysis according to the PRISMA guidelines. The primary outcomes of interest were morbidity and short-term complications.

**Results:** We identified 4,328 potential references. In the end we included 13 randomized controlled trials (RCTs). We did not find any significant differences in terms of morbidity, haemorrhage, ureter injury, anastomotic leakage, mortality, intra-abdominal abscess or postoperative ileus. We found significant differences in the rate of surgical site infections, operative time, blood loss, length of hospital stay and time to first bowel movement.

**Conclusions:** This systematic review based on available RCTs confirms that laparoscopic rectal cancer surgery is associated with short-term outcomes comparable to the open approach. Moreover, in some aspects it provides better results (e.g. functional postoperative recovery, lower rate of surgical site infections (SSIs)). The quality of evidence is high; therefore in our opinion it is very unlikely that future trials will alter these results, and for this reason the laparoscopic approach can be considered the gold standard for the treatment of the majority of patients.

Key words: laparoscopy, rectal cancer, short-term outcomes.

# Introduction

Over the past years the incidence of colorectal cancers has increased worldwide. Currently it is the most common gastrointestinal malignancy worldwide. Approximately one third of all large bowel can-

cers are located in the rectum [1]. So far, the primary treatment option for rectal adenocarcinoma remains surgery, supported by neoadjuvant and adjuvant therapy [2, 3].

Since the development of laparoscopic surgery, the minimally invasive approach for rectal opera-

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tions has been rapidly replacing open procedures [4]. There have been many studies reporting better short-term outcomes after laparoscopic surgery such as lower morbidity, reduced blood loss, reduced pain and faster recovery [5]. Moreover, the operative technique is constantly modified in order to improve postoperative and oncological outcomes [6]. Although according to many surgeons, laparoscopy should be considered the gold standard for the treatment of rectal cancers, the results of recently published well-designed randomized controlled trials, such as COLOR II, ALACART, and ACOSOG Z6051, surprisingly showed no significant differences in terms of short-term morbidity between laparoscopy and open surgery, with very narrow 95% confidence intervals [7-9]. In addition, a recently published meta-analysis including randomized controlled trials showed no difference in short- and long-term oncological outcomes of laparoscopy for treating rectal cancer [10]. This raises the question whether in the era of modern perioperative care laparoscopy is still advantageous in terms of short-term outcomes.

# Aim

Therefore, we aimed to answer whether laparoscopic surgery is clinically justified based on the highest quality studies.

# Material and methods

# Search strategy

A search was conducted by three researchers (MM, JW and GT) in November 2017 of Medline, Embase and the Cochrane library covering the period from January 1966 to November 2017. Aiming for the highest possible comprehensiveness of our

review, our search had no language limitations. The full search strategy for the OVID platform is available in Figure 1. Reference lists of relevant publications were assessed for additional studies of interest. Furthermore, bibliographies from previous systematic reviews or meta-analyses on the subject were searched.

A paper was included when: the study concerned adult patients who underwent colorectal surgery for neoplasm and reported short-term morbidity. Included studies had to be randomized controlled trials (RCTs). All criteria mentioned above were required to enrol a study for further evaluation. Exclusion criteria were: the study was a review, guidelines, single group or non-randomized study.

Three researchers (MM, JW and GT) identified and selected citations from the search independently. In case of doubt about inclusion, a third reviewer was consulted (PM or MP) until a consensus was reached. Data from included studies were extracted independently by the three researchers. Study quality and risk of bias were assessed using The Cochrane Collaboration's tool for assessing risk of bias.

#### Outcome measures

The primary outcome measures of this systematic review were overall short-term morbidity including intraoperative haemorrhage, ureter injury, anastomotic leakage, mortality, intra-abdominal abscesses, surgical site infections and postoperative ileus rate. Secondary outcomes were operative time, blood loss, length of hospital stay, and time to first flatus.

# Statistical analysis

Analysis was performed using RevMan 5.3 (freeware from The Cochrane Collaboration). Statistical

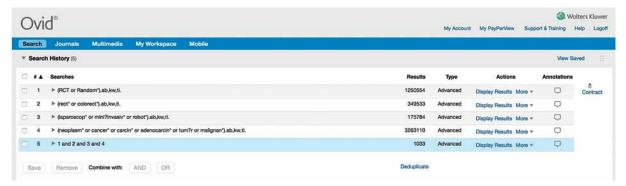


Figure 1. Search strategy for OVID

**Table I.** Baseline characteristics

First author (trial name)	Year	Single or multicenter design (SC/MC)	Tumor stage exclusion criteria	Number of participants LAP/OPEN (n)	Female/ male (n)	Mean age LAP/OPEN [years]	Mean distance of the tumor to anal verge LAP/OPEN [cm]	Types of surgery	Neoadjuvant treatment LAP/OPEN n (%)	lleostomy LAP/OPEN n (%)	Conversion rate n (%)
Araujo	2003	SC	Astler- Coller D	13/15	19/28	59.1/56.4	ND	APR	15/15	ON	0
Zhou	2004	SC	Dukes D	82/89	82/89	44.0/45.0	ΟN	TME	ND	ND	ND
Guillou (CLASICC)	2005	MC	Acute intestinal obstruction	253/128	ON	N	QN	TME, APR	ND	ND	86 (34)
Braga	2006	SC	Т4	83/85	49/119	62.8/65.3	9.1/8.6	TME, APR	14 (16.9)/ 12 (14.1)	22 (26.5)/ 21 (24.7)	6 (7.2)
Pechlivanides	2007	SC	14	34/35	30/43	72.0/69.0	8/9	TME, APR	13 (38.2)/ 15 (43.6)	QN	1 (3)
8 N	2008	SC	T4, size > 6 cm	51/48	38/61	63.7/63.5	ND	TME	0/0	QN	5 (9.8)
Lujan	2009	SC	Т4	101/103	78/126	0.8/66.0	5.5/6.2	TME, APR	74 (73.0)/ 79 (77.0)	48 (47.5)/ 48 (46.6)	8 (7.9)
Kang (COREAN)	2010	MC	T4, M1	170/170	120/220	57.8/59.1	5.6/5.3	TME, APR	170 (100)/ 170 (100)	138 (81.2)/ 129 (75.9)	2 (1.2)
van der Pas (COLOR II)	2013	MC	Т4	699/345	385/669	8.59/8.99	QN	PME, TME, APR	636 (91.0)/ 317 (92.0)	243 (34.8)/ 131 (38.0)	119 (17)
Gong	2012	SC	M1	67/71	82/09	58.4/59.6	QN	TME, APR	QN	QN	2 (3.0)
Kennedy (ENROL)	2014	WC	Acute intestinal obstruction	29/27	Q N	O N	Q	TME, APR	QN	22 (75.9)/ 19 (70.4)	ΩN
80 N	2014	SC	Т4	40/40	34/46	60.2/62.1	6.9/7.1	TME	QN	20 (50.0)/ 26 (65.0)	3 (7.5)
Fleshman (ACOSOG Z6051)	2015	MC	T4, M1	240/222	148/314	57.7/57.2	6.1/6.3	TME, APR	236 (98.3)/ 215 (96.7)	171 (71.3)/ 165 (74.3)	27 (11.3)
Stevenson (ALaCaRT)	2015	MC	47	Stevenson 2015 MC T4 238/237 162/311 65.0/65.0 ND TME, 119 (50.0)/ 68.1/59.5 21 (8.8) (ALaCaRT)	162/311	65.0/65.0	QN	TME, APR	119 (50.0)/	68.1/59.5	21 (8.8)

MC – multicenter, SC – single center, TME – total mesorectal excision (anterior resection), APR – abdominoperineal resection, PME – partial (upper) mesorectal excision, ND – no data, LAP – laparoscopic approach, OPEN – open approach.

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heterogeneity and inconsistency were measured using Cochran's Q tests and I2, respectively. Qualitative outcomes from individual studies were analyzed to assess individual and pooled risk ratios (RR) with pertinent 95% confidence intervals (CI) favouring the mini-invasive approach over an open procedure and by means of the Mantel-Haenszel random-effects method. When study included medians and interquartile ranges, we calculated the mean ± SD using a method proposed by Hozo et al. [11]. Weighted mean differences (WMD) with 95% CI are presented for quantitative variables using the inverse variance fixed-effects or random-effects method. Statistical significance was observed with a two-tailed 0.05 level for a hypothesis and with 0.10 for heterogeneity testing, while unadjusted p-values were reported accordingly. This study was performed according to the Preferred Reporting Items for Systematic reviews (PRISMA) guidelines [12].

# Results

Our strategy resulted in 4,328 references. After removing duplicates, and evaluating titles and abstracts, we chose 245 papers suitable for full-text review. In the end 16 studies were selected for extraction [7–9, 13–25]. There were 3 trials (COLOR II, CLASICC and COREAN) in which results were reported in more than one paper [8, 17, 18, 20, 21, 23,

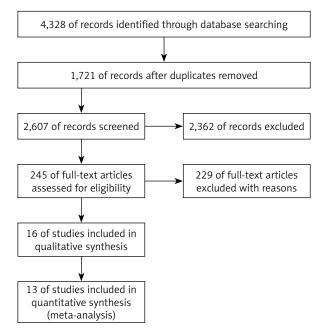


Figure 2. PRISMA flowchart

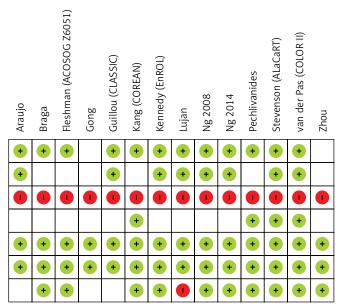
26]. The relevant data were extracted only once from these studies. Two studies by Kennedy et al. (EnROL Trial) and Stevenson et al. (ALaCaRT Trial) reported complications, but they did not report overall complication rates. Due to lack of overall morbidity we decided to exclude these studies from the morbidity analysis to avoid potential bias of overestimation [9, 25]. However, we included them in secondary outcomes and specific complications. Our review covers 3,646 patients in total (2,066 patients in the laparoscopic group and 1,580 patients in the open group) (Table I). The PRISMA flowchart for the review is presented in Figure 2. Risk of bias in the studies is assessed in Figure 3. In general, the risk of bias in the presented studies is low. Due to the nature of the treatment (differences in operative technique), blinding of participants and personnel was impossible to perform. A factor which was mainly unclear was the outcome assessment, as most of the studies did not clearly define how and by whom they were performed.

Morbidity rate was reported in 11 studies. The total morbidity in the analysed material was 664/1797 (36.95%) in the laparoscopy group vs. 483/1316 (36.7%): p=0.6, RR = 0.97; 95% CI: 0.87–1.08. Seven studies reported overall morbidity, whereas 4 other studies reported short-term morbidity only. Due to this fact we introduced subgroups to analyse potential differences. There were no significant variations within subgroups (p=0.6 in overall group and p=0.49 in short-term group) (Figure 4). Three of the included studies additionally provided information on intra-operative complications, but the analysis revealed similar results (RR = 1.01, 95% CI: 0.73–1.39). The heterogeneity of all mentioned outcomes was low.

Intra-operative haemorrhage was reported in 8 studies. There was no statistically significant difference between the groups, 61/1834 (3.33%) vs. 33/1342 (2.46%) (RR = 1.19, 95% CI: 0.78–1.81). There was no heterogeneity in the analysed material,  $I^2 = 0\%$  (Figure 5).

Ureter injuries were reported in 5 studies. There were 11/1341 (0.82%) cases in the laparoscopic group and 6/855 (0.7%) in the open group. Analysis revealed no significant difference: RR = 1.11, 95% CI: 0.18–6.67 (Figure 6).

Anastomotic leakage was reported in 9 studies. There was no statistically significant difference between the groups, 107/1473 (7.26%) vs. 64/1126 (5.68%) (RR = 1.08, 95% CI: 0.79–1.47). There was



Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other bias

Figure 3. Risk of bias summary

Study or subgroup	Laparo	scopic	Ope	n	Weight	Risk ratio	Year	Risk ratio	
	Events	Total	Events	Total	(%)	M-H, random, 95% CI		M-H, random, 95% CI	
1.1.1. Overall									
Araujo	9	13	7	15	2.5	1.48 (0.77-2.85)	2003		
Zhou	5	82	11	89	1.1	0.49 (0.18-1.36)	2004	<del></del>	
Ng 2008	23	51	25	48	6.2	0.87 (0.58-1.30)	2008	<del></del>	
Lujan	34	101	34	103	6.7	1.02 (0.69–1.50)	2009	<del></del>	
Kang (COREAN)	36	170	40	170	6.5	0.90 (0.61–1.34)	2010	<del></del>	
Gong	4	67	6	71	0.7	0.71 (0.21–2.39)	2012	-	
Fleshman (ACOSOG Z605	1) 137	240	129	222	28.1	0.98 (0.84–1.15)	2015	#	
Subtotal (95% CI)		724		718	51.8	0.97 (0.85–1.10)		Y	
Total events	248		252						
Heterogeneity: $\tau^2 = 0.00$ ,	$\chi^2 = 4.22$	$f$ , $\mathrm{d}f = 6$	5(p = 0)	.65), <i>l</i> ²	= 0%				
Test for overall effect: $Z =$	0.52 (p =	= 0.60)							
1.1.2. Short-term									
Guillou (CLASSIC)	101	253	47	128	12.4	1.09 (0.83-1.43)	2005		
Braga	24	83	34	85	5.7	0.72 (0.47-1.11)	2007	<del></del>	
van der Pas (COLOR II)	278	697	128	345	26.3	1.08 (0.91–1.27)	2013	*	
Ng 2014	13	40	22	40	3.8	0.59 (0.35–1.00)	2014		
Subtotal (95% CI)		1073		598	48.2	0.92 (0.72–1.17)		•	
Total events	416	231							
Heterogeneity: $\tau^2 = 0.03$ ,	$\chi^2 = 7.15$	, $df = 1$	3 (p = 0)	.07), 12	= 58%				
Test for overall effect: $Z =$	0.69 (p =	= 0.49)							
Total (95% CI)		1797		1316	100.0	0.97 (0.87-1.08)		<b></b>	
Total events	664		483					Ĭ	
Heterogeneity: $\tau^2 = 0.00$ ,	$y^2 = 11.4$	5. d <i>f</i> =	10 (p =	= 0.32)	$J^2 = 139$	%	+	<del>-   -   -  </del>	
Test for overall effect: $Z =$				,	,		0.05	0.2 1 5	20
Test for subgroup differen	4	,		n = 0.7	71). $l^2 = 0$	0%		urs laparoscopy Favours op	
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Figure 4. Pooled estimates of morbidity comparing laparoscopy and open surgery

 ${\it CI-confidence}$  interval,  ${\it df-degrees}$  of freedom.

no heterogeneity in the analysed material,  $I^2 = 0\%$  (Figure 7).

Mortality was reported in 9 studies. There were 8 (0.5%) cases of death in the laparoscopic group and 10 (0.81%) cases in the open group (Figure 8). There was no significant difference between the groups (RR = 0.71, 95% CI: 0.28-1.81).

Intra-abdominal abscess was reported in 8 studies. There was no statistically significant difference between the groups, 60/1466 (3.14%) vs. 31/1102 (2.81%) (RR = 1.11, 95% CI: 0.73–1.70). There was no heterogeneity in the analysed material,  $I^2 = 0\%$  (Figure 9).

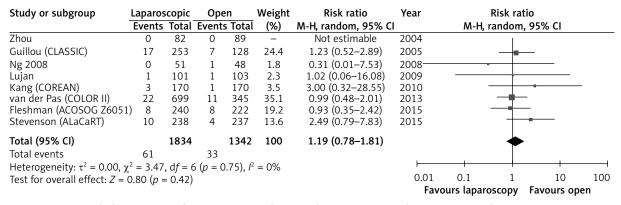
Surgical site infection was reported in 10 studies. Analysis revealed a 33% (89/1784 vs. 93/1316) low-

er risk of developing surgical site infection in favour of laparoscopy (RR = 0.67, 95% CI: 0.46–0.96). The heterogeneity of the analysed outcome was at an acceptable level,  $I^2 = 19\%$  (Figure 10).

Postoperative ileus was reported in 8 studies. There was no statistically significant difference between the groups, 74/1622 (4.56%) vs. 75/1250 (6%) (RR = 0.79, 95% CI: 0.57–1.1). There was no

heterogeneity in the analysed material,  $l^2 = 0\%$  (Figure 11).

Operative time was reported in 11 studies. Open procedures were significantly shorter in all studies (218 min in laparoscopy vs. 177 min in open) with a weighed mean difference of 40 min (MD = 40.01 min, 95% CI: 28.16–51.86). The heterogeneity of mentioned papers is high. We performed sensitivity



**Figure 5.** Pooled estimates of intra-operative haemorrhage comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

Study or subgroup	Laparos	copic	Ope	n	Weight	Risk ratio	Year	Risk ra	tio	
	Events	Total	Events	Total	(%)	M-H, random, 95% C	I	M-H, random	ı, 95% CI	
Zhou	0	82	0	89	-	Not estimable	2004			
Guillou (CLASSIC)	0	253	4	128	22.1	0.06 (0.00-1.04)	2005——	-		
Gong	1	67	0	71	19.9	3.18 (0.13-76.64)	2012		-	-
van der Pas (COLOR II)	9	699	2	345	38.2	2.22 (0.48-10.22)	2013	-		
Fleshman (ACOSOG Z6051	.) 1	240	0	222	19.8	2.78 (0.11–67.79)	2015		-	,
Total (95% CI)		1341		855	100.0	1.11 (0.18-6.67)			<b>-</b>	
Total events	11		6							
Heterogeneity: $\tau^2 = 1.59$ , $\chi$	$z^2 = 5.76$	df = 3	3(p=0)	.12), /2	= 48%			+ +		
Test for overall effect: $Z = 0$	0.11 (p =	0.91)					0.002	0.1 1	10	500
	4	,					Favoi	urs laparoscopy	Favours op	en

Figure 6. Pooled estimates of ureter injury comparing laparoscopy and open surgery

CI – confidence interval, df – degrees of freedom.

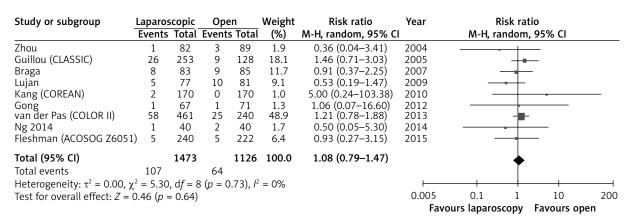


Figure 7. Pooled estimates of anastomotic leakage comparing laparoscopy and open surgery

CI – confidence interval, df – degrees of freedom.

analysis which identified three papers that generated the whole heterogeneity: Zhou *et al.*, Lujan *et al.* and Stevenson *et al.* Despite high heterogeneity generated by those papers, we decided to include the primary analysis (Figure 12) due to the fact that

their exclusion did not alter the results (MD = 50.45 min, 95% CI: 44.71-56.18).

Blood loss was reported in 11 studies. Only three studies did not report smaller blood loss in laparoscopy [15, 17, 24]. There was a significant difference

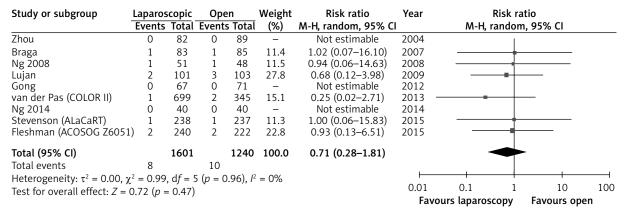


Figure 8. Pooled estimates of mortality comparing laparoscopy and open surgery

CI – confidence interval, df – degrees of freedom.

Study or subgroup	Laparos	copic	Ope	n	Weight	Risk ratio	Year	Risk r	atio	
	Events	Total	Events	Total	(%)	M-H, random, 95% C	l	M-H, rando	m, 95% CI	
Zhou	0	82	0	89	-	Not estimable	2004			
Braga	3	83	4	85	8.4	0.77 (0.18-3.33)	2007			
Ng 2008	1	51	1	48	2.4	0.94 (0.06-14.63)	2008	-		
Lujan	3	101	2	103	5.8	1.53 (0.26–8.96)	2009	-		
Kang (COREAN)	0	170	1	170	1.8	0.33 (0.01–8.13)	2010—	-		
van der Pas (COLOR II)	51	699	22	345	77.5	1.14 (0.71–1.85)	2013	-	-	
Ng 2014	1	40	1	40	2.4	1.00 (0.06–15.44)	2014			
Fleshman (ACOSOG Z6051	.) 1	240	0	222	1.8	2.78 (0.11–67.79)	2015	-	-	
Total (95% CI)		1466		1102	100.0	1.11 (0.73–1.70)		•	•	
Total events	60		31			, ,				
Heterogeneity: $\tau^2 = 0.00$ , $\gamma$	$r^2 = 1.26$	df = e	5(n = 0)	97) 12	= 0%		<u> </u>	$\rightarrow$		$\overline{}$
Test for overall effect: $Z = 0$	•	,	*	,,.			0.01	0.1 1	10	100
rest for overall effect. Z = 1	υ. <del>-</del> τυ ( <i>p</i> -	- 0.03)					Favo	urs laparoscopy	Favours op	en

**Figure 9.** Pooled estimates of intra-abdominal abscess comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

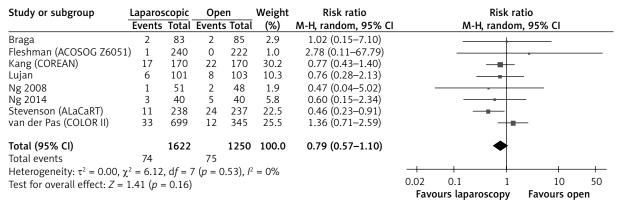
Study or subgroup	Laparos	copic	Ope	n	Weight	Risk ratio	Year	Risk ra	tio	
	Events	Total	Events	Total	(%)	M-H, random, 95% C	l	M-H, random	, 95% CI	
Zhou	2	82	3	89	3.9	0.72 (0.12-4.22)	2004			
Guillou (CLASSIC)	33	253	15	128	23.1	1.11 (0.63-1.97)	2005	_	_	
Braga	6	83	13	85	12.1	0.47 (0.19-1.18)	2007			
Ng 2008	10	51	10	48	15.3	0.94 (0.43-2.06)	2008	-	_	
Lujan	0	101	2	103	1.4	0.20 (0.01-4.20)	2009 —			
Kang (COREAN)	2	170	11	170	5.3	0.18 (0.04–0.81)	2010			
Gong	1	67	2	71	2.2	0.53 (0.05-5.71)	2012	-		
van der Pas (COLOR II)	28	699	17	345	22.3	0.81 (0.45–1.46)	2013			
Ng 2014	1	40	7	40	2.9	0.14 (0.02-1.11)	2014 -			
Stevenson (ALaCaRT)	6	238	13	237	11.4	0.46 (0.18–1.19)	2015			
Total (95% CI)		1784		1316	100.0	0.67 (0.46-0.96)		•		
Total events	89		93					•		
Heterogeneity: $\tau^2 = 0.06$ ,	$\chi^2 = 11.1$	5, d <i>f</i> =	9(p = 0)	0.27),	$I^2 = 19\%$		-	+	+	
Test for overall effect: Z =				,,			0.01	0.1 1	10	100
		,					Favo	urs laparoscopy	Favours op	en

Figure 10. Pooled estimates of surgical site infection comparing laparoscopy and open surgery

CI – confidence interval, df – degrees of freedom.

among analysed groups (168 ml in laparoscopy vs. 303 ml in open group). Blood loss was on average 89 ml less (MD = -94.24, 95% CI: -123.12 - -65.36) (Figure 13). Due to high heterogeneity,  $I^2 = 90\%$ , we

performed a sensitivity test. Excluding studies by Kang *et al.*, van der Pas *et al.* and Gong *et al.* reduced heterogeneity to  $l^2 = 60\%$ , with no effect on the results (MD = -96.63, 95% CI: -122.68 - -69.97).



**Figure 11.** Pooled estimates of postoperative ileus comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

Study or subgroup Weight Mean difference Mean difference Laparoscopic Mean SD Total Mean SD Total (%) IV, random, 95% CI IV, random, 95% CI Zhou 120 18.3 82 106 25 89 10.8 14.00 (7.47–20.53) 2004 Braga 262 72 83 209 70 85 8.2 53.00 (31.52-74.48) 2007 Ng 2008 43.4 49.80 (32.15-67.45) 213.5 46.2 51 163.7 48 9.0 2008 45.1 101 59.4 103 9.6 20.80 (6.34-35.26) 2009 Lujan 193.7 172.9 48.00 (33.28–62.72) 53.00 (33.89–72.11) Kang (COREAN) 170 63 9.5 Gong 216 68 67 163 43 27 2012 van der Pas (COLOR II) 240 86 699 188 66.7 345 10.4 52.00 (42.50-61.50) 2013 Kennedy (EnROL) 67 29 2014 220 186 48 6.4 34.00 (3.63-64.37) Ng 2014 Stevenson (ALaCaRT) 40 153 40 8.3 58.60 (37.82-79.38) 211.6 53 41.1 2014 66.7 237 20.00 (8.65–31.35) 210 238 190 59.26 10.1 Fleshman 266 102 240 92 8.9 45.00 (27.31-62.69) 2015 221 222 (ACOSOG Z6051) Total (95% CI) 1800 1437 100.0 40.01 (28.16-51.86) -50 -25 25 Heterogeneity:  $\tau^2 = 326.87$ ,  $\chi^2 = 77.95$ , df = 10 (p < 0.00001),  $l^2 = 87\%$ Favours laparoscopy Favours open

**Figure 12.** Pooled estimates of operative time comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

Study or subgroup	Lap	arosco	opic		Open	١	Neigh	t Mean difference	Year	Mean difference
	Mean	SD	Tota	Mean	SD	Tota	(%)	IV, random, 95% CI		IV, random, 95% CI
Zhou	0	19.7	82	92	25	89	15.3	-72.00 (-78.72, -65.28)	2004	- 1
Braga	231	236	83	396	367	85	5.9	-183.00 (-276.09, -89.91	.) 2007	<del></del>
Ng 2008	321.7	750	51	555.6	1,180	48	0.5	-233.90 ( <del>-</del> 626.08, 158.28	3) 2008	
Lujan	127.8	113.3	101	234.2	174.3	103	11.9	-106.40 (-146.67, -66.13	2009	+
Kang (COREAN)	200	148	170				12.5	-17.00 (-52.61, 18.61)	2010	+
Gong	86.9	37.6	67	119.1	32.7	71	15.0	-32.20 (-43.99, -20.41)		•
van der Pas (COLOR I		222	699					–200.00 (–242.41, –157.5°		
Kennedy (EnROL)	181	146	29	450	397	27		-269.00 (-427.90, -110.1		<del></del>
Ng 2014	141.8	500	40		623.75			-219.30 (-467.04, 28.44)		
Stevenson (ALaCaRT)		111			159.26			-90.00 (-114.70, -65.30)		*
Fleshman	256.1	305.8	240	318.4	331.7	222	9.5	-62.30 ( <del>-</del> 120.62, <del>-</del> 3.98)	2015	-
(ACOSOG Z6051)									-1	<b>A</b>
Total (95% CI)			1800					0 –94.24 (–123.12, –65.3	6)	
Heterogeneity: $\tau^2 = 1$	407.61	$, \chi^2 =$	102.2	9, d <i>f</i> =	10 (p ·	< 0.00	0001),	$I^2 = 90\%$		-500 -250 0 250 500
Test for overall effect	: Z = 6.	40 (p	< 0.00	0001)					_	
		4		,					Favou	rs laparoscopy Favours open

Figure 13. Pooled estimates of blood loss comparing laparoscopy and open surgery

CI – confidence interval, df – degrees of freedom.

Test for overall effect: Z = 6.62 (p < 0.00001)

Length of hospital stay (LOS) was reported in 12 studies. Five studies reported shorter LOS in favour of the laparoscopic approach, whereas the remainder did not reach a similar conclusion. In general LOS differed significantly between groups (9 days in the laparoscopic group vs. 11 days in the open open). Our analysis revealed that on average, the LOS is 1.6 days shorter in the case of laparoscopy (MD = -1.62, 95% CI: -2.37 - -0.86) (Figure 14). Due to high heterogeneity ( $l^2 = 92\%$ ) we performed sensitivity analysis and managed to reduce heterogeneity to 67% when studies by Zhou *et al.*, Guillou *et al.* and Braga *et al.* were excluded (MD = -0.78, 95% CI: -1.44 - -0.12) [14, 20, 22].

Time to first flatus was reported in 5 studies, whereas time to first bowel movement was reported in 7 studies. Gong *et al.*, Kang *et al.* and Stevenson *et al.* reported a shorter time to first flatus in fa-

vour of laparoscopy [9, 17, 19]. The mean time to first flatus was 1.93 days in the laparoscopic group, whereas in the open procedure it was 3 days. Due to high heterogeneity, we decided not to perform a meta-analysis of this outcome. In the case of time to first bowel movement only Stevenson et al. and Ng et al. did not report a shorter time for laparoscopy [9, 24]. The mean time to first bowel movement for laparoscopy was 2.97 days, while for the open group it was 3.82 days. Meta-analysis showed a 0.75 shorter time to first bowel movement in favour of laparoscopy (MD = -0.75, 95% CI: -1.29 - -0.22). The heterogeneity was high,  $I^2 = 92\%$ ; thus we performed a sensitivity test which revealed two studies generating all the heterogeneity. The result was not affected and still in favour of laparoscopy (MD = -1.03, 95% CI: -1.25-- 0.81) (Figure 15).

Study or subgroup	Lap	arosc	opic		Open	Weight	Mean difference	Year	Mean difference	
	Mean	SD	Total	Mean	SD	Total (%)	IV, random, 95% CI		IV, random, 95% CI	
Zhou	8.1	3.1	82	13.3	3.4	89 10.5	-5.20 (-6.17, -4.23)	2004	+	
Guillou (CLASSSIC)	11	1	253	13	1.5	128 12.5	-2.00 (-2.29, -1.71)	2005	-	
Braga	10	4.9	83	13.6	10	85 5.6	-3.60 (-5.97, -1.23)	2007		
Ng 2008	10.8	5.5	51	11.5	8.25	48 4.7	-0.70 (-3.48, 2.08)	2008	<del></del>	
Lujan	8.2	7.3	101	9.9	6.8	103 6.9	-1.70 (-3.64, 0.24)	2009		
Kang (COREAN)	8	0.83	170	9	0.67	170 12.6	-1.00 (-1.16, -0.84)	2010	-	
Gong	10.4	4.3	67	13.8	5.9	71 7.7	-3.40 (-5.12, -1.68)	2012		
van der Pas (COLOR		11.8	699	12.1	10.6	345 8.8	-0.20 (-1.62, 1.22)	2013	-	
Ng 2014	10.5	7.5	40	15	40.25		-4.50 (-17.19, 8.19)	2014 —	-	
Kennedy (EnROL)	5	1.85	29	6	3.7	27 8.3	-1.00 (-2.55, 0.5 <u>5</u> )	2014	<del> </del>	
Fleshman (ACOSOG Z6051)	7.3	5.4	240	7	3.4	222 11.1	0.30 (-0.52, 1.12)	2015	†	
Stevenson (ALaCaRT)	8	4.44	238	8	4.44	237 11.1	0.00 (-0.80, 0.80)	2015	·+	
Total (95% CI)			2053				-1.62 (-2.37, -0.86)	1	•	
Heterogeneity: $\tau^2 = 1$	$.16, \chi^2$	= 134	.47, d <i>f</i>	f = 11 (	p < 0.0	00001), $I^2 = 9$	2%			
Test for overall effect					-			-20	-10 0 10	20
		4.		,				Favours	laparoscopy Favours o	pen

**Figure 14.** Pooled estimates of length of hospital stay comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

Study or subgroup	Lap	arosc	opic		Open	Weight	Mean difference	Year	Mean difference	
	Mean	SD	Total	Mean	SD	Total (%)	IV, random, 95% CI		IV, random, 95% CI	
Zhou	1.5	1.3	82	2.7	1.5	89 15.7	-1.20 (-1.62, -0.78)	2004		
Guillou (CLASSSIC)	5	2.22	253	6	2.22	128 15.3	-1.00(-1.47, -0.53)	2005		
Ng 2008	4.3	5.25	51	6.3	2.75	48 6.7	-2.00 (-3.64, -0.36)	2008		
van der Pas (COLOR I	I) 2.9	3.8	699	3.7	3.6	345 15.3	-0.80 (-1.27, -0.33)	2013		
Ng 2014	3.1	1.3	40	3.1	1.5	40 14.1	0.00 (-0.62, 0.62)	2014	+	
Fleshman	2	2.5	240	3	2	222 15.7	-1.00 (-1.41, -0.59)	2015		
(ACOSOG Z6051)										
Števenson (ALaĆaRT)	2	0.3	234	2	0.5	233 17.3	0.00 (-0.07, 0.07)	2015	•	
Total (95% CI)			1599			1105 100.0	-0.75 (-1.29, -0.22)		•	
Heterogeneity: $\tau^2 = 0$	.44, $\chi^2$	= 79.2	24, d <i>f</i> =	= 6 (p <	< 0.00	001), $I^2 = 92\%$	•		<del>-                                    </del>	+
Test for overall effect						,,			1 -2 0 2	4
	<b></b> ,	(		-,				Favours	laparoscopy Favours oper	n

**Figure 15.** Pooled estimates of time to first bowel movement comparing laparoscopy and open surgery *CI – confidence interval, df – degrees of freedom.* 

# Discussion

Our systematic review, based on 13 RCTs and 3,646 patients, revealed that although laparoscopy is associated with longer operative time it has significantly shorter LOS, lower blood loss and faster return of bowel function. In addition, there are no significant differences in intra-operative complications, postoperative overall morbidity and specific complications (postoperative ileus, anastomotic leakage and mortality). The quality of analysed studies was considered high. All of the studies lacked blinding of the staff and patients, which in surgery is impossible to perform.

Since the first laparoscopic rectal resection over 25 years ago, the minimally invasive approach in rectal cancer treatment has established a well-based position in the medical world [27]. Currently nearly 45% (85% in some studies) of rectal resections in developed countries are performed laparoscopically [28]. Even though laparoscopic rectal resections are challenging and their learning curve is longer, most patients and surgeons consider the short-term benefits to be determining factors in the decision regarding choice of approach. Nowadays laparoscopy is the gold standard for the treatment of most benign conditions and has been shown to be safe and feasible or even beneficial in many oncologic indications. In terms of rectal cancer surgery, there are no differences in long-term outcomes between laparoscopic and open surgery when analysing all recently published randomized trials. This systematic review and meta-analyses aims to provide the best available evidence on short-term outcomes.

We identified 16 papers eligible for inclusion in the analysis, covering 3,618 patients (3 studies were based on the same database). Our primary outcome, morbidity rate, did not show any significant difference in all included studies, both in the early and in the latest publications. Studies by Kennedy et al. and Stevenson et al. were excluded from this analysis due to the impossibility of assessing the exact morbidity rate without overestimation. This, along with low heterogeneity within and among the groups, allows us to reach a strong conclusion that the laparoscopic approach is safe. Similar findings were presented by Zhang et al. [5] in their systematic review from 2014. Since that time the ACOSOG Z6051 and ALaCaRT trials and a study by Ng et al. have been published, and their results only strengthened Zhang's conclusions in our updated review. This, however, stands in contrast to the results of a recent systematic review by Chen et al., which was based on studies published in the last 5 years, which shows lower morbidity in the laparoscopy group [29]. The reason for the discrepancies is that in their study they included high quality nonrandomized studies which alter the results, since subgroup analysis in fact revealed no differences in the RCT subgroup. Furthermore, the most recent studies by Stevenson et al. Fleshman et al. or Ng et al. were not included, probably leading to biased results. Apart from surgical site infection, there were no significant differences in terms of specific surgical complications or mortality. A lower rate of surgical site infection is typical for laparoscopic surgery and is mainly associated with smaller wounds.

All studies included in the analysis found operative time longer in the case of laparoscopic surgery. Our study shows on average a 40 min shorter time. We noted high heterogeneity among the studies in regard to this outcome. On one hand laparoscopy is for obvious reasons associated with a shorter time for wound closure, while on the other it is more technically demanding and the learning curve is longer. Most of the studies do not indicate whether surgeons are still on the learning curve or how far beyond it have they have come. In a study by Araujo et al. the operative time for laparoscopy was shorter, which is in contrast to all remaining RCTs [13]. However, this study was performed on a small group, which may underpower its results. It was not included in the meta-analysis due to lack of standard deviation in the results. Furthermore, some studies do not explicate how operative time is calculated – whether it is from the skin incision to closure or from entering to leaving the operating theatre. The differences between some studies are major. For example, the mean operative time for laparoscopy in the study by Zhou et al. is 120 min, whereas in the study by Fleshman et al. it is 266 min.

Time to first bowel movement was shorter for laparoscopy, which should result in faster recovery and thus shorter LOS. This is confirmed in our meta-analysis – LOS was 1.6 days shorter in the laparoscopic approach. Zhang *et al.* in their systematic review obtained similar results [5]. What is interesting is the fact that the most recent RCTs present data in which LOS does not differ [7, 9, 25]. There are several possible explanations for this observa-

tion. Firstly, there is a change in the perioperative care and thanks to the introduction of multimodal clinical pathways to enhance patients' recovery earlier recovery after open surgery has become feasible [30]. Enhanced recovery after surgery was first introduced by Kehlet several years ago. Currently this holistic approach to patient care has evolved and established a firm position in the surgical world. Many studies have shown that introduction of the ERAS protocol improved patients' postoperative outcomes [31-33]. It has also been associated with reduced treatment costs, which is of great importance in the discussion on full acceptance and wider adoption of laparoscopic surgery, which is still very limited in some countries [34, 35]. Even though patients in the open arms had greater surgical trauma, there is a possibility that elements of modern perioperative care allowed for discharge at a comparable time to the laparoscopic group. Unfortunately, none of the analysed studies considered this aspect and the information regarding perioperative care was not included in the methodology. It is difficult to compare length of hospital stay between various countries and hospitals. In general the length of stay is usually too long and it is more associated with local customs rather than meeting objective discharge criteria.

Lower blood loss associated with laparoscopy is in line with what was presented by Zhang *et al.*, as well as studies regarding laparoscopy in different surgical fields [36]. Low blood loss is enforced by laparoscopic technique since even a small amount of blood may obscure the view. Another advantage of lower blood loss is the fact greater blood loss and perioperative blood transfusions are associated with greater risk of postoperative adverse events and worse outcomes [37, 38]. Of course, there is always the chicken-or-egg causality dilemma as to what comes first: increased blood loss due to difficult operative conditions resulting in inferior quality of surgery or the real influence of blood loss. It seems that this question will long remain unanswered.

The quality of data in this review has several limitations. Surgeons' experience and hospital volume in rectal surgery are beyond all doubt the most important factors influencing outcomes, and this aspect must be taken into consideration when analysing data of laparoscopic and open surgery. Most of the analysed studies where performed in high-volume centres. However, in this review surgeons' ex-

perience was not analysed. In our study we focused only on surgical management of rectal cancer. The results may be biased by possible differences caused by neoadjuvant treatment which may alter post-operative complications occurrence, especially anastomotic leakage. Additionally, we did not analyse late complications such as hernias or adhesive bowel obstruction. We also did not consider postoperative functional disorders such as faecal incontinence or quality of life in general.

# **Conclusions**

This systematic review based on available RCTs confirms that laparoscopic rectal cancer surgery is associated with short-term outcomes comparable to the open approach. Moreover, in some aspects it provides better results (e.g. functional postoperative recovery, lower rate of SSIs). The quality of evidence is high; therefore in our opinion it is very unlikely that future trials will alter these results, and for this reason the laparoscopic approach can be considered the gold standard for the treatment of majority of patients.

# Conflict of interest

The authors declare no conflict of interest.

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