Laparoscopy for rectal cancer is oncologically adequate: a systematic review and meta-analysis of the literature

Review

Laparoscopy for rectal cancer is oncologically adequate: a systematic review and meta-analysis of the literature

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Abstract
Background
This review of cancer outcomes is based on key literature searches of the medical databases and meta-analysis of short-term benefits of laparoscopy in rectal cancer treatment.
Methods
We carried out a systematic review of randomized clinical trials (RCTs) and prospective non-randomized controlled trials (non-RCTs) published between January 2000 and September 2013 listed in the MEDLINE and EMBASE databases (PROSPERO Registration number: CRD42013005076). The primary endpoint was clearance of the circumferential resection margin. Meta-analysis was performed using a fixed-effect model, and sensitivity analysis by a random-effect model; subgroup analysis was performed on subsets of patients with extraperitoneal cancer of the rectum. Relative risk (RR) and mean difference (MD) were used as outcome measures.
Results
Twenty-seven studies (10,861 patients) met the inclusion criteria; eight were RCTs (2,659 patients). The RCTs reported involvement of the circumferential margin in 7.9 % of patients who underwent laparoscopic and in 6.9 % of those undergoing open surgery; the overall RR was 1.00 (95 % confidence interval 0.73–1.35) with no heterogeneity. Subgroup analysis of patients with extraperitoneal cancer showed equivalent involvement of the circumferential margin in the two treatment groups. Although significantly more lymph nodes were retrieved in the surgical specimen after open surgery, the MD of −0.56 was of marginal clinical significance. The sensitivity and subgroup analyses revealed no other significant differences between laparoscopic and open surgery in the rate of R0 resections, distal margin clearance, mesorectal fascia integrity, or local recurrence at 5 years.
Conclusions
Based on the evidence from RCTs and non-RCTs, the short-term benefit and oncological adequacy of laparoscopic rectal resection appear to be equivalent to open surgery, with some evidence potentially pointing to comparable long-term outcomes and oncological adequacy in selected patients with primary resectable rectal cancer.
Keywords
Rectal cancer Rectal neoplasms Laparoscopy Meta-analysis Systematic review

The prognosis of rectal cancer patients has dramatically changed with the introduction of total mesorectal excision (TME), which has significantly reduced local recurrence of rectal cancer [*1*] and improved long-term survival [*2*]. In a recent systematic review and meta-analysis, we reported lower mortality and morbidity after laparoscopic as compared to open surgery for rectal cancer [*3*], also on subgroup analysis of extraperitoneal cancers [*4*]. Although laparoscopic resection of colon

cancer has gained wider acceptance [*5–8*], its role in the treatment of rectal cancer remains controversial. Several reports published during the last decade have demonstrated the feasibility of laparoscopic TME in expert centers, but consistent data on short- and long-term oncological outcomes are still lacking.

Open rectal resection combined with TME is the mainstay of treatment for rectal cancer. Recent randomized controlled trials (RCTs) have investigated the oncological adequacy of laparoscopic rectal resection and TME as compared to open surgery in terms of local recurrence and long-term survival rates. Insofar as laparoscopic resection may provide equivalent oncological outcomes to open rectal resection for rectal cancer, it might be argued that laparoscopy, because of its minimal invasiveness, could be the preferred approach in selected cases.

This systematic review and meta-analysis were designed to compare the oncological outcomes of patients treated with laparoscopy or open surgery for rectal cancer and to determine whether laparoscopy offers improved short-term outcomes or at least equivalent long-term outcomes as compared with open resection.

Materials and methods

The methods for the analysis and generation of inclusion criteria were based on the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement [*9*]. On the basis of population, interventions, comparators, outcome measures, and setting (PICOS) criteria, patients were included if affected with rectal cancer for which laparoscopic or open resection was indicated. The study methods were documented in a protocol registered and accessible at http://www.crd.york.ac.uk/prospero/ (Registration number: CRD42013005076).

Types of studies

As recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [*10*], only randomized controlled trials (RCTs) or prospective controlled clinical trials (non-RCTs) were considered. Studies were excluded if the study population included colon cancers, unless the data were presented separately. When multiple studies from the same institution were identified, the most recent or the most informative was selected. Only full-text papers in English were considered.

Types of intervention

All surgical procedures involving resection of the rectum were considered, including rectal anterior resection (RAR), Hartmann's resection (HR), and abdominoperineal resection (APR). The types of intervention were noted in order to separately analyze those in which bowel anastomosis was performed. Rectal resections were grouped as either laparoscopic procedures via a mini-invasive approach (i.e., in a space generated by an insufflated pneumoperitoneum with operative field visualization by video laparoscopy and performed using only laparoscopic trocars) or open or conventional surgery via an abdominal midline incision.

Types of outcome measures

The primary endpoint was clearance of the circumferential resection margin (defined as positive when <1 mm in the binary outcome analysis). The secondary endpoints were short-term and long-term oncological outcomes: number of lymph nodes harvested; distal margin clearance (defined as

the distance between the distal margin of bowel resection and the tumor); distal margin (defined as positive when <1 mm in the binary outcome analysis); circumferential margin clearance (defined as the distance between the circumferential margin of bowel resection and the tumor); R0 resection rate (defined as the rate of lesions excised with margins free of disease); mesorectal fascia integrity as assessed by the pathologist; and local recurrence rate at 5 years.

Search strategy and data collection

We searched the MEDLINE and EMBASE databases for articles published between January 2000 and September 2013. The search terms included the following and words derived from the following: (rect* OR colorect*) AND (neoplas* OR adenocarcinoma OR carcinoma OR cancer) AND [laparoscop* OR (minima* AND invasive AND surgery) OR therapy] AND (anterior OR abdominoperineal AND resection OR proctectomy) OR (total AND mesorectal AND excision) AND (2000–2013)/py AND (humans)/lim. The literature search was closed on October 1, 2013.
All retrieved abstracts were screened by two authors (AA and AS) independently; when an abstract was deemed relevant by at least one of them, the full-text version was retrieved. The reference lists were manually searched for potentially relevant studies for inclusion.
Data extraction was carried out in duplicate independently by two authors (AA and AS). Disagreements were resolved by discussion with a third author (SA). The following data were collected when available: study features, patient characteristics [gender, age, body mass index (BMI)], American Society of Anesthesiologists (ASA) class, cancer localization and stage, neoadjuvant therapy, type of procedure, data for study quality assessment, and the outcome measures.

Assessment of risk of bias

All studies meeting the selection criteria were assessed for methodological quality according to the Cochrane Collaboration guidelines [*11*] for RCTs and to the Newcastle-Ottawa Scale for non-RCTs [*12*]. Assessment was performed by three reviewers (AA, AS, and SA); disagreements were resolved by discussion. In order to assess comparability of treatment groups at baseline, a single-proportion meta-analysis was performed for tumor stage, neoadjuvant therapy, and loop ileostomy [*13*].

Statistical analysis

All analyses were carried out according to original treatment allocation (intention-to-treat analysis). For binary outcome data, the relative risk (RR) and 95 % confidence intervals (CI) were estimated using the Mantel–Haenszel method; a RR <1 was in favor of laparoscopy. For continuous outcome data, the mean differences and 95 % CIs were estimated using inverse variance weighting; a negative MD was in favor of laparoscopy. When means and/or standard deviations (SDs) were not reported in the original paper, they were estimated from the reported medians, ranges, and sample size, as described by Hozo [*14*]. The exact RR or MD for each analysis, both overall and by RCT and non-RCT, are reported as Forest plots, together with the relative CI for statistical significance.
A fixed-effects model was used in all meta-analyses; the same analyses were repeated using a random-effects model [*15*]. Publication bias was assessed by generating a funnel plot and performing a linear regression test for funnel plot asymmetry. Heterogeneity was assessed by the I^2 measure of inconsistency, which was statistically significant if $I^2 > 50$ %. A fixed-effects model was primarily used; a random-effects model was used for the sensitivity analysis.

Potential sources of heterogeneity were explored using sensitivity analyses: comparison of fixed- versus random-effects models (thus incorporating heterogeneity using the latter method); subgroup analyses (to compare RCTs vs. non-RCTs and evaluate the subsets of patients with extraperitoneal cancer of the rectum separately); analysis of cumulative (sequentially including studies by date of publication); and influence meta-analyses (calculating pooled estimates by omitting one study at a time). R meta package, version R 3.0.2, was used for all analyses [*15*].

Results

Study selection

The database search retrieved 6,124 studies. Figure 1 illustrates the PRISMA flowchart for study inclusion and exclusion criteria.

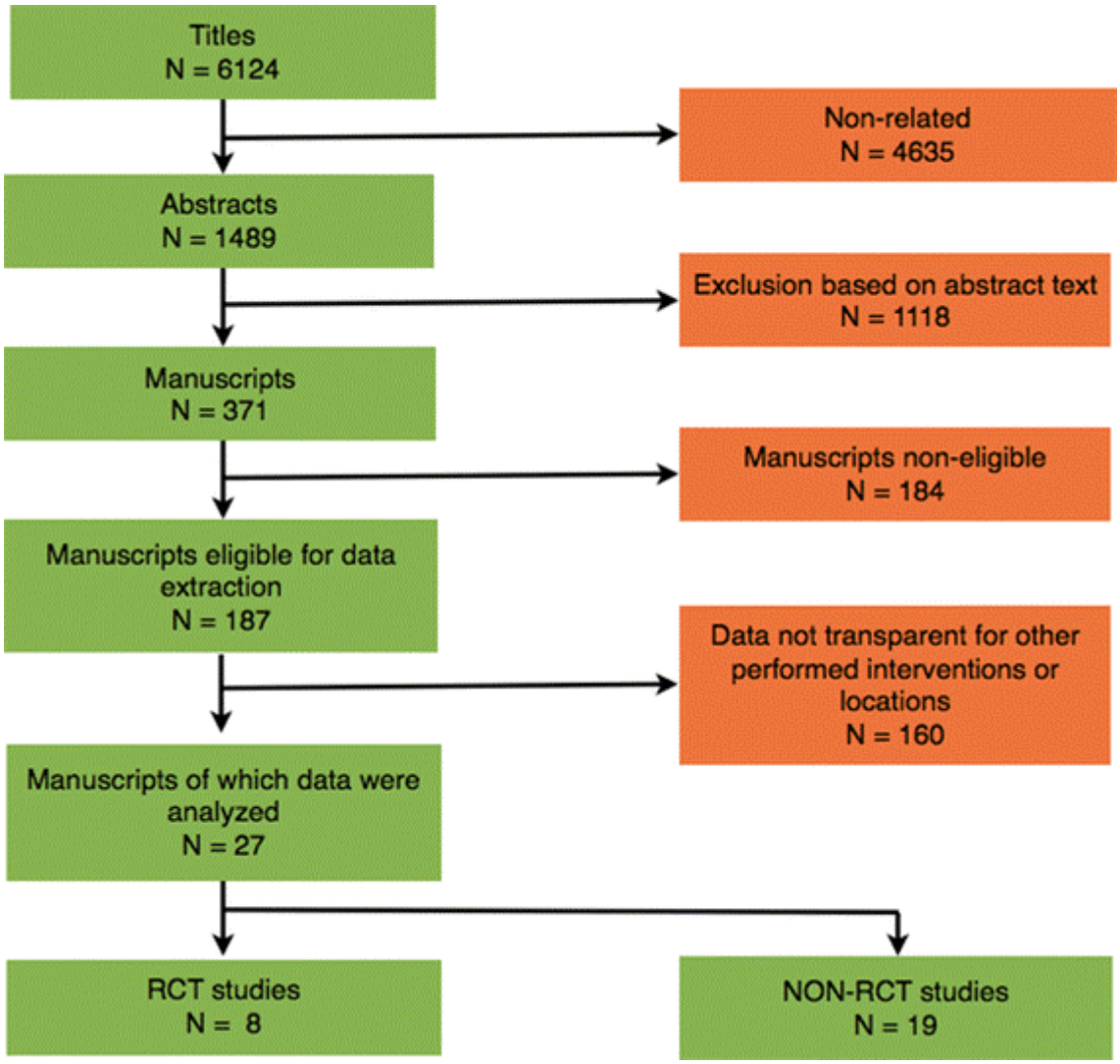

Fig. 1
Flowchart diagram illustrating paper selection process

Characteristics of studies

The characteristics of the 27 studies meeting the inclusion criteria are summarized in Table 1 [*6*, *16–41*]. All studies were reported as full papers and included a total of 10,861 patients: Eight studies were RCTs (2,659 patients), and 19 were non-RCTs (8,202 patients). Because the study by Guillou et al. [*6*] included patients with colorectal carcinoma, only the data referring to rectal cases were collected.

Table 1

Summary of the studies included in the systematic review and meta-analysis

Author and publication year	Country and study period	Inclusion criteria	Exclusion criteria	Eligible patients	LAP surgery patients	Open surgery patients	Gender (M/F)		Age (mean ± SD)		BMI (mean ± SD)		Conversion rate (%)
							Lap	Open	Lap	Open	Lap	Open	
non-RCT													
Leung [*26*]	Hong-Kong Jan 1993–Jan 1996	Low rectal cancer	2, 11	59	25	34	15/10	21/13	62.2 ± 13.3	63.5 ± 15.2	N/A	N/A	8.0
Anthuber [*27*]	Germany Jan 1996–March 2002	Primary rectal cancer	2, 4, 7, 9, 12	435	101	334	59/42	236/98	61.6 ± 11.1	61.7 ± 11.0	26.9 ± 3.6	26.2 ± 4.2	10.9
Wu [*16*]	China Apr 2002–May 2003	N/A	2, 9, 19	36	18	18	9/9	10/8	52.4 ± 7.9	54.1 ± 6.8	N/A	N/A	0
Breukink [*17*]	Netherlands LAP: Oct 2000–March 2003; OPEN: Apr 1996–Nov 2001	Primary rectal cancer after preoperative radiotherapy	9, 19	82	41	41	25/16	23/18	68*	70*	25*	25*	9.8
Morino [*18*]	Italy Apr 1994–Apr 2002	Rectal cancer ≤12 cm from AV	2, 9, 12, 19	191	98	93	59/39	57/36	64.9	61.4	N/A	N/A	18.4
Bretagnol [*38*]	France Sept 2000–Sept 2003	Rectal cancer ≤12 cm from AV	6, 9, 16	288	144	144	88/56	88/56	63	63	24	N/A	14
Law [*28*]	Hong-Kong June 2000–Dec 2004	Rectal cancer 8–20 cm from AV	2, 15	265	98	167	68/30	112/55	69*	70*	N/A	N/A	12.2
Lelong [*29*]	France LAP: Jan 2002–Oct 2004; OPEN: Jan 1998–Dec 2000	Primary rectal cancer ≤15 cm from AV	2, 9, 14, 16	172	104	68	N/A	N/A	N/A	N/A	N/A	N/A	14.4
Veenhof [*19*]	Netherlands LAP: Apr 2002–Nov 2005; OPEN: Febr 1999–Apr 2002	Rectal cancer ≤17 cm from AV	20	100	50	50	28/22	32/18	67*	64.5*	25*	26*	8.0
Strohlein [*31*]	Germany 1998–2005	Rectal cancer ≤16 cm from AV	N/A	389	114	275	72/42	163/112	65.0 ± 9.9	65.5 ± 11.3	N/A	N/A	21.9
Koulas [*24*]	Greece Oct 1998–Dec 2006	Rectal cancer ≤17 cm from AV	1, 4, 9, 11, 14, 15, 16, 18, 20	117	57	60	33/24	35/25	63.8 ± 12.7	68.9 ± 12.6	23.0	25.0	7.0
Laurent [*22*]	France LAP: 2000–2006	Rectal cancer ≤15 cm from AV	4, 6, 9, 12, 15, 16	471	238	233	140/98	156/77	66.0	67.3	24.0	25.0	15.1

Author and publication year	Country and study period	Inclusion criteria	Exclusion criteria	Eligible patients	LAP surgery patients	Open surgery patients	Gender (M/F)		Age (mean ± SD)		BMI (mean ± SD)		Conversion rate (%)
							Lap	Open	Lap	Open	Lap	Open	
	OPEN: 1994–1996												
Khaikin [*20*]	USA Nov 2004–July 2006	Rectal cancer ≤15 cm from AV	6, 7, 9, 16	82	32	50	13/19	30/20	56.3	63.7	25.3	29.1	12.5
Baik [*33*]	USA Sept 2001–Sept 2005	Rectal cancer ≤12 cm from AV	4, 5, 6, 9, 14	162	54	108	37/17	62/46	60.0 ± 12.7	60.6 ± 13.6	27.3 ± 4.2	28.9 ± 5.2	11.1
Jefferies [*41*]	UK Feb 2007–June 2010	Low rectal cancer	1, 6, 9	41	16	25	10/6	24/1	67	71	N/A	N/A	12.5
Seshadri [*40*]	India Jan 2004–Jan 2010	Middle and low rectal cancer	1, 2, 9, 11, 15, 20	144	72	72	47/25	45/27	48*	48*	21*	22*	4.2
McKay [*34*]	Australia Jan 2001–Dec 2008	Rectal cancer	2, 3, 6, 9	545	157	388	108/49	271/117	67.3 ± 12.5	65.7 ± 12.2	26.9 ± 6.4	26.9 ± 5.3	8.3
Kellokumpu [*35*]	Finland 1999–2006	Carcinomas growing within the mesorectum	6, 9, 16, 18	191	100	91	65/35	65/26	66.5 ± 11.8	68.0 ± 10.2	25.4 ± 3.1	25.9 ± 4.6	22
Lujan [*36*]	Spain 2006–July 2003	Rectal cancer ≤15 cm from AV	2, 12	4405	1387	3018	903/484	2022/996	66.4 ± 13.2	67.5 ± 13.4	N/A	N/A	17.4
RCT													
Guillou [*6*]	UK July 1996–July 2002	Cancer of the colon and rectum	2, 3, 4, 5, 6	381	253	128	N/A	N/A	N/A	N/A	N/A	N/A	32.4
Braga [*30*]	Italy Not reported	Rectal cancer	2, 9, 13, 14, 17	168	83	85	55/28	64/21	62.8 ± 12.6	65.3 ± 10.3	N/A	N/A	7.2
Ng [*32*]	Hong-Kong July 1994 – Febr 2005	Rectal cancer ≤5 cm from AV	2, 7, 9, 10, 11	99	51	48	31/20	30/18	63.7 ± 11.8	63.5 ± 12.6	N/A	N/A	9.8
Lujan [*23*]	Spain Jan 2002–Feb 2007	Mid and low rectal cancer	2, 9, 15	204	101	103	62/39	64/39	67.8 ± 12.9	66.0 ± 9.9	N/A	N/A	7.9
Kang [*25*]	South Korea Apr 2006–Aug 2009	Rectal cancer ≤9 cm from AV	2, 4, 5, 9, 14, 16	340	170	170	110/60	110/60	57.8 ± 11.1	59.1 ± 9.9	24.1 ± 3.2	24.1 ± 3.2	1.2
Liang [*21*]	China May 2004–Apr 2008	Rectal cancer	2, 11, 16, 17, 18, 19, 20	343	169	174	104/65	92/82	57.3*	57.4*	21.5*	22.3*	0.6
Van der Pas [*37*]	Europe Jan 2004–May 2010	Rectal cancer ≤15 cm from AV	2, 9, 16	1044	699	345	448/251	211/134	66.8 ± 10.5	65.8 ± 10.9	26.1 ± 4.5	26.5 ± 4.7	17
Ng [*39*]	Hong-Kong Aug 2001–Aug 2007	Rectal cancer ≥5 ≤12 cm from AV	2, 4, 7, 9, 11, 19	80	40	40	24/16	22/18	60.2 ± 11.3	62.1 ± 12.6	23.1 ± 3.4	22.4 ± 3.2	7.5

AV anal verge, LAP laparoscopic, OPEN laparotomic, N/A not available

1 = neoplasm other than adenocarcinoma (e.g., lymphoma); 2 = emergency situations (e.g., acute obstruction, hemorrhage, perforation); 3 = contraindications to pneumoperitoneum; 4 = malignant diseases in the past 5 years or synchronous adenocarcinoma; 5 = pregnancy; 6 = associated gastrointestinal diseases needing surgical intervention; 7 = recurrent disease; 8 = lowest margin of tumor within 1.5 cm above the dentate line; 9 = Dukes stage D or T4 TNM stage; 10 = tumor larger than 6 cm; 11 = patients unwilling to take part in the study; 12 = local surgery candidates; 13 = age <18 or >80 years; 14 = respiratory dysfunction, cardiovascular dysfunction, hepatic dysfunction, ASA IV; 15 = familial adenomatous polyposis; 16 = presence of metastases;

17 = ongoing infections, low plasma neutrophil levels; 18 = BMI >30 kg/m^2; 19 = previous colon or rectal surgery and/or previous neoadjuvant chemotherapy; 20 = previous abdominal surgery
* Median value

Table 2 presents the baseline characteristics of patients undergoing laparoscopic or open rectal resection. Tumor location and stage, use of neoadjuvant therapy, and percentage of diverting ileostomy are reported in Table 3.

Table 2
Comparison of baseline patients characteristics

	Number of patients		**Gender (M/F)***		**Mean age, years**		**Mean BMI Kg/m^2**	
	LAP	**Open**	**LAP**	**Open**	**LAP**	**Open**	**LAP**	**Open**
Non-RCT	2933	5269	1779/1023	3452/1749	62,4	66,1	25,4	26.1
RCT	1566	1093	834/479	593/372	60,4	63,2	22,3	22.9
Overall	4499	6362	2613/1502	4045/2121	61,9	65,5	24,2	24,8

* Number of males and females are not equal to total number since the gender data were not available in two studies (Guillou [*6*] and Lelong [*29*])

Table 3
Comparison of tumor location, cancer stage, neoadjuvant therapy, and protective ileostomy

	Number of patients		**Mean distance from the anal verge, cm**		**Tumor stage, T0–T2, %***		**Tumor stage, T3–T4, %***		**Neoadjuvant therapy, %****		**Protective ileostomy, %*****	
	LAP	**Open**	**LAP**	**Open**	**LAP**	**Open**	**LAP**	**Open**	**LAP**	**Open**	**LAP**	**Open**
Non-RCT	2,933	5,269	5.15	5.57	52.2	47.5	47.8	52.5	60.2	59.8	52.2	47.5
RCT	1,566	1,093	5.11	5.24	53.7	48.1	46.3	51.9	36.4	34.0	53.7	48.1

Test for subgroup differences, random-effects single-proportion meta-analysis: * P = 0.806, ** P = 0.170, *** P = 0.962

Risk of bias of included studies

Assessment of quality according to the Cochrane Collaboration tool for assessing risk of bias for RCTs and to the Newcastle-Ottawa Scale for prospective non-RCTs is presented in Tables 4 and 5, respectively.

Table 4
Quality assessment of the included randomized controlled studies based on the cochrane collaboration's tool for assessing risk of bias

Author and publication year	**Random sequence generation**	**Allocation concealment**	**Blinding of participants, personnel and outcome**	**Incomplete outcome data**	**Selective outcome reporting**	**Other source of bias**
Guillou [*6*]	Unclear	Yes**	Unclear	Unclear	Unclear	Yes
Braga [*30*]	Yes*	Yes**	Unclear	Yes	Yes	Yes
Ng [*32*]	Yes *	Yes**	Unclear	Yes	Yes	Yes
Lujan [*23*]	Yes*	Yes**	Unclear	Yes	Yes	Yes
Kang [*25*]	Yes*	Yes**	Yes***	Yes	Yes	Yes

Author and publication year	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome	Incomplete outcome data	Selective outcome reporting	Other source of bias
Liang [*21*]	Unclear	Yes**	Yes***	Yes	Yes	Yes
Van der Pas [*37*]	Yes*	Yes**	No	Yes	Yes	Yes
Ng [*39*]	Yes*	Yes**	No	No	Yes	Yes

In all cases, "Yes" indicates a low risk of bias, "No" indicates high risk of bias, and "Unclear" indicates unclear or unknown risk of bias

* In Braga [*30*], Ng [*32*], Lujan [*23*], Kang [*25*], Van der Pas [*37*], and Ng [*39*] randomization sequence were generated by a computer program

** In Guillou [*6*] and Kang [*25*], allocation concealment was done by telephone by the trial coordinator; in Braga [*30*], Lujan [*23*], and Liang [*21*] by means of sealed envelopes; in Ng [*32*] and Ng [*39*] by an independent operating theater coordinator

*** In Kang [*25*], pathologists who examined the resected specimen were masked to patients' allocation; in Liang [*21*], patients were assessed for postoperative complications by a reviewer unaware of patients' allocation

Table 5

Quality assessment of the included non-randomized controlled studies based on the Newcastle-Ottawa Scale

Authors	Selections			Comparability		Outcome assessment		Score
	1	2	3	4	5	6	7	
Leung [*26*]	*			*	**		*	5
Anthuber [*27*]	*	*	*	*	*	*	*	7
Wu [*16*]	*	*	*	**	**	*		8
Breukink [*17*]	*	*	*	*	**	*	*	8
Morino [*18*]	*	*	*	**	*	*	*	8
Bretagnol [*38*]	*	*	*	*		*	*	8
Law [*28*]	*	*	*	**		*	*	7
Lelong [*29*]	*	*	*	**	*	*	*	8
Veenhof [*19*]	*	*	*	*	**	*		7
Ströhlein [*31*]	*	*	*	*	**	*	*	8
Koulas [*24*]	*	*	*			*	*	5
Laurent [*22*]	*	*	*			*		4
Khaikin [*20*]	*	*	*			*		4
Baik [*33*]	*	*	*	**	**	*	*	9
Jefferies [*41*]	*	*	*		*		*	5
Seshadri [*40*]	*	*	*	**	**	*		8
McKay [*34*]	*	*	*	**		*		6
Kellokumpu [*35*]	*	*	*	**	**	*	*	9
Lujan [*36*]	*	*	*			*	*	5

Selection: 1. Assignment for treatment (if yes, one point). 2. How representative was the laparoscopic group in comparison with the general population undergoing rectal resections (if yes, one point; no points if the patients were selected or selection of group was not described). 3. How representative was the open group in comparison with the general population undergoing rectal resections (if yes, one point; no points if the patients were selected or selection of group was not described)
Comparability: 4. Group comparable for 1–3 (if yes, two points; one point if one of these three characteristics was not reported even if there were no other differences between the two groups and other characteristics had been controlled for; no points were assigned if the two groups differed). 5. Group comparable for 4–7 (if yes, two points; one point if one of these four characteristics was not reported even if there were no other differences between the two groups and other characteristics had been controlled for; no points were assigned if the two groups differed)
Outcome assessment: 6. Clearly defined outcome of interest (if yes, one point for information ascertained by medical records or interview; no points if this information was not reported). 7. Follow-up equal between the two groups (if yes, one point; no points if follow-up not reported)
Comparability variables: 1 = age, 2 = gender, 3 = ASA, 4 = neoadjuvant/adjuvant therapy, 5 = tumor location, 6 = stage, 7 = procedure
The level of agreement among trials for the main outcome is displayed as a L'Abbé plot (Fig. 2).

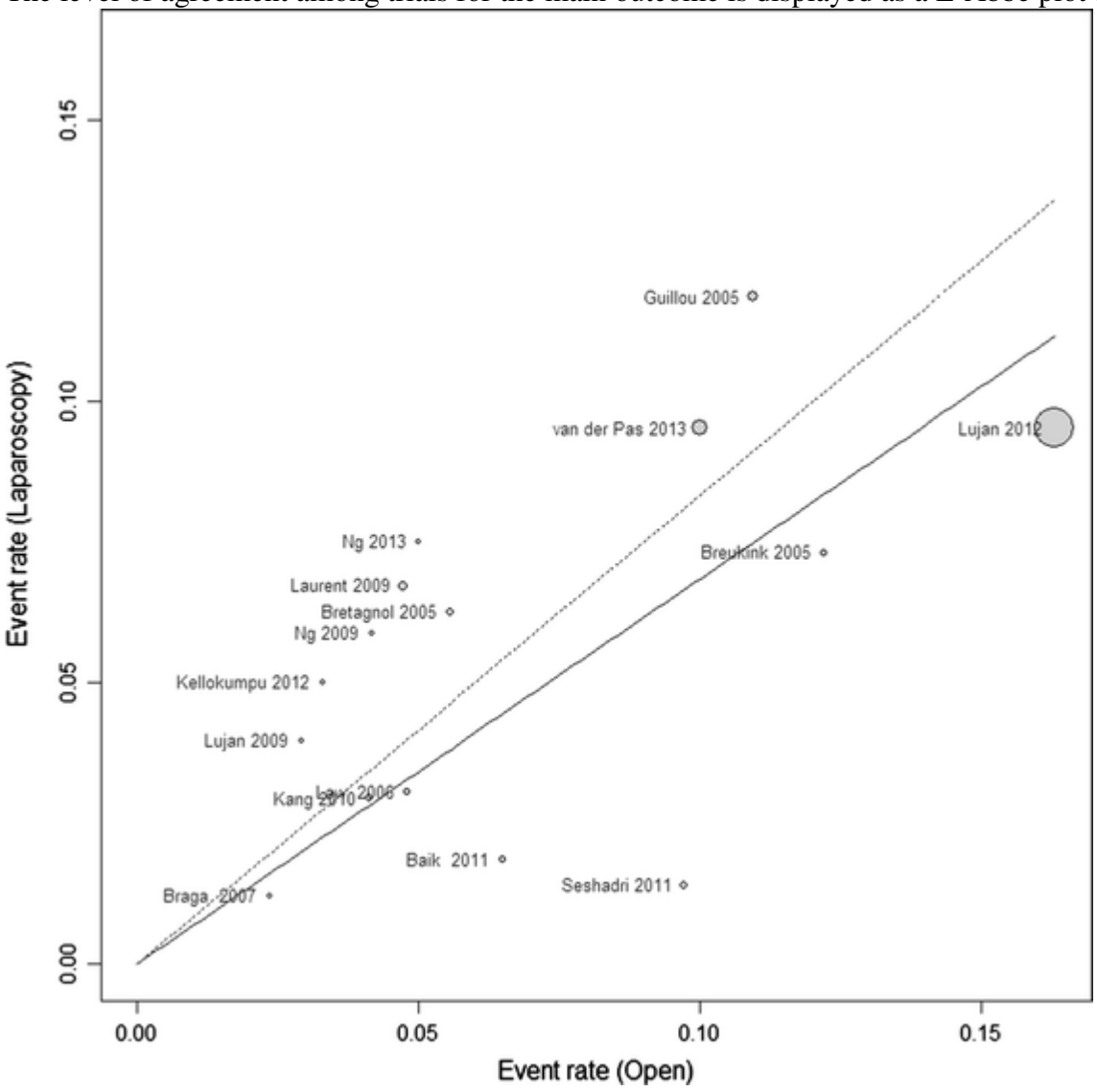

Fig. 2
L'Abbé plot of all trials to identify potential sources of heterogeneity in the primary outcome, positive circumferential margin

Primary outcome

The meta-analysis investigated as primary outcome the involvement of the circumferential resection margin (defined as positive when <1 mm). RCTs reported a positive circumferential margin in 7.9 % of patients who underwent laparoscopic and 6.9 % of those undergoing open surgery; the overall RR was 1.00 (95 % CI 0.73–1.35) (Fig. 3) with no heterogeneity ($I^2 = 0$ %). After adding the data from the non-RCTs, a positive circumferential margin was reported in 8.0 % of patients who underwent laparoscopic and in 12.7 % of those undergoing open surgery; the overall RR was 0.68 (95 % CI 0.59–0.79; P < 0.001) (Fig. 3) with low heterogeneity ($I^2 = 26.0$ %). The sensitivity analysis showed a significant difference between non-RCTs and RCTs (RR 0.62 vs. 1.00; P = 0.008). In the cumulative meta-analysis, the RR was generally around 1.0 from 2005 until 2012, when Lujan et al. [*36*] published their results, which significantly shifted the RR in favor of the laparoscopic technique.

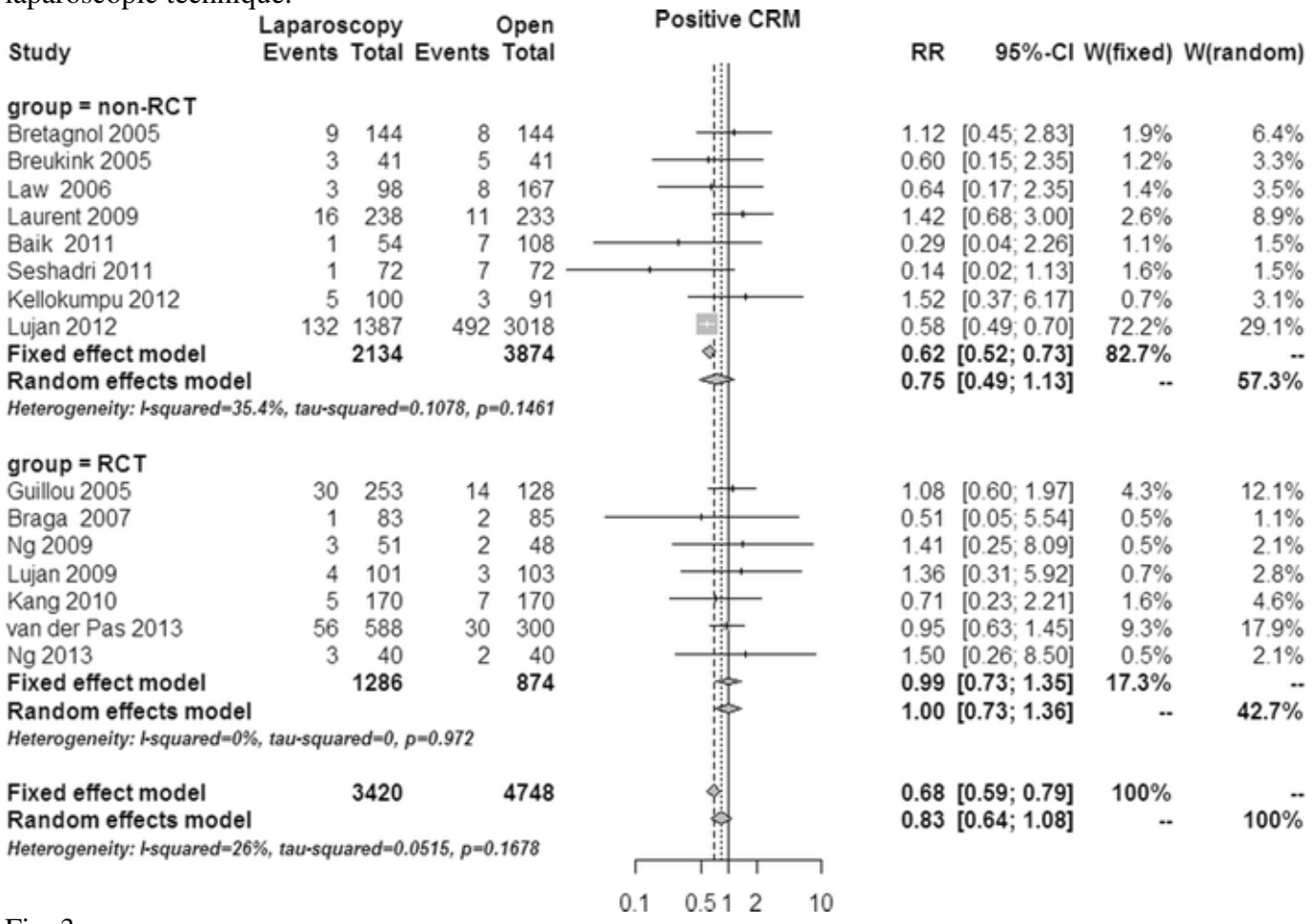

Fig. 3
Forest plot of positive circumferential margin

Secondary outcomes

The mean number of lymph nodes harvested was 13.1 in patients who underwent laparoscopic and 14.5 in those undergoing open surgery; the overall mean difference (MD) was −0.56 lymph nodes (95 % CI −1.09 to −0.03; P = 0.038) (Fig. 4), with no significant difference between non-RCTs and RCTs (MD −0.73 vs. −0.32; P = 0.497) but with very large heterogeneity ($I^2 = 88.0$ %).

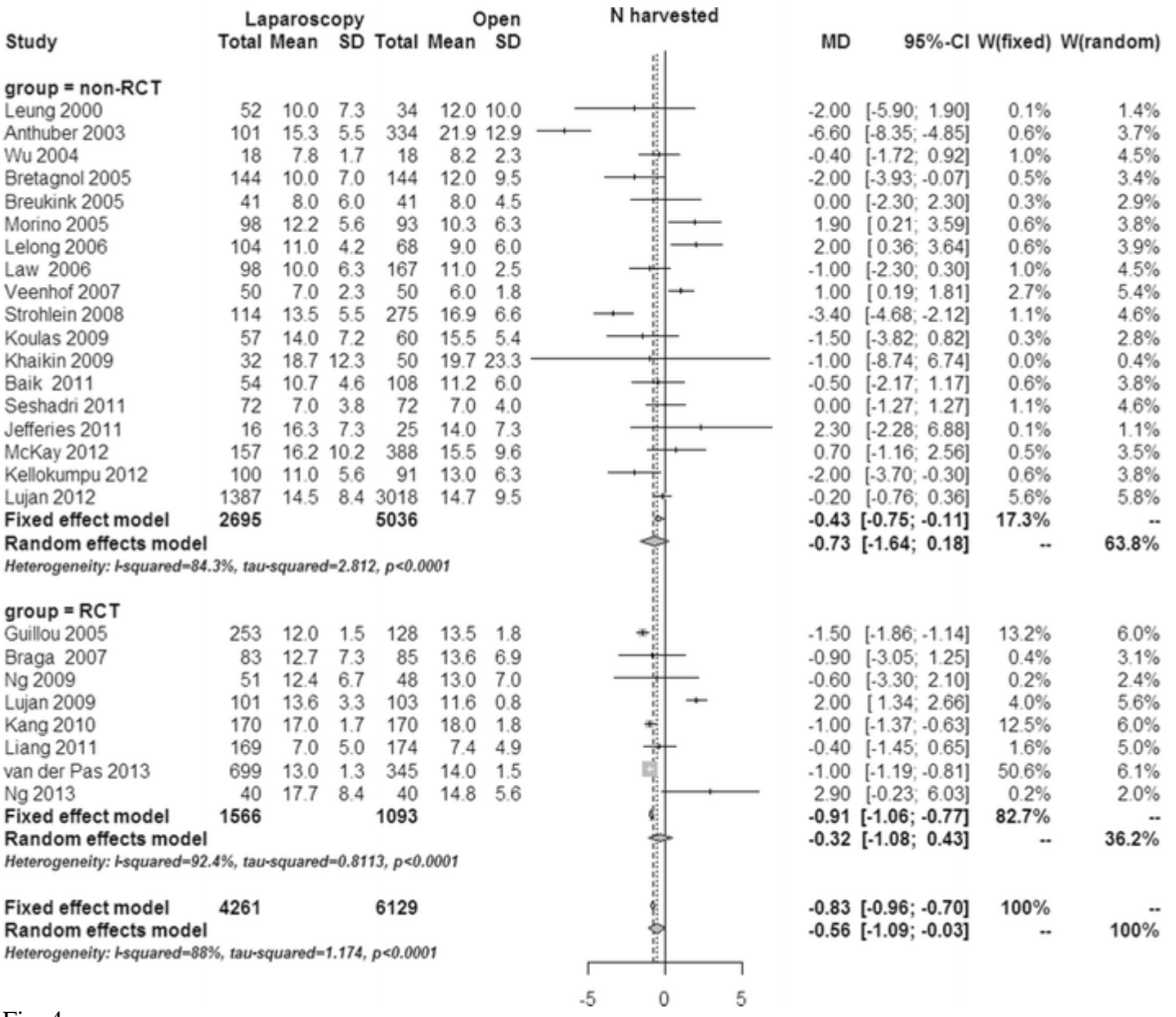

Fig. 4
Forest plot of number of lymph nodes harvested

The mean distal margin (defined as the distance between the distal margin of bowel resection and the tumor) was 2.8 cm in patients who underwent laparoscopic and 3.0 cm in those undergoing open surgery; the overall MD was −0.04 cm (95 % CI −0.27 to 0.19; P = 0.721) (Fig. 5), with no significant difference between non-RCTs and RCTs (MD −0.08 vs. 0.05; P = 0.618) but, again, with very large heterogeneity (I^2 = 89.2 %).

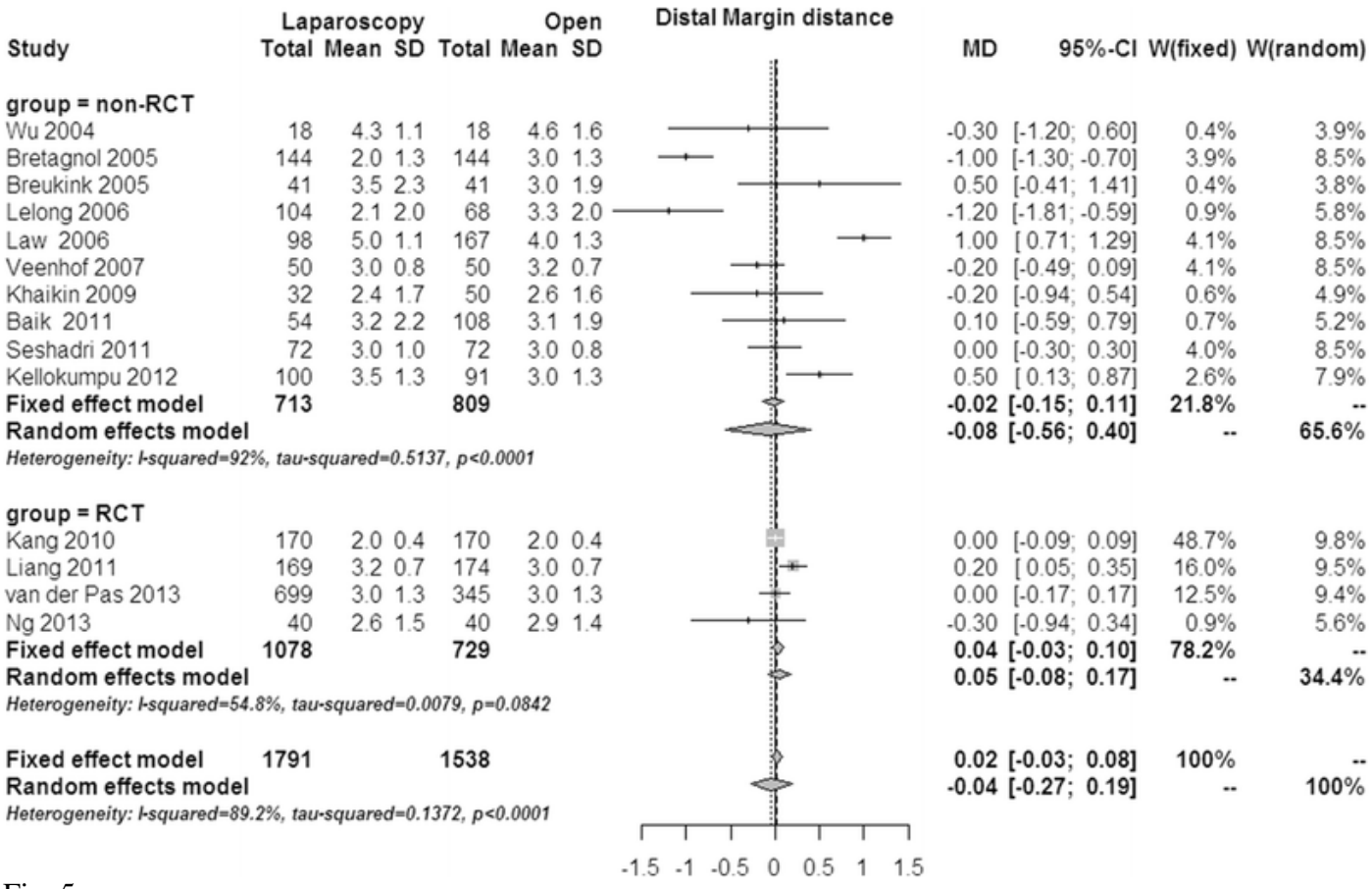

Fig. 5
Forest plot of distal margin distance

A positive distal margin (<1 mm) was reported in 1.0 % of patients who underwent laparoscopic and in 1.2 % of those undergoing open surgery; the overall RR was 0.73 (95 % CI 0.41–1.31; P = 0.292) (Fig. 6), with moderate heterogeneity (I^2 = 49.2 %); no subgroup analysis was performed because all the trials were non-RCTs.

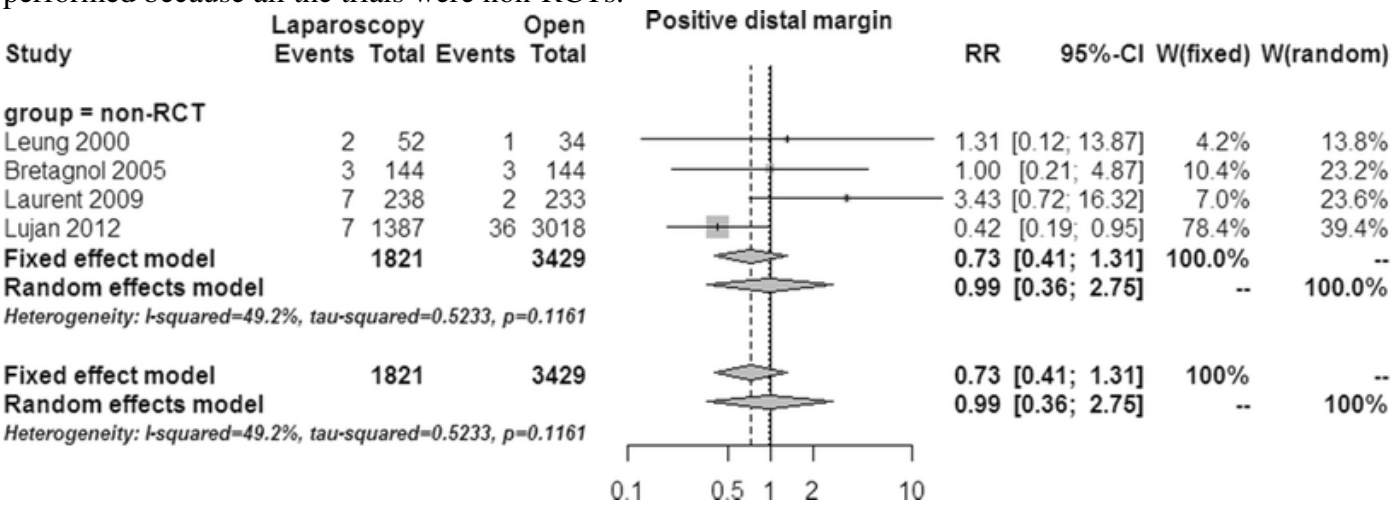

Fig. 6
Forest plot of positive distal margin

The mean circumferential margin (defined as the distance between the circumferential margin of bowel resection and the tumor) was 0.9 cm in both the laparoscopic and the open surgery arms; the overall MD was −0.02 cm (95 % CI −0.10 to 0.06; P = 0.626) (Fig. 7), with no significant difference between non-RCTs and RCTs (MD −0.10 vs. 0.05; P = 0.139) but, again, with very large heterogeneity (I^2 = 91.9 %).

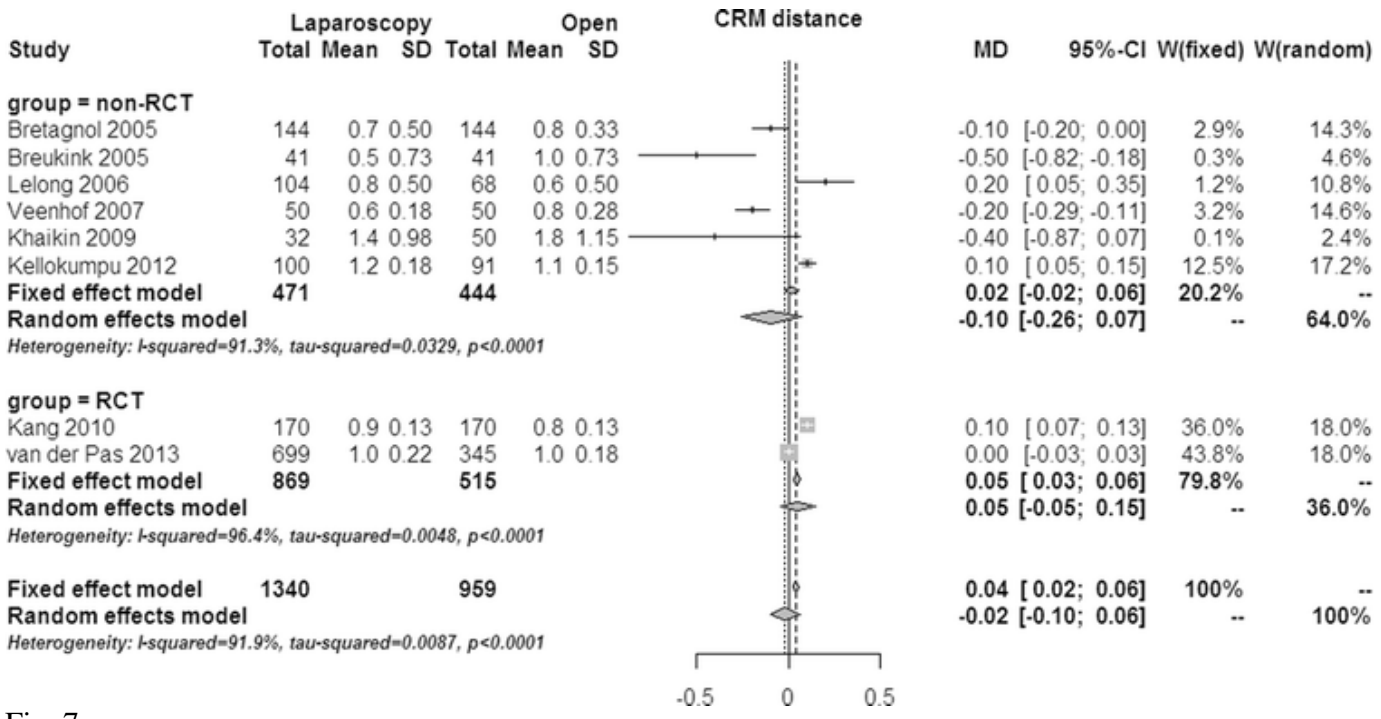

Fig. 7
Forest plot of circumferential margin distance

Overall, a R0 resection (defined as the rate of lesions excised with margins free of disease) was reported in 83.1 % of patients who underwent laparoscopic and in 77.0 % of those undergoing open surgery; the overall RR was 1.00 (95 % CI 0.94–1.07; P = 0.969) (Fig. 8), with no significant difference between non-RCTs and RCTs (RR 1.00 vs. 0.97; P = 0.683) but with very large heterogeneity (I^2 = 75.1 %).

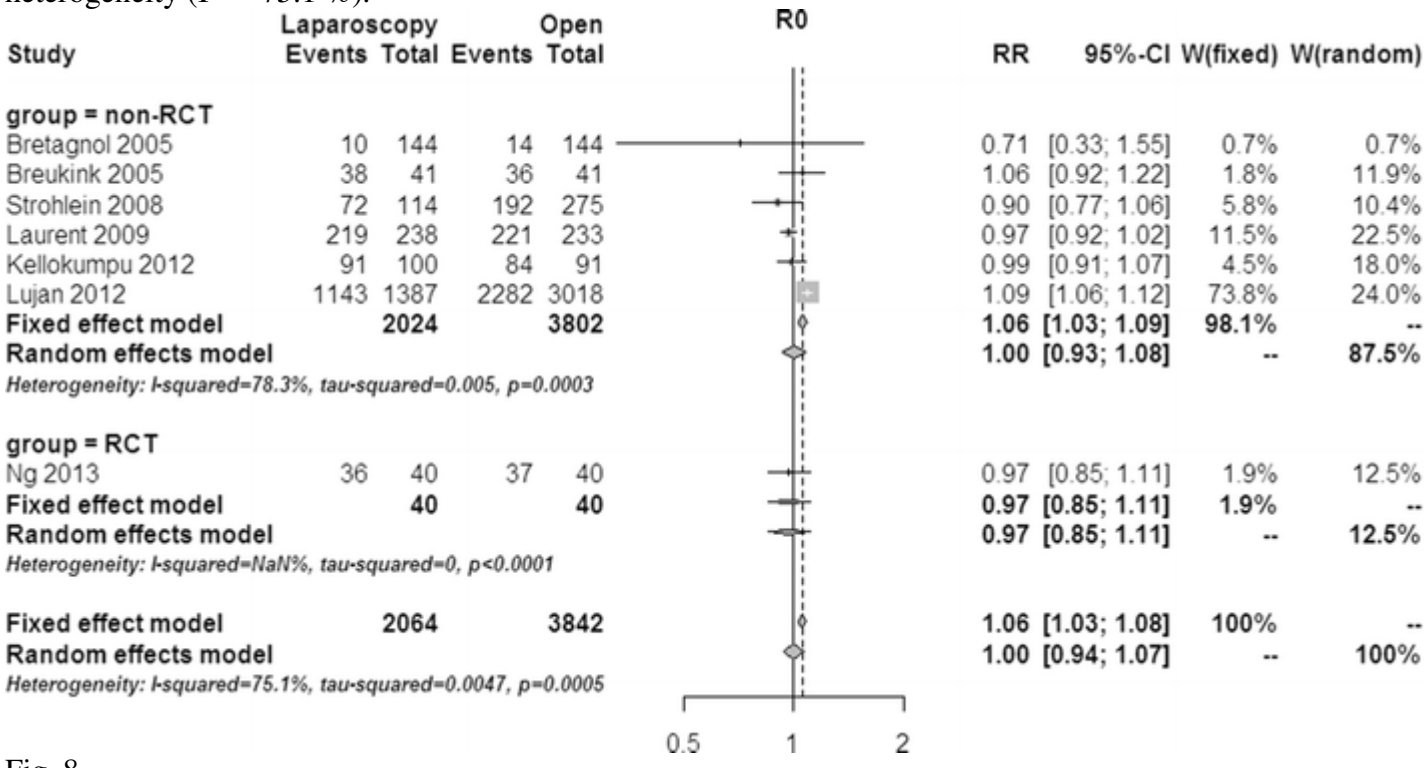

Fig. 8
Forest plot of R0 resection

Mesorectal fascia integrity, as assessed by the pathologist, was reported in 85.2 % of patients who underwent laparoscopic and in 85.8 % of those undergoing open surgery; the overall RR was 1.10

(95 % CI 0.82–1.48; P = 0.539) (Fig. 9), with notable heterogeneity (I^2 = 67.5 %); no subgroup analysis was performed because all the trials were RCTs.

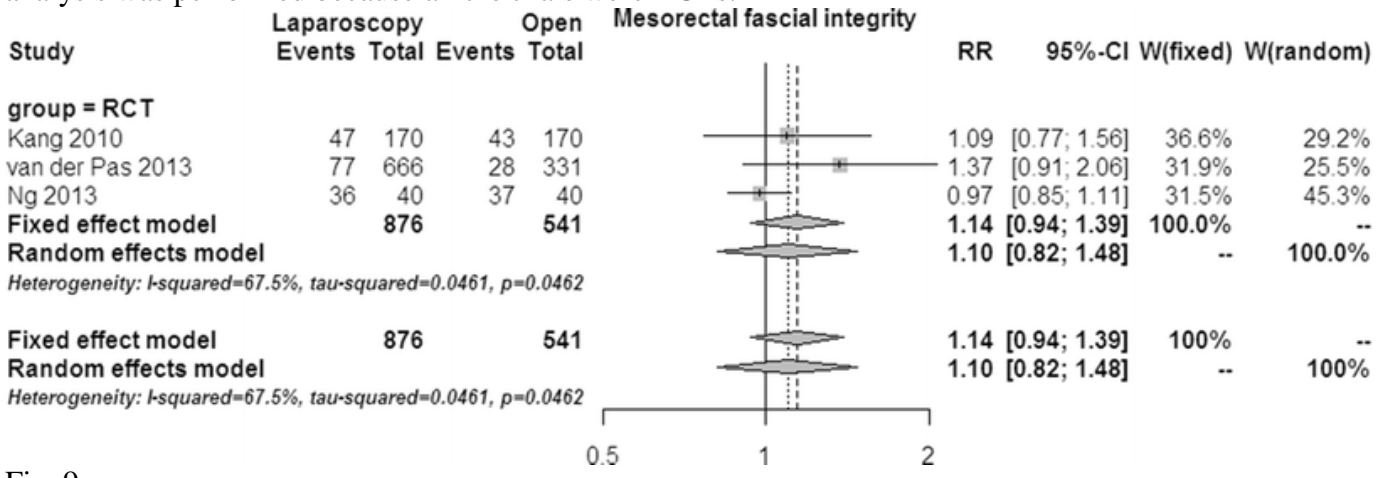

Fig. 9
Forest plot of mesorectal fascia integrity

Finally, the raw incidence of local recurrence at 5 years was lower in patients who underwent laparoscopic than in those undergoing open surgery (4.1□% vs. 5.0 %). The overall RR was 0.77 (95 % CI 0.43–1.36; P = 0.366), with no significant difference between RCTs and non-RCTs (RR 0.82 vs. 0.76; P = 0.929) (Fig. 10) and no heterogeneity (I^2 = 0 %).

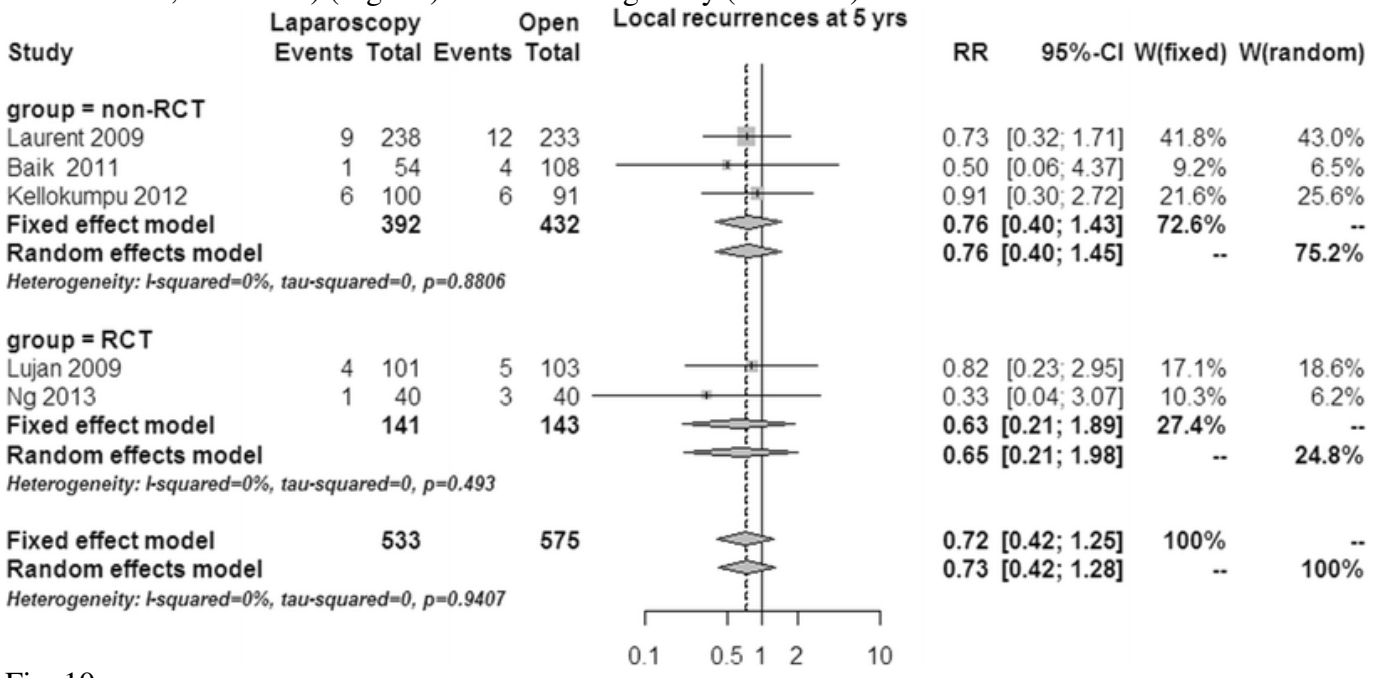

Fig. 10
Forest plot of local recurrence at 5 years

Subgroup analyses

Subgroup analyses were conducted on patients with extraperitoneal cancer of the rectum (defined as lesions in the mid or low rectum or the extraperitoneal rectum or up to 12 cm from the anal verge); the analyses also included abdominoperineal resections (APR). Eleven studies (2,552 patients) met the inclusion criteria [*3*, *17*, *18*, *23*, *25*, *26*, *32*, *37–41*]; five were RCTs (1,720 patients) and six were non-RCTs (832 patients).

As the primary outcome, a positive circumferential margin (<1 mm) was reported in 10.3 % of patients who underwent laparoscopic and in 11.6 % of those undergoing open surgery; the overall

RR was 0.87 (95 % CI 0.63–1.21; P = 0.420), with no heterogeneity (I^2 = 0 %). The sensitivity analysis showed no significant difference between non-RCTs and RCTs (RR 0.65 vs. 0.96; P = 0.432).

Among the secondary outcomes, the average number of lymph nodes harvested was 12.8 in patients who underwent laparoscopic and 13.3 in those undergoing open surgery; the overall MD was −0.11 lymph nodes (95 % CI −0.98 to 0.77; P = 0.812), with no difference between non-RCTs and RCTs (MD −0.52 vs. 0.16; P = 0.406) but with very large heterogeneity (I^2 = 89.5 %).

The mean distal margin was 2.4 cm in patients who underwent laparoscopic and 2.5 cm in those undergoing open surgery; the overall MD was 0.04 cm (95 % CI −0.48 to 0.55; P = 0.894), with no difference between non-RCTs and RCTs (MD −0.23 vs. 0.62; P = 0.295) but, again, with very large heterogeneity (I^2 = 92.1 %).

A positive distal margin (<1 mm) was reported in 2.6 % of patients who underwent laparoscopic and in 2.2 % of those undergoing open surgery; the overall RR was 1.09 (95 % CI 0.29–4.04; P = 0.899), with no heterogeneity (I^2 = 0 %).

The mean circumferential margin was 0.92 cm in patients who underwent laparoscopic and 0.91 cm in those undergoing open surgery; the overall MD was −0.03 cm (95 % CI −0.13 to 0.07; P = 0.558), with no significant difference between non-RCTs and RCTs (MD −0.27 vs. 0.05; P = 0.116) but with very large heterogeneity (I^2 = 93.6 %).

Overall, an R0 resection was reported in 93.0 % of patients who underwent laparoscopic and in 89.7 % of those undergoing open surgery; the overall RR was 1.04 (95 % CI 0.97–1.10; P = 0.268), with no heterogeneity (I^2 = 0 %).

Mesorectal fascia integrity was reported in 85.4 % of patients who underwent laparoscopic and in 86.3 % of those undergoing open surgery; the overall RR was 0.97 (95 % CI 0.93–1.01; P = 0.124), with no heterogeneity (I^2 = 0 %).

The raw incidence of local recurrence at 5 years after surgery was lower in patients who underwent laparoscopic than in those undergoing open surgery (3.5□% vs. 5.6 %); the overall RR was 0.63 (95 % CI 0.21–1.89; P = 0.413), with no heterogeneity (I^2 = 0 %).

Discussion

Now, more than 20 years after the first report of laparoscopic colon resection [*42*], laparoscopy is widely accepted, but its use in the treatment of rectal cancer remains debated. In 2012, we reported that the advantages of a minimally invasive approach such as with laparoscopy carry over to rectal resection. In a large systematic review and meta-analysis of the lay literature published during the previous decade, we found a significant reduction in short-term mortality and overall morbidity after laparoscopic as compared to open surgery [*3*]. Moreover, no significant difference in the anastomotic leakage rate was observed, while a clear advantage in favor of laparoscopy was observed for earlier bowel activity restoration, time to oral intake, and duration of postoperative hospital stay, the only clear disadvantage being the relatively longer operating time. Some limitations notwithstanding, we concluded from the evidence of both the randomized and the prospective controlled series that although technically demanding, laparoscopic rectal resection appears to have clinically measurable short-term advantages in patients with primary resectable rectal cancer. In a subsequent study, we were able to confirm similar results even after limiting the analysis to patients with extraperitoneal rectal cancer [*4*].

Here, we focus on the oncological adequacy of the laparoscopic technique as compared to open rectal resection. The foremost concern of cancer patients is to be cured of their disease, no matter by which technique; however, they are unlikely to recognize the potential benefits of minimally invasive treatment unless it is shown to be as oncologically effective as open surgery. For this reason, the present analysis is of even major importance than the previous one, insofar as it

indicates the correct way forward in the application of the concept of minimally invasiveness in the treatment of rectal cancer.

Since 2000, 27 studies [*6*, *16–41*] have been published comparing laparoscopic and open rectal resection. Although a meta-analysis of only RCTs would be ideal, we thought it wiser to extend the criteria to include prospective controlled clinical trials (non-RCTs), as suggested by the MOOSE group [*10*]. This was done to increase the body of data for analysis, while maintaining an acceptable level of evidence, as confirmed by risk of bias analysis and heterogeneity testing. No significant difference was observed at baseline for tumor stage, use of neoadjuvant therapy, or construction of a diverting ileostomy in either the global or the extraperitoneal cancer group. A sensitivity analysis to verify the reliability of the RCTs alone was performed nonetheless.

Due to these restrictions in how the papers were selected, the heterogeneity of the results was quite low in the primary outcome analysis, where the sample size was more consistent. This was true even though some of the sample populations were relatively small and most of the studies lacked criteria for determining a formal sample size. The sensitivity analyses showed that, within the whole time frame, no single study had an influential effect on RR, except the Lujan 2012 study [*36*]. The results of this trial significantly shifted the RR in favor of the laparoscopic technique in the primary outcome analysis, which was also reflected in the significant difference between RCTs and non-RCTs. In contrast, heterogeneity was greater only in the secondary outcomes analysis, although the sensitivity analysis consistently demonstrated agreement of results between RCTs and non-RCTs.

Unfortunately, it was not possible to analyze overall survival and disease-free survival at 5 years, though this would have been of extreme interest. As illustrated by Parmar [*43*], the correct way to do it, in fact, would be to perform a survival meta-analysis based on hazard ratios and standard errors derived from Cox regression models. Except for one case [*35*], these data were not reported in the selected studies.

Some of the findings of our analysis merit closer and careful attention. The main finding of the present meta-analysis is that the RCTs reported a positive circumferential margin (<1 mm) in 7.9 % of patients who underwent laparoscopic and in 6.9 % of those undergoing open surgery, with perfect oncological equivalence between the two techniques (RR = 1.00) and no heterogeneity of data. This was confirmed in the subgroup analysis of patients with extraperitoneal cancer of the rectum. When the non-RCT data were added, the results reported by Lujan et al. [*36*] tipped the balance in favor of laparoscopy, probably because of selection bias, so that due caution when interpreting this effect is warranted.

In order to assess the oncological adequacy of resection, we compared several other oncological short-term outcomes as secondary endpoints, including the number of lymph nodes harvested, margin clearance, and mesorectal fascia integrity. Owing to the marked heterogeneity of the results found in these analyses, they should be interpreted cautiously. Indeed, whenever heterogeneity is high after pooling RCTs and non-RCTs, the results should be eyed critically and pooling would not be recommended. For instance, the average number of harvested lymph nodes was significantly higher in the patients who underwent open surgery though heterogeneity was extremely high, but this difference was not confirmed on either the sensitivity analysis of the RCTs or the subgroup analysis of patients with extraperitoneal cancer of the rectum. Moreover, the mean difference of −0.56 lymph nodes, although statistically significant, seems to be of little clinical relevance. Furthermore, there were no significant differences between the two treatment groups in the average distal margin and its involvement, the average circumferential margin, the rate of R0 resections, and the mesorectal fascia integrity, as assessed by the pathologist. Even the local recurrence rate at 5 years was similar in patients who underwent laparoscopic and those undergoing open surgery. Neither the sensitivity analysis of RCTs versus non-RCTs nor the subgroup analysis of patients with extraperitoneal cancer, despite the consistent number of patients included, showed any statistically significant difference between laparoscopic and open surgeries.

The studies in this and in our previous review included patients selected by several exclusion criteria, such as advanced neoplasms (Dukes D or T4 or >6 cm), emergency situations (acute

obstruction, bleeding, or perforation), and previous colorectal or abdominal surgery. Therefore, these findings and observations are limited to patients selected against such criteria. Furthermore, to the extent that laparoscopic resection affords clear advantages in terms of short-term mortality and morbidity [*3*, *4*], an equivalent oncological outcome would be sufficient to justify its use in the surgical treatment of rectal cancer. The data analyzed in this meta-analysis suggest, in fact, that laparoscopy obtains equivalent oncological results based on pathology criteria, as reflected in the similar local recurrence rates at 5 years.

Still, these results should be interpreted carefully due to potential sources of bias and methodological limitations. As measured by the Cochrane Collaboration tool for Assessing Risk of Bias scale and the Newcastle-Ottawa Scale, most studies fell short on quality and some did not report oncological results as the primary outcome. Hence, there is a need for quality RCTs comparing the short-term outcome of open and laparoscopic TME, like the large North American (ACOSOG Z6051) and the Australasian Laparoscopic Cancer of the Rectum Trial (A La CaRT). Based on the evidence from the RCTs and non-RCTs examined in this systematic review, the short-term benefit and oncological adequacy of laparoscopic rectal resection appear to be equal to open surgery, with some evidence potentially pointing to comparable long-term outcomes and oncological adequacy in selected patients with primary resectable rectal cancer.

References

1.
Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK (1998) Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg 133:894–899
2.
Ries LA, Wingo PA, Miller DS et al (2000) The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer 88:2398–2424
3.
Arezzo A, Passera R, Scozzari G, Verra M, Morino M (2013) Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis. Surg Endosc 27:1485–1502
4.
Arezzo A, Passera R, Scozzari G, Verra M, Morino M (2013) Laparoscopy for extraperitoneal rectal cancer reduces short-term morbidity: results of a systematic review and meta-analysis. United European Gastroenterol J 1:32–47
5.
Lacy AM, Garcia-Valdecasas JC, Delgado S et al (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 359:2224–2229
6.
Guillou PJ, Quirke P, Thorpe H et al (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 365:1718–1726
7.
Clinical Outcomes of Surgical Therapy Study Group (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 350:2050–2059
8.
Veldkamp R, Kuhry E, Hop WC et al (2005) Colon cancer laparoscopic or open resection study group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 6:477–484
9.

Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:65–94
10.
Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283:2008–2012
11.
Higgins JPT, Green S (editors). Cochrane Handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed 1 Jan 2012
12.
Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomised studies in meta-analyses. Eur J Epidemiol 25:603–605
13.
DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
14.
Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13
15.
Schwarzer G (2007) Meta: an R package for meta-analysis. R News 7:40–45
16.
Wu WX, Sun YM, Hua YB et al (2004) Laparoscopic versus conventional open resection of rectal carcinoma: a clinical comparative study. World J Gastroenterol 10:1167–1170
17.
Breukink SO, Pierie JP, Grond AJ et al (2005) Laparoscopic versus open total mesorectal excision: a case-control study. Int J Colorectal Dis 20:428–433
18.
Morino M, Allaix ME, Giraudo G, Corno F, Garrone C (2005) Laparoscopic versus open surgery for extraperitoneal rectal cancer: a prospective comparative study. Surg Endosc 19:1460–1467
19.
Veenhof AA, Engel AF, Craanen ME et al (2007) Laparoscopic versus open total mesorectal excision: a comparative study on short-term outcomes. A single-institution experience regarding anterior resections and abdominoperineal resections. Dig Surg 24:367–374
20.
Khaikin M, Bashankaev B, Person B et al (2009) Laparoscopic versus open proctectomy for rectal cancer: patients' outcome and oncologic adequacy. Surg Laparosc Endosc Percutan Tech 19:118–122
21.
Liang X, Hou S, Liu H, Li Y, Jiang B, Bai W, Li G, Wang W, Feng Y, Guo J (2011) Effectiveness and safety of laparoscopic resection versus open surgery in patients with rectal cancer: a randomised, controlled trial from China. J Laparoendosc Adv Surg Tech A 21:381–385
22.
Laurent C, Leblanc F, Wütrich P et al (2009) Laparoscopic versus open surgery for rectal cancer: long-term oncologic results. Ann Surg 250:54–61
23.
Lujan J, Valero G, Hernandez Q et al (2009) Randomised clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 96:982–989
24.
Koulas SG, Pappas-Gogos G, Spirou S (2009) Evaluations of laparoscopic proctocolectomy versus traditional technique in patients with rectal cancer. JSLS 13:564–573

25.
Kang SB, Park JW, Jeong SY et al (2010) Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 11:637–645
26.
Leung KL, Kwok SP, Lau WY, Meng WC, Chung CC, Lai PB, Kwong KH (2000) Laparoscopic-assisted abdominoperineal resection for low rectal adenocarcinoma. Surg Endosc 14:67–70
27.
Anthuber M, Fuerst A, Elser F, Berger R, Jauch KW (2003) Outcome of laparoscopic surgery for rectal cancer in 101 patients. Dis Colon Rectum 46:1047–1053
28.
Law WL, Lee YM, Choi HK, Seto CL, Ho JW (2006) Laparoscopic and open anterior resection for upper and mid rectal cancer: an evaluation of outcomes. Dis Colon Rectum 49:1108–1115
29.
Lelong B, Bege T, Esterni B, Guiramand J, Turrini O, Moutardier V, Magnin V, Monges G, Pernoud N, Blache JL, Giovannini M, Delpero JR (2007) Short-term outcome after laparoscopic or open restorative mesorectal excision for rectal cancer: a comparative cohort study. Dis Colon Rectum 50:176–183
30.
Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V (2007) Laparoscopic resection in rectal cancer patients: outcome and cost-benefit analysis. Dis Colon Rectum 50:464–471
31.
Ströhlein MA, Grützner KU, Jauch KW, Heiss MM (2008) Comparison of laparoscopic versus open access surgery in patients with rectal cancer: a prospective analysis. Dis Colon Rectum 51:385–391
32.
Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Teoh AY, Leung WW (2008) Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol. 15:2418–2425. Erratum in: Ann Surg Oncol 2009;16:229
33.
Baik SH, Gincherman M, Mutch MG, Birnbaum EH, Fleshman JW (2011) Laparoscopic versus open resection for patients with rectal cancer: comparison of perioperative outcomes and long-term survival. Dis Colon Rectum 54:6–14
34.
McKay GD, Morgan MJ, Wong SK, Gatenby AH, Fulham SB, Ahmed KW, Toh JW, Hanna M, Hitos K, South Western Sydney Colorectal Tumour Group (2012) Improved short-term outcomes of laparoscopic versus open resection for colon and rectal cancer in an area health service: a multicenter study. Dis Colon Rectum 55:42–50
35.
Kellokumpu IH, Kairaluoma MI, Nuorva KP, Kautiainen HJ, Jantunen IT (2012) Short- and long-term outcome following laparoscopic versus open resection for carcinoma of the rectum in the multimodal setting. Dis Colon Rectum 55:854–863
36.
Lujan J, Valero G, Biondo S, Espin E, Parrilla P, Ortiz H (2013) Laparoscopic versus open surgery for rectal cancer: results of a prospective multicentre analysis of 4,970 patients. Surg Endosc 27:295–302
37.
van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ, COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group (2013) Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 14:210–218

38.
Bretagnol F, Lelong B, Laurent C, Moutardier V, Rullier A, Monges G, Delpero JR, Rullier E (2005) The oncological safety of laparoscopic total mesorectal excision with sphincter preservation for rectal carcinoma. Surg Endosc 19:892–896
39.
Ng SS, Lee JF, Yiu RY, Li JC, Hon SS, Mak TW, Ngo DK, Leung WW, Leung KL (2013) Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomised trial. Surg Endosc. 7 Sep 2013 [Epub ahead of print]
40.
Seshadri RA, Srinivasan A, Tapkire R, Swaminathan R (2012) Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: a matched case-control study of short-term outcomes. Surg Endosc 26:154–161
41.
Jefferies MT, Evans MD, Hilton J, Chandrasekaran TV, Beynon J, Khot U (2012) Oncological outcome after laparoscopic abdominoperineal excision of the rectum. Colorectal Dis 14:967–971
42.
Jacobs M, Verdeja JC, Goldstein HS (1991) Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc 1:144–150
43.
Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834