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Pathologic Outcomes of Laparoscopic vs Open Mesorectal Excision for Rectal Cancer
A Systematic Review and Meta-analysis

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IMPORTANCE Rectal resection with mesorectal excision is the mainstay treatment for rectal cancer.

OBJECTIVE To review and analyze the evidence concerning the pathologic outcomes of laparoscopic (LRR) vs open (ORR) rectal resection for rectal cancer.

DATA SOURCES The Cochrane Central Register of Controlled Trials, MEDLINE (through PubMed), EMBASE, Scopus databases, and clinicaltrials.gov were searched for randomized clinical trials (RCTs) comparing LRR vs ORR.

STUDY SELECTION Only RCTs published in English from January 1, 1995, to June 30, 2016, that compared LRR with ORR for histologically proven rectal cancer in adult patients and reported pathologic outcomes (eg, positive circumferential resection margin, and complete mesorectal excision) were eligible for inclusion. Of 369 records screened, 14 RCTs were selected for the qualitative and quantitative analyses.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers performed the study selection and quality assessment. Random-effects models were used to summarize the risk ratio (RR) and mean differences.

MAIN OUTCOMES AND MEASURES The rate of positive circumferential resection margin (CRM), defined as 1 mm or less from the closest tumor to the cut edge of the tissue, and the quality of mesorectal excision (complete, nearly complete, or incomplete).

RESULTS The meta-analysis included 14 unique RCTs with 4034 unique patients. Of 2989 patients undergoing rectal resection, a positive CRM was found in 135 (7.9%) of 1697 patients undergoing LRR and 79 (6.1%) of 1292 patients undergoing ORR (RR, 1.17; 95% CI, 0.89-1.53; $P = .26$; $I^2 = 0\%$) in 9 studies. A noncomplete (nearly complete and incomplete) mesorectal excision was reported in 179 (13.2%) of 1354 patients undergoing LRR and 104 (10.4%) of 998 patients undergoing ORR (RR, 1.31; 95% CI, 1.05-1.64; $P = .02$; $I^2 = 0\%$) in 5 studies. The distal resection margin involvement (RR, 1.12; 95% CI, 0.34-3.67; $P = .86$), the mean number of lymph nodes retrieved (mean difference, 0.05; 95% CI, −0.77 to 0.86; $P = .91$), the mean distance to the distal margin (mean difference, 0.01 cm; 95% CI, −0.12 to 0.15 cm; $P = .87$), and the mean distance to radial margins (mean difference, −0.67 mm; 95% CI, −2.16 to 0.83 mm; $P = .38$) were not significantly different between LRR and ORR. The risk for bias was assessed as low in 10 studies, high in 3, and unknown in 1. The overall quality of the evidence emerging from the literature was rated as high.

CONCLUSIONS AND RELEVANCE Based on the available evidence, the risk for achieving a noncomplete mesorectal excision is significantly higher in patients undergoing LRR compared with ORR. These findings question the oncologic safety of laparoscopy for the treatment of rectal cancer. However, long-term results of the ongoing RCTs are awaited to assess whether these pathologic results have an effect on disease-free and overall patient survival.

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Invited Commentary
Supplemental content

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Colorectal cancers are the third most common malignant tumors worldwide.[1-3] In particular, rectal cancers constitute one-third of these tumors and account for nearly 40 000 new cases per year in the United States.[4]

The mainstay treatment for rectal cancer remains surgical resection, for which outcomes have markedly improved during the last 20 years, mostly owing to the introduction of total mesorectal excision (TME). This surgical technique demonstrated reductions in tumor recurrence because the radial spread of cancer cells is resected entirely with the complete removal of the mesorectal tissues. Radiotherapy and chemotherapy also have major roles in the management of locally advanced rectal cancer.[5]

In the era of TME, the accuracy and safety of mesorectal dissection and the achievement of free resection margins are considered the most important pathologic outcomes used to measure the quality of surgery. Indeed, negative circumferential resection margin (CRM) and complete TME are associated with lower local and distal recurrence rates and better long-term survival.[6-10] A recent study of a cohort of 563 patients with locally advanced rectal cancer who were treated with neoadjuvant chemoradiotherapy and surgery found that the 5-year local recurrence-free survival was 66% in patients with a CRM of 1 mm or less and 98% in patients with a CRM of greater than 1 mm.[11] In another recent study evaluating achievement of complete mesorectal excision, the estimated 3-year local recurrence rate was 4% for complete, 7% for nearly complete, and 13% for incomplete mesorectal excision.[6]

Although minimally invasive rectal excision has been regarded as one of the most complex operations in the field of colorectal surgery, laparoscopy is a widespread technique performed by more than 70% of experienced colorectal surgeons worldwide and more than 80% in the United States.[12] Large randomized clinical trials (RCTs) showed that laparoscopic TME is associated with less blood loss, earlier return of bowel movement, and shorter length of hospital stay compared with open surgery.[13-15] These short-term benefits of laparoscopy were confirmed in previous meta-analyses,[16-19] which found no difference in terms of overall survival, disease-free survival, and pathologic outcomes between the laparoscopic and open approaches.[19] Thus, evidence appears to support laparoscopic TME as a valuable, safe, and feasible alternative to open TME, but the 2 most recent RCTs[20,21] (not included in the previously published meta-analyses) found contradictory results and opened the existing conclusions to debate.

In this study, we conducted a new systematic review and meta-analysis of RCTs comparing laparoscopic rectal resection (LRR) vs open rectal resection (ORR) to evaluate the pathologic outcomes of surgery in light of the most recent evidence on the topic. We investigated whether any differences are found in terms of CRM involvement (≤1 mm) and achievement of a complete mesorectal excision between LRR and ORR for rectal cancer.

Key Points

Question What are the pathologic outcomes of laparoscopic rectal resection compared with open rectal resection for rectal cancer?

Finding Based on this systematic review and meta-analysis of 14 randomized clinical trials, the risk of achieving a noncomplete (incomplete or nearly complete) mesorectal excision is significantly higher in patients undergoing laparoscopic compared with open rectal resections.

Meaning These pathologic findings challenge the oncologic safety of laparoscopy for the treatment of rectal cancer.

Methods

Study Design and Inclusion Criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements checklist.[22] The eligibility and selection criteria were defined before initiating the data search to ensure the proper identification of all eligible studies. Only RCTs on rectal cancer that compared LRR and ORR and reported at least 1 of the outcomes of interest were retrieved and analyzed. No trial duration limitation was applied. Prospective nonrandomized studies, retrospective studies, case reports, reviews, commentaries, and conference abstracts were not considered. Moreover, articles reporting the results of surgical teams during their learning curve for LRR were also discarded. The study methods and analyses were reviewed to ensure the respect of the ethical principles for biomedical research.

By applying the PICO (Problem/Population, Intervention, Comparison, and Outcome) framework, we defined study selection criteria. Participants included adult patients with histologically proven rectal cancer requiring surgical resection. Interventions consisted of LRR (including laparoscopic-assisted) and ORR (ie, TME or partial mesorectal excision). Studies were included independently of the surgical technique (eg, abdominoperineal resection or anterior resection) and the performance of a primary anastomosis. In all included studies, LRR was compared with ORR. Primary outcome measures consisted of the rate of positive CRM (defined as ≤1 mm from the closest tumor to the cut edge of the tissue) and the rate of complete mesorectal excision, as classified by Nagtegaal et al[23] (ie, achievement of intact mesorectum with only minor irregularities of a smooth mesorectal surface with no defects deeper than 5 mm and no coning toward the distal margin of the specimen). The secondary outcomes included the distance of the free radial margin (in millimeters), the rate of positive distal margins, the distance to the distal margin (in centimeters), and the total number of lymph nodes retrieved.

Literature Search Strategy

A literature search was performed of the Cochrane Central Register of Controlled Trials, MEDLINE (through PubMed), EMBASE, and Scopus databases. Specific research equations were formulated for each database using the following keywords and/or MeSH terms: *rectal/colorectal cancer/carcinoma*, *treatment*, *therapy*, *management*, *surgery*, *laparoscopy/laparoscopic surgery*, *open surgery/laparotomy*, and *randomized trial/trial*. Moreover, the reference lists of the eligible studies and relevant review articles were cross-checked to identify additional pertinent studies. The clinicaltrials.gov registry was also searched to look for any possible ongoing RCT for

which results might be published in the near future. We retrieved articles published in English from January 1, 1995, to June 30, 2016, that met the selection criteria.

Study Selection and Quality Assessment

The title and abstract of the retrieved studies were independently and blindly screened for relevance according to the CONSORT Statement 2010 for RCTs (http://www.consort-statement.org) by 2 reviewers (A.M.-P. and N.de'A.). To enhance sensitivity, records were removed only if both reviewers excluded the record at the title and abstract screening level. Subsequently, both reviewers performed a full-text analysis of the selected articles. Both reviewers independently assessed the risk for bias using the Cochrane tool for assessing risk for bias, as described in the Cochrane Handbook for Systematic Reviews of Interventions.[24] In addition, the Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to grade the body of evidence emerging from this study.[25] All disagreements between the 2 reviewers in the selection and evaluation processes were resolved by discussion with a third reviewer (F.B.).

Data Extraction and Analysis

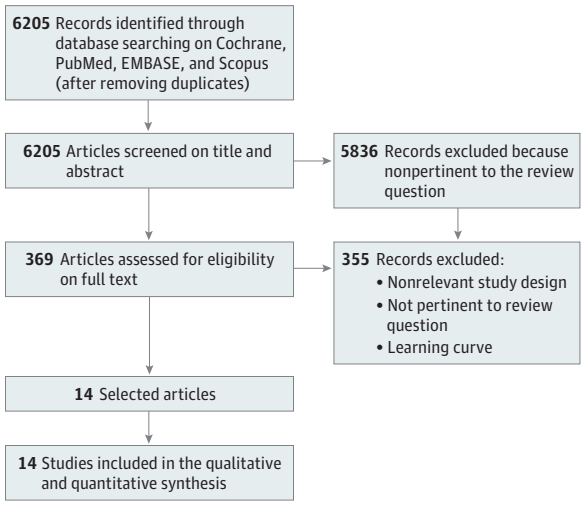
Data from the included studies were processed for the qualitative and quantitative analyses. For binary outcome data, the risk ratio (RR) and 95% CIs were estimated using the Mantel-Haenszel method; a RR of less than 1.00 favored laparoscopy. For continuous data, the mean differences and 95% CIs were estimated using inverse variance weighting. Outcome measures (mean [SD] and median [interquartile range] values) were extracted for each surgical treatment. If necessary and possible, outcome variables were calculated based on the data available in the individual selected studies. If the SE was provided instead of the SD, the SD was calculated based on the sample size (SE = SD/$\sqrt{N}$). The 95% CI was then calculated as SE × 1.96 (upper boundary) and SE × −1.96 (lower boundary). In studies in which the mean or SD was not reported, these values were estimated from the median, range (interquartile range), or *P* value.[26,27] Heterogeneity was assessed by the I^2 statistic,[24,28,29] and values of 25%, 50%, and 75% were considered low, moderate, and high, respectively.[24,29] The pooled estimates of the mean differences were calculated using random-effects models to take into account potential interstudy heterogeneity and to adopt a more conservative approach. Then, the robustness of the results and the potential sources of heterogeneity were explored by performing sensitivity analyses. The pooled effect was considered significant if $P < .05$. The meta-analysis was performed using RevMan software (version 5.3; Cochrane Collaboration).

Results

Literature Search and Selection

Overall, the combined search identified 6205 articles, of which 5836 were rejected based on the title and abstract evaluation. The remaining 369 articles underwent full-text evaluation, and 355 were excluded. No additional study was identified through manual search, cross-check of reference lists, or search of clinicaltrials.gov. Fourteen unique RCTs were found eligible and were evaluated for the qualitative and quantitative analyses. The PRISMA diagram of the literature search and the study selection process is shown in **Figure 1**.

Figure 1. PRISMA Diagram



The flowchart shows the literature search and study selection process according to the PRISMA guidelines.

Study Characteristics

The 14 selected studies were published from May 2003 through October 2015. They included patients who underwent surgery from September 1993 through November 2014. Overall, these studies analyzed a total of 4034 unique patients undergoing LRR or ORR (**Table**). The LRR group included 2265 patients with a mean (SD) age of 63.3 (4.6) years, and 1272 (56.2%) were male; 293 of 2230 patients (13.1%) required conversion from an LRR to ORR. The ORR group included 1769 patients with a mean (SD) age of 62.5 (3.9) years, and 1033 (58.4%) were male.

Primary Outcomes

Nine studies reported the rate of CRM involvement by considering CRM as positive when 1 mm or less.[13-15,20,21,30,33-35] Data from Braga et al[37] were not included in the meta-analysis owing to the lack of a precise definition of CRM involvement. The pooled data from the RCTs found positive CRM in 135 (7.9%) of 1697 patients who underwent LRR and in 79 (6.1%) of 1292 patients who underwent ORR; the RR was 1.17 (95% CI, 0.89-1.53; $P = .26$) with no heterogeneity ($I^2 = 0\%$) (**Figure 2**A).

Five studies[13,14,20,21,30] reported the rate of complete mesorectal excision. A noncomplete mesorectal excision (nearly complete or incomplete) was observed in 179 (13.2%) of 1354 patients who underwent LRR and in 104 (10.4%) of 998 patients who underwent ORR; the RR was 1.31 (95% CI, 1.05-1.64; $P = .02$) with no heterogeneity ($I^2 = 0\%$) (Figure 2B). The sensitivity analysis showed no difference between random- and fixed-effects models. Moreover, confirmatory results were observed when performing a subgroup analysis by including only the 4 major multicentric RCTs.[13,14,20,21]

Table. Summary of the Included Randomized Clinical Trials

Source	No. of Institutions (Country) and Study Period	Criteria		Total No. of Participants (No. Included)	No. of Procedures (No. Included)		Age, Mean (SD), y		No. (%) of Participants				
									Male		Neoadjuvant Therapy		Conversion to ORR
		Inclusion	Exclusion[a]		LRR Group	ORR Group	LRR Group	ORR Group	LRR Group	ORR Group	LRR Group	ORR Group	
Fleshman et al,[20] 2015	35 (United States and Canada) October 2008 to September 2013	Stages II-III rectal cancer ≤12 cm from AV	1-11	481 (462)	242 (240)	239 (222)	57.7 (11.5)	57.2 (12.1)	156 (64.5)	158 (66.1)	242 (100)	239 (100)	27/240 (11.2)
Stevenson et al,[21] 2015	24 (Australia and New Zealand) March 2010 to November 2014	T1-T3 rectal cancer ≤15 cm from AV	1, 2, 4, 7, 10, 12, 13	475 (473)	238 (238)	237 (235)	65 (56-74)[b]	65 (56-73)[b]	160 (67.2)	151 (63.7)	119 (50.0)	116 (48.9)	21/238 (8.8)
Ng et al,[30] 2014	1 (Hong Kong) August 2001 to August 2007	Rectal cancer with low margin 5-12 cm from AV	13, 16, 17, 23, 24, 25	80 (80)	40 (40)	40 (40)	60.2 (11.3)	62.1 (12.6)	24 (60.0)	22 (55.0)	0	0	3/40 (7.5)
van der Pas et al,[13] 2013	30 (Europe, Canada, and South Korea) January 2004 to May 2010	T1-T3 rectal cancer ≤15 cm from AV	1, 2, 9, 10, 13-22	1103 (1044)	739 (699)	364 (345)	66.8 (10.5)	65.8 (10.9)	448 (64.1)	211 (61.2)	RT 59%, CT 32%	RT 58%, CT 34%	114/688 (16.6)
Liang et al,[31] 2011	1 (China) May 2004 to April 2008	Rectal cancer	16, 25, 26, 31, 34, 35	343 (343)	169 (169)	174 (174)	57.3 (14.1)	57.36 (13.1)	104 (61.5)	92 (52.9)	0	0	1/169 (0.6)
Kang et al,[14] 2010	3 (South Korea) April 2006 to August 2009	T1-T3 rectal cancer ≤9 cm from AV	1, 5, 10, 13, 16, 21, 23, 26	340 (340)	170 (170)	170 (170)	57.8 (11.1)	59.1 (9.9)	110 (64.7)	110 (64.7)	170 (100)	170 (100)	2/170 (1.2)
Liu et al,[32] 2010	1 (China) February 2005 to October 2008	Rectal cancer	16, 17, 23	186 (186)	98 (98)	88 (88)	59.3 (9.7)	61.5 (8.9)	56 (57.1)	50 (56.8)	NA	NA	0/98
Ng et al,[33] 2009	1 (Hong Kong) September 1993 to October 2002	Rectal cancer with low margin 12-15 cm from AV	1, 16, 23, 24, 27, 28	153 (153)	76 (76)	77 (77)	66.5 (11.9)	65.7 (12.0)	37 (48.7)	48 (62.3)	0	0	23/76 (30.3)
Luján et al,[34] 2009	1 (Spain) January 2002 to February 2007	Middle or low rectal cancer	1, 13, 18, 29	204 (204)	101 (101)	103 (103)	67.8 (12.9)	66.0 (9.9)	62 (61.4)	64 (62.1)	73 (72.3)	77 (74.8)	8/101 (7.9)
Ng et al,[35] 2008	1 (Hong Kong) September 1994 to February 2005	Low rectal cancer	13, 16, 23, 24, 30	99 (99)	51 (51)	48 (48)	63.7 (11.8)	63.5 (12.6)	31 (60.8)	30 (62.5)	0	0	5/51 (9.8)
Pechlivanides et al,[36] 2007	3 (Greece) NA	Rectal cancer ≤12 cm from AV	NA	73 (73)	34 (34)	39 (34)	72 (31-84)[c]	69 (41-85)[c]	20 (58.8)	23 (59.0)	13 (38.2)	17 (43.6)	1/34 (2.9)
Braga et al,[37] 2007	1 (Italy) NA	Rectal cancer	1, 2, 10, 13, 31	168 (168)	83 (83)	85 (85)	62.8 (12.6)	65.3 (10.3)	55 (66.3)	64 (75.3)	14 (16.9)	12 (14.1)	6/83 (7.2)
Guillou et al,[15] 2005	27 (United Kingdom) July 1996 to July 2002	Colorectal cancer (excluded transverse)	11, 16, 17, 21, 32, 33	381 (200)	253 (193)	128 (97)	NA	NA	NA	NA	0	0	82/242 (33.9)
Araujo et al,[38] 2003	1 (Brazil) September 1997 to September 2000	Low rectal cancer not responding to RCT	1	28 (28)	13 (13)	15 (15)	59.1 (31-75)[d]	56.4 (24-78)[d]	9 (69.2)	10 (66.7)	13 (100)	15 (100)	NA

Abbreviations: AV, anal verge; CRT, chemoradiotherapy; CT, chemotherapy; LRR, laparoscopic rectal resection; NA, not available; ORR, open rectal resection; RCT, radiochemotherapy; RT, radiotherapy.

[a] Exclusion criteria are defined as follows: (1) other tumor than histologically proven adenocarcinoma; (2) younger than 18 years; (3) body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 34; (4) Eastern Cooperative Oncology Group performance score of 3 or more (range, 3-5, with higher scores indicating higher disability); (5) not receiving neoadjuvant CRT or RT; (6) operation not performed within 4 to 12 weeks of the final radiation treatment; (7) history of invasive pelvic malignancy within 5 years; (8) psychiatric or addictive disorders that affected adherence to the protocol; (9) American Society of Anesthesiologists classification IV or V; (10) severe systemic disease; (11) conditions that limit the success of laparoscopic resection; (12) life expectancy of less than 12 weeks; (13) T4 tumors or involved circumferential resection margin pretreatment; (14) T1 tumor treated with local transanal excision; (15) history of other malignant neoplasm except basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri; (16) signs of acute intestinal obstruction; (17) need for synchronous colorectal surgery; (18) familial adenomatous polyposis coli/hereditary nonpolyposis; (19) colorectal cancer; (20) active Crohn disease or ulcerative colitis; (21) pregnancy; (22) T3 rectal cancer within 2 mm from the endopelvic fascia; (23) tumor perforation; (24) tumor larger than 6 cm; (25) neoadjuvant CRT; (26) distant metastasis; (27) distal tumor needing anastomosis within 5 cm of the dentate line; (28) previous abdominal operations near the region of the colorectal operation; (29) emergency surgery; (30) recurrent disease; (31) ongoing infection or plasma neutrophil level of less than 2×10^9/L; (32) associated gastrointestinal tract disease needing surgical intervention; (33) malignant disease in the past 5 years; (34) BMI greater than 30; and (35) previous abdominal surgery.

[b] Reported as mean (interquartile range).

[c] Reported as median (range).

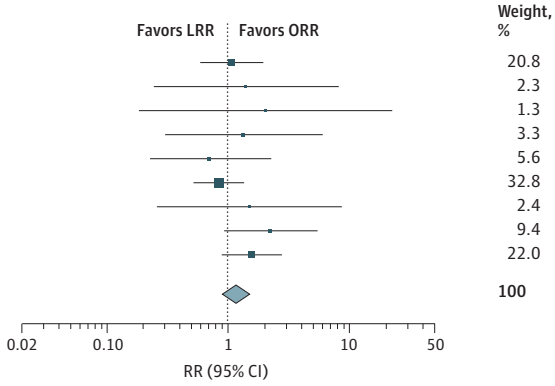
[d] Reported as mean (range).

Figure 2. Forest Plots of the Primary Outcomes

A Circumferential resection margin involvement

Source	LRR No. of Events	LRR Participants	ORR No. of Events	ORR Participants	RR (95% CI)
Guillou et al,[15] 2005	30	193	14	97	1.08 (0.60-1.93)
Ng et al,[35] 2008	3	51	2	48	1.41 (0.25-8.09)
Ng et al,[33] 2009	2	76	1	77	2.03 (0.19-21.88)
Luján et al,[34] 2009	4	101	3	103	1.36 (0.31-5.92)
Kang et al,[14] 2010	5	170	7	170	0.71 (0.23-2.21)
van der Pas et al,[13] 2013	43	588	26	300	0.84 (0.53-1.35)
Ng et al,[30] 2014	3	40	2	40	1.50 (0.26-8.50)
Stevenson et al,[21] 2015	16	238	7	235	2.26 (0.95-5.39)
Fleshman et al,[20] 2015	29	240	17	222	1.58 (0.89-2.79)
Total	**135**	**1697**	**79**	**1292**	**1.17 (0.89-1.53)**

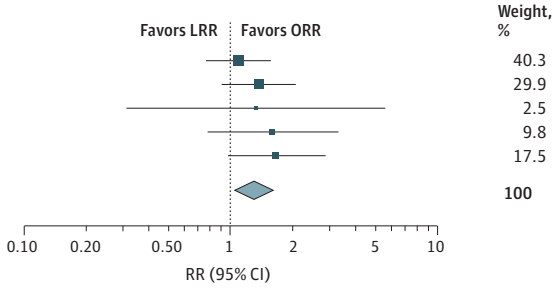
Heterogeneity $\tau^2 = 0.00$, $\chi^2_8 = 6.32$ ($P = .61$), $I^2 = 0\%$
Test for overall effect: $Z = 1.13$ ($P = .26$)



B Noncomplete mesorectal excision

Source	LRR No. of Events	LRR Participants	ORR No. of Events	ORR Participants	RR (95% CI)
Kang et al,[14] 2010	47	170	43	170	1.09 (0.77-1.56)
van der Pas al,[13] 2013	77	666	28	331	1.37 (0.91-2.06)
Ng et al,[30] 2014	4	40	3	40	1.33 (0.32-5.58)
Fleshman et al,[20] 2015	19	240	11	222	1.60 (0.78-3.28)
Stevenson et al,[21] 2015	32	238	19	235	1.66 (0.97-2.85)
Total	**179**	**1354**	**104**	**998**	**1.31 (1.05-1.64)**

Heterogeneity $\tau^2 = 0.00$, $\chi^2_4 = 2.11$ ($P = .71$), $I^2 = 0\%$
Test for overall effect: $Z = 2.36$ ($P = .02$)



Circumferential resection margin involvement was defined as 1 mm or less. Noncomplete mesorectal excision included incomplete or nearly complete resections. Risk ratios (RRs) and 95% CIs were calculated using the random-effects Mantel-Haenszel method. LRR indicates laparoscopic rectal resection; ORR, open rectal resection. Different size markers indicate weight.

Secondary Outcomes

The rate of positive distal margins was reported in 4 studies only.[20,21,34,37] Two of these studies reported no involvement in the LRR and ORR groups.[34,37] Positivity of distal margins was reported in 6 (0.9%) of 662 patients who underwent LRR and in 5 (0.8%) of 645 patients who underwent ORR ($P = .86$) (**Figure 3**A). Similarly, no significant difference was observed between LRR and ORR for the distance to the distal margin,[13,14,20,21] the distance to the radial margin,[13,14,20,21,31,32] or the number of lymph nodes harvested[13,14,20,30-38] (Figure 3B-D). The distal resection margin involvement (RR, 1.12; 95% CI, 0.34-3.67; $P = .86$) was not different between LRR and ORR (Figure 3A). Similarly, the mean difference in the distance to the radial margin was −0.67 mm (95% CI, −2.16 to 0.83 mm; $P = .38$; heterogeneity, $I^2 = 74\%$) (Figure 3B); the mean difference in the distance to the distal margin was 0.01 cm (95% CI, −0.12 to 0.15 cm; $P = .87$; heterogeneity, $I^2 = 36\%$) (Figure 3C); and the mean difference in the number of lymph nodes harvested was 0.05 (95% CI, −0.77 to 0.86; $P = .91$; heterogeneity, $I^2 = 60\%$) (Figure 3D) without significant differences between LRR and ORR.The sensitivity analyses performed confirmed the results of the main analysis.

Study Quality Assessment

The assessment of study quality and the risk for bias is shown in the eFigure in the Supplement. Overall, 10 studies were classified at a low risk,[13-15,20,21,30,33-35,37] 1 at an unknown risk,[31] and 3 at a high risk for bias.[32,36,38] By applying the GRADE system, the quality of the evidence was rated as high for 10 studies[13-15,20,21,30,33-35,37] and as moderate for the remaining 4 studies.[31,32,36,38]

Discussion

The present systematic review and meta-analysis focusing on the pathologic outcomes of laparoscopic resections for rectal cancer demonstrates that the rate of noncomplete mesorectal excision is significantly higher in patients undergoing LRR than for patients undergoing ORR. Moreover, no benefit compared with open surgery has been observed in terms of CRM involvement rates and all other pathologic variables investigated after LRR.

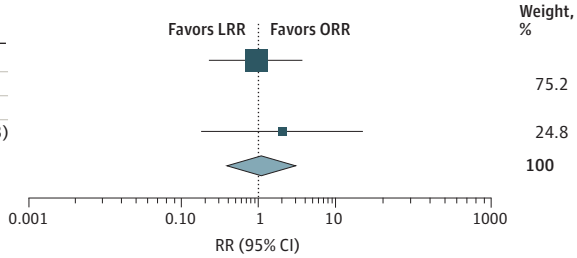
The completeness of the mesorectal resection is a valuable item to assess the oncologic safety of rectal surgery and a predictor of tumor recurrence in the pelvis.[6,10,39] Indeed, the

Figure 3. Forest Plots of Secondary Outcomes

A Distal resection margin involvement

Source	LRR No. of Events	LRR Participants	ORR No. of Events	ORR Participants	RR (95% CI)	Weight, %
Braga et al,[37] 2007	0	83	0	85	Not estimable	
Fleshman et al,[20] 2015	4	240	4	222	0.93 (0.23 to 3.65)	75.2
Luján et al,[34] 2009	0	101	0	103	Not estimable	
Stevenson et al,[21] 2015	2	238	1	235	1.97 (0.18 to 21.63)	24.8
Total	**6**	**662**	**5**	**645**	**1.12 (0.34 to 3.67)**	**100**

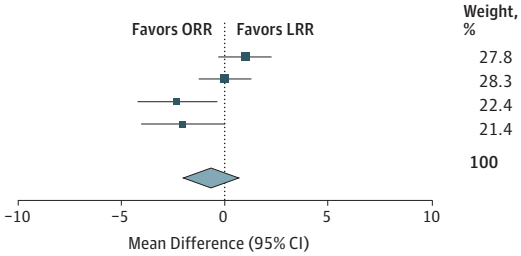
Heterogeneity $\tau^2 = 0.00$, $\chi^2_1 = 0.29$ ($P = .59$), $I^2 = 0\%$
Test for overall effect: $Z = 0.18$ ($P = .86$)



B Distance to radial margin

Source	Distance, mm: LRR Mean	LRR (SD)	LRR Total	ORR Mean	ORR (SD)	ORR Total	Mean Difference (95% CI)	Weight, %
Kang et al,[14] 2010	9	(5.92)	170	8	(5.92)	170	1.00 (−0.26 to 2.26)	27.8
van der Pas et al,[13] 2013	10	(9.62)	588	10	(8.14)	300	0.00 (−1.21 to 1.21)	28.3
Fleshman et al,[20] 2015	10.5	(9.2)	240	12.8	(11.2)	222	−2.30 (−4.18 to −0.42)	22.4
Stevenson et al,[21] 2015	10	(10.37)	211	12	(10.37)	201	−2.00 (−4.00 to 0.00)	21.4
Total			**1209**			**893**	**−0.67 (−2.16 to 0.83)**	**100**

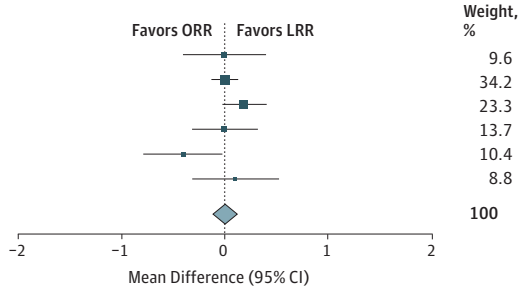
Heterogeneity $\tau^2 = 1.69$, $\chi^2_3 = 11.46$ ($P = .009$), $I^2 = 74\%$
Test for overall effect: $Z = 0.87$ ($P = .38$)



C Distance to distal margin

Source	Distance, cm: LRR Mean	LRR (SD)	LRR Total	ORR Mean	ORR (SD)	ORR Total	Mean Difference (95% CI)	Weight, %
Kang et al,[14] 2010	2	(1.85)	170	2	(1.85)	170	0.00 (−0.39 to 0.39)	9.6
Liu et al,[32] 2010	3	(0.375)	98	2	(0.5)	88	0.00 (−0.13 to 0.13)	34.2
Liang et al,[31] 2011	3.22	(0.738)	86	3.03	(0.684)	104	0.19 (−0.01 to 0.39)	23.3
van der Pas et al,[13] 2013	3	(2.07)	618	3	(2.37)	310	0.00 (−0.31 to 0.31)	13.7
Stevenson et al,[21] 2015	2.6	(2.22)	240	3	(1.77)	201	−0.40 (−0.77 to −0.03)	10.4
Fleshman et al,[20] 2015	3.2	(2.6)	240	3.1	(1.9)	222	0.10 (−0.31 to 0.51)	8.8
Total			**1452**			**1095**	**0.01 (−0.12 to 0.15)**	**100**

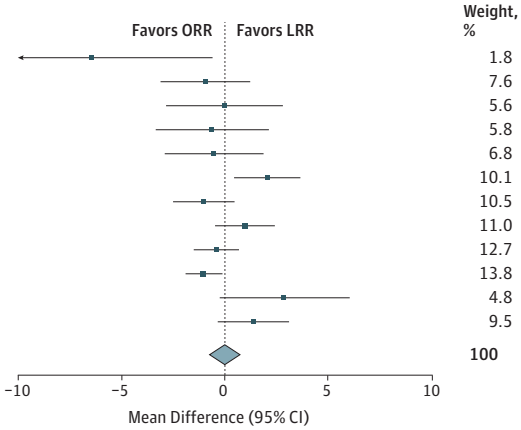
Heterogeneity $\tau^2 = 0.01$, $\chi^2_5 = 7.82$ ($P = .17$), $I^2 = 36\%$
Test for overall effect: $Z = 0.16$ ($P = .87$)



D Lymph nodes harvested

Source	No. of Lymph Nodes: LRR Mean	LRR (SD)	LRR Total	ORR Mean	ORR (SD)	ORR Total	Mean Difference (95% CI)	Weight, %
Araujo et al,[38] 2003	5.5	(7.81)	13	11.9	(7.81)	15	−6.40 (−12.20 to −0.60)	1.8
Braga et al,[37] 2007	12.7	(7.3)	83	13.6	(6.9)	85	−0.90 (−3.05 to 1.25)	7.6
Pechlivanides et al,[36] 2007	19.2	(5.5)	34	19.2	(6.66)	39	0.00 (−2.79 to 2.79)	5.6
Ng et al,[35] 2008	12.4	(6.7)	51	13	(7)	48	−0.60 (−3.30 to 2.10)	5.8
Ng et al,[33] 2009	11.5	(7.9)	76	12	(7)	77	−0.50 (−2.87 to 1.87)	6.8
Luján et al,[34] 2009	13.63	(6.26)	101	11.57	(5.1)	103	2.06 (0.49 to 3.63)	10.1
Kang et al,[14] 2010	17	(7.29)	170	18	(6.66)	170	−1.00 (−2.48 to 0.48)	10.5
Liu et al,[32] 2010	16	(5)	98	15	(4.9)	98	1.00 (−0.39 to 2.39)	11.0
Liang et al,[31] 2011	7.05	(5.05)	169	7.44	(4.89)	174	−0.39 (−1.44 to 0.66)	12.7
van der Pas et al,[13] 2013	13	(5.92)	683	14	(6.66)	341	−1.00 (−1.83 to −0.17)	13.8
Ng et al,[30] 2014	17.7	(8.4)	40	14.8	(5.6)	40	2.90 (−0.23 to 6.03)	4.8
Fleshman et al,[20] 2015	17.9	(10.1)	240	16.5	(8.4)	222	1.40 (−0.29 to 3.09)	9.5
Total			**1758**			**1412**	**0.05 (−0.77 to 0.86)**	**100**

Heterogeneity $\tau^2 = 1.07$, $\chi^2_{11} = 27.72$ ($P = .004$), $I^2 = 60\%$
Test for overall effect: $Z = 0.11$ ($P = .91$)



Risk ratios (RRs) and 95% CIs were calculated using the random-effects Mantel-Haenszel method. Mean difference data and 95% CIs were calculated using random-effects inverse variance weighting. LRR indicates laparoscopic rectal resection; ORR, open rectal resection. Different size markers indicate weight.

violation of the peritonealized posterior surface of the mesorectum was an important risk factor for local recurrence in patients with negative CRM. As can be observed in this meta-analysis, pooled data from the included RCTs showed a significantly higher rate of complete mesorectal excision in ORR (894 of 998 [89.6%]) compared with LRR (1175 of 1354 [86.8%]). These findings are based on 5 studies,[13,14,20,21,30] among which the 4 most recent and largest multicentric RCTs specifically

focused on the surgical and pathologic outcomes of LRR (ie, the COLOR II [Colorectal Cancer Laparoscopic or Open Resection II],[13] COREAN [Comparison of Open vs Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemoradiotherapy],[14] ALACART [Australasian Laparoscopic Cancer of the Rectum],[21] and ACOSOG Z6051 [Laparoscopic-Assisted Resection or Open Resection in Treating Patients With Rectal Cancer][20] studies). Conversely, the rate of positive CRM (defined as ≤1 mm) was found to be similar between LRR and ORR based on 9 RCTs.[13-15,20,21,30,33-35] Among these studies, only the COLOR II and COREAN trials show a slight, although statistically nonsignificant, benefit in terms of CRM involvement for the laparoscopic approach. However, the COLOR II trial,[13] which reported rates of CRM involvement of 7.3% in the LRR group and 8.7% in the ORR group, had a remarkably high proportion of missing CRM data (12% in the laparoscopic group and 8% in the open group). The COREAN study[14] showed a lower rate of positive CRM in patients undergoing LRR (2.9%) compared with ORR (4.1%), but this trial included only patients who received preoperative chemoradiotherapy; a careful reading of the article discloses that major pathologic responses (grades 3 and 4)[40] and the rate of T0 to T1 findings in the final pathologic report were higher in the LRR group than in the ORR group (43.7% vs 27.0% and 31.7% vs 18.2%, respectively). Thus, the LRR group included more patients with better responses to neoadjuvant therapies and less viable tumors, which can drastically affect CRM involvement.[41]

Achieving negative CRM is challenging in clinical practice, with a rate of CRM positivity reaching 15% of TME despite optimal cylindrical or extralevator resections[42,43]; achieving this might be even harder with laparoscopy. However, the cutoff value for defining positive CRM is still under debate, with the threshold of 1 mm or less as the most frequently used in the literature. Nevertheless, some investigators proposed 2 mm or less rather than 1 mm or less to define a positive CRM—a potential source of confusion and heterogeneity in the literature.[44,45]

The 2 most recent multicenter RCTs that specifically focused on the pathologic outcomes of surgery[20,21] used a composite variable, including complete mesorectal excision[23] and negative radial and distal margins (both >1 mm) to assess the oncologic efficacy of LRR and ORR. The proposed composite outcome represents a stricter and more precise variable to assess the pathologic adequacy of the surgical resection compared with the CRM or TME quality taken separately, although the validity and usefulness of the composite outcome as a prognostic factor must be confirmed with the long-term results. The ACOSOG Z6501 and ALACART trials had a noninferiority design for the LRR vs ORR approaches and reached the same conclusion. Compared with open surgery, the noninferiority of laparoscopic surgery for successful resection was not established; thus, the authors did not support the routine use of laparoscopy in patients with rectal cancer.[20,21] The present meta-analysis is in accordance with these recent findings and in contrast with previous ones.[17-19] Indeed, a meta-analysis based on 8 RCTs and 19 prospective and retrospective studies published in 2015[19] showed no differences in terms of oncologic safety between the LRR and ORR approaches, but as previously mentioned, the 3 most recent RCTs published[20,21,30] were not included. What remains to be assessed are the outcomes of surgery according to the tumor location (eg, low, middle, and high rectal cancer), tumor stage, and type of surgical procedure (eg, low anterior resection, abdominoperineal resection). Based on the available literature, we could not ascertain reliable data about the effect of these factors on the pathologic outcomes of the surgical approach. However, reading future studies focused on particular subsets of tumor or surgical settings would be of interest to explore all applications of laparoscopy in the broad spectrum of rectal cancers.

In the past, the improvement of pelvic visualization provided by laparoscopy was expected to result in better pathologic outcomes. However, as can be observed in the present meta-analysis, the rate of complete mesorectal excision for LRR was lower than that for ORR. A possible explanation would be that conventional laparoscopic instruments can be highly challenging to use and jeopardize the achievement of the best plane of dissection for complete mesorectal removal, especially in the narrow or irradiated pelvis. From this perspective, mesorectal excision might be one of the interventions in which robotic methods could have an important role in contemporary digestive surgery.[46-49] The remote control, along with the placement of wristed instruments in line with pelvic walls, allows the surgeon to perform the rectal resection much more ergonomically. A recent systematic review including 1776 patients who underwent robotic surgery for rectal cancer[50] showed a rate of CRM positivity ranging from 0% to 7.5%. However, evidence is lacking; only a small-sized RCT has been published comparing the outcomes of robotic vs laparoscopic surgery, and that RCT shows a significantly shorter length of hospital stay in the robotic group.[51] The results of the ROLARR (Robotic vs Laparoscopic Resection for Rectal Cancer) trial,[52] awaited in the near future, will probably help to elucidate the role of robotic surgery for rectal cancer treatment.

Alternatively, rectal cancer can be approached by transanal TME.[53] The COLOR III study[54] was designed to compare transanal TME and laparoscopic TME for middle and low rectal cancers. This trial is just at the recruitment phase, although the investigators expect that transanal TME would be superior to laparoscopic TME in terms of oncologic outcomes.[54]

Limitations

The present meta-analysis relies solely on RCTs; this type of study is considered to provide the best level of evidence. However, potential bias cannot be completely ruled out. For instance, the protocols of neoadjuvant chemoradiotherapy were not standardized among all of the included studies; various surgical procedures (eg, anterior resections, abdominoperineal amputations, hand-assisted minimally invasive surgery) were performed in different proportions in the included RCTs; missing data about positive distal margins and missing definitions of resection margin involvement were observed.[20,21] Despite these limitations, the robustness and consistency of the results were supported by the sensitivity analyses and the low heterogeneity observed. More-

over, the overall level of evidence emerging from the literature was judged as high.

Conclusions

Based on the available data pooled from the most recent RCTs, the complete mesorectal excision rate is significantly higher in patients undergoing ORR than LRR for rectal cancer. No differences between the 2 surgical approaches were observed for CRM involvement and the other pathologic outcomes. These findings dampen enthusiasm in support of laparoscopy as an oncologically safe approach for the treatment of rectal cancer. However, the long-term results of the ongoing RCTs are awaited to provide a definitive response to the question of whether these results have an influence on disease-free and overall patient survival.

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Study concept and design: All authors.
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