UNIVERSITÀ DEGLI STUDI DI TORINO

Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis

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Abstract

Background

Although definitive long-term results are not yet available, the global safety of laparoscopic surgery for rectal cancer treatment remains controversial. We evaluated differences in the safety of laparoscopic rectal resection versus open surgery for cancer.

Methods

A systematic review from 2000 to 2011 was performed searching the Medline and Embase databases (prospero registration CRD42012002406). We included randomized and prospective controlled clinical studies comparing laparoscopic and open resection for rectal cancer. Primary end points were 30-day mortality and overall morbidity. Then a meta-analysis was conducted by a fixed-effect model, performing a sensitivity analysis by a random-effect model. Relative risk (RR) was used as an indicator of treatment effect; a RR of less than 1.0 was in favor of laparoscopy. Publication bias was assessed by funnel plot and heterogeneity by the I^2 test and subgroup analysis on surgical and medical complications.

Results

Twenty-three studies, representing 4,539 patients, met the inclusion criteria; eight were randomized for a total of 1,746 patients. Mortality was observed in 1.0 % of patients in the

laparoscopic group and in 2.4 % of patients in the open group. The overall RR was 0.46 (95 % confidence interval 0.21–0.99, p = 0.048). The raw incidence of overall complications was lower in the laparoscopic group (31.8 %) compared to the open group (35.4 %). The overall RR was 0.83 (95 % confidence interval 0.76–0.91, p < 0.001).

Conclusions

On the basis of evidence of both randomized and prospective controlled series, mortality and morbidity RR, including subgroup analysis, were significantly lower after laparoscopic compared to open surgery.

Keywords

Laparoscopy Meta-analysis Rectal cancer Rectal neoplasms Systematic review

Although laparoscopic resection of colon cancer is recently gaining acceptance [1-4], the role of laparoscopy in the treatment of rectal cancer is still controversial.

Excellence of surgical technique is of particular relevance in the treatment of rectal cancer. Routine excision of the intact mesorectum during resection of cancers of the middle and lower rectum has resulted in a consistent reduction of local recurrences [5] and in an increase of long-term survival rates [6]. At present, open surgery is considered the treatment of choice for elective rectal resection in malignant diseases. Nevertheless, different reports have been presented in the literature during the past 10 years showing the feasibility of laparoscopic total mesorectal excision (TME) in expert centers. Although still lacking long-term oncological results, these studies have reported on postoperative course and short-term results. Some of them have advocated advantages of laparoscopy compared to open surgery for rectal cancer in terms of less pain, better postoperative pulmonary function, shorter postoperative ileus, shorter hospital stay, less fatigue, and better quality of life [7,8].

Whereas randomized, controlled trials (RCT) to evaluate recurrence rates and long-term survival of patients undergoing laparoscopic or open resection of rectal carcinoma will require a large number of patients and a long follow-up [9], clinically important short-term benefits of the minimal-access approach may be identified by analyzing the existing literature. The analysis of the short-term benefits of laparoscopy should be a prerequisite for the analysis of long-term results.

The aim of this study was to evaluate in a meta-analysis whether there are clinically relevant short-term advantages of either laparoscopy or laparotomy for surgical treatment of rectal cancer in the published literature.

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 [10]. According to population, interventions, comparators, outcome measures, and setting criteria, patients were included if they had rectal cancer for which laparoscopic or laparotomic treatment was indicated. The study methods were documented in a protocol registered and accessible at http://www.crd.york.ac.uk/prospero/ (registration CRD42012002406).

Types of studies

Only RCTs or prospective controlled clinical trials were considered for this analysis, as suggested by the MOOSE group [11]. 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. All and only full-text articles written in the English language were considered.

Types of participants

This meta-analysis compares laparoscopic and laparotomic resection for rectal cancer with regard to possible benefits of laparoscopy or laparotomy in the short-term postoperative period, defined as up to 30 days after surgery.

Types of intervention

All surgical procedures involving resection of the rectum were considered, including rectal anterior resection, coloanal anastomosis, Hartmann resection, and abdominoperineal resection. The type of interventions performed were noted in order to analyze separately those involving bowel anastomosis. For the laparoscopic group, any rectal resection performed through a mini-invasive approach (i.e., in a space generated by an insufflated pneumoperitoneum with the operative field visualization obtained by a video laparoscope and performed only through laparoscopic trocars) was included, while for open surgery, all

procedures described as “open” or “conventional” and performed through an abdominal laparotomic incision were considered.

Types of outcome measures

Primary end points were overall mortality and morbidity at 30 days after surgery. Intraoperative and early (<30 days) postoperative complications directly related to surgery, and early (<30 days) postoperative medical complications were the objects of different sensitivity analyses. Anastomotic leakage, bleeding and blood loss, wound infection and/or wound dehiscence, pelvic and/or abdominal abscesses, and bowel and/or vascular and/or urological injuries were classified as surgical complications. Paralytic ileum and/or nonsurgical bowel obstruction, respiratory events, cardiovascular events, deep venous thrombosis and/or pulmonary embolism, urinary infection, urinary retention, nonsurgical infections, and sepsis were classified as medical complications.

The secondary outcome measures were incidence of anastomotic leakage, abscesses, blood loss, time to first bowel movement, time for intake recovery, need for transfusion, length of hospital stay, wound infections, injuries to internal organs, need for reintervention, and operating time.

Search strategy and data collection

We searched the Medline and Embase databases for articles published from January 2000 to December 2011. The search strategy was performed using the following terms: (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 [2000–2011]/py AND [humans]/lim. The literature search was closed on December 31, 2011.

All abstracts retrieved from the electronic databases were screened independently by two authors (AA and GS); when an abstract was deemed relevant by at least one of them, the full text was retrieved. The reference lists of all relevant articles were manually searched for potentially relevant studies for inclusion.

Data extraction was carried out in duplicate independently by two authors (AA and GS). Disagreements were resolved by discussion with a third author (MM). Data collection was carried out using a self-developed spreadsheet in Excel format. The following data were

collected when available: study features, patients' characteristics (gender, age, body mass index, American Society of Anesthesiology classification score, cancer localization and stage, neoadjuvant therapy, type of procedures performed), data needed for study quality assessment, and outcome measures.

Assessment of risk of bias

All studies meeting the selection criteria were assessed for methodological quality according to the Cochrane collaboration guidelines [12] for RCTs and to the Newcastle–Ottawa scale for prospective controlled clinical trials [13]. This judgement was performed by three reviewers (AA, GS, and MV); disagreements were resolved by discussion and consensus.

Statistical analysis

All analyses were performed according to original treatment allocation (intention-to-treat analysis). For binary outcome data, the relative risks (RR) and 95 % confidence intervals (CI) were estimated by the Mantel–Haenszel method; a RR < 1 was in favor of laparoscopy. For continuous outcome data, the mean difference (MD) and 95 % CIs were estimated by the inverse variance weighting. A negative MD value was in favor of laparoscopy. When means and/or standard deviations were not reported in the original article, they were estimated from reported medians, ranges, and sample size as described by Hozo et al. [14].

A fixed-effects model was used in all meta-analyses, with the same analyses always redone by a random-effects model as described by DerSimonian and Laird [15]. Publication bias was assessed, generating a funnel plot, and we performed a rank correlation test of funnel plot asymmetry. Heterogeneity was assessed by the I^2 measure of inconsistency, considered statistically significant if I^2 was >50 %; whenever I^2 was <50 %, the fixed-effects model was used. Otherwise the random-effects model was preferred.

Potential sources of heterogeneity were explored by different sensitivity analyses: comparing fixed- versus random-effects models (thus incorporating heterogeneity by using the second method), performing subgroup analyses (always comparing RCTs versus prospective controlled clinical observational studies), checking the results of cumulative (sequentially including studies by date of publication), and influence meta-analyses

(calculating pooled estimates, omitting one study at a time). All analyses were conducted by the R 2.15.0 software package meta [16].

Results

Study selection

The search retrieved 4,613 studies. Figure 1 illustrates the PRISMA flow chart for study inclusion and exclusion criteria.

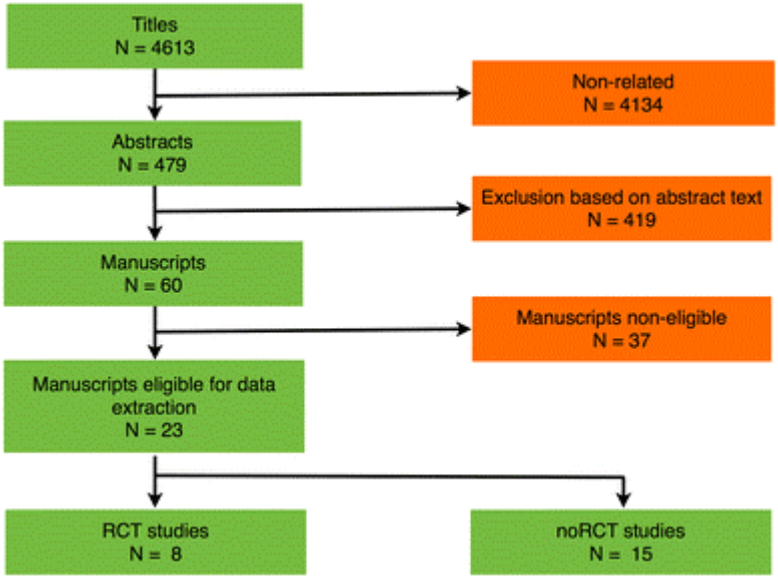

Fig. 1

Flow chart detailing the article selection process

Characteristics of included studies

The characteristics of the 23 studies meeting the inclusion criteria are summarized in Table1 [2,17-38]. All 23 studies were reported as full articles and included a total of 4,539 patients; eight were RCTs for a total of 1,746 patients, and 15 were prospective controlled clinical trials for a total of 2,793 patients. Guillou et al. [2] included patients affected by colorectal carcinoma; only data referring to rectal cases were collected for our meta-analysis.

Table 1

Summary of studies included in the meta-analysis

Study	Country and study period	Inclusion criteria	Exclusion criteria[a]	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	
Prospective controlled clinical trials													
Leung et al. [29]	Hong-Kong, Jan 1993–	Low rectal cancer	2, 11	59	25	34	15/10	21/13	62.2 ± 13.3	63.5 ± 15.2	NA	NA	8.0

Study	Country and study period	Inclusion criteria	Exclusion criteria[a]	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	
	Jan 1996												
Anthuber et al. [30]	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
Hu et al. [28]	China, Oct 2001–July 2002	Rectal cancer <15 cm from AV	2, 3, 4, 5, 9, 13, 14, 16, 19, 20	45	20	25	9/11	16/9	61.6 ± 8.4	58.0 ± 10.7	NA	NA	0
Wu et al. [18]	China, Apr 2002–May 2003	NA	2, 9, 19	36	18	18	9/9	10/8	52.4 ± 7.9	54.1 ± 6.8	NA	NA	0
Breukink et al. [19]	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[b]	70[b]	25[b]	25[b]	9.8
Morino et al. [25]	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	NA	NA	18.4
Law et al. [31]	Hong-Kong, June 2000–Dec 2004	Rectal cancer 8–20 cm from AV	2, 15	265	98	167	68/30	112/55	69[b]	70[b]	NA	NA	12.2
Lelong et al. [33]	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	NA	NA	NA	NA	NA	NA	14.4
Staudacher et al. [37]	Italy, Jan 1998–Sept 2005	Middle and low rectal cancer	2	187	108	79	65/43	42/37	63.9 ± 12.2	64.7 ± 13.0	26.3 ± 3.8	25.8 ± 4.1	12.0
Veenhof et al. [21]	Netherlands, Lap: Apr 2002–Nov 2005; open: Feb 1999–Apr 2002	Rectal cancer ≤17 cm from AV	20	100	50	50	28/22	32/18	67[b]	64.5[b]	25[b]	26[b]	8.0
Ströhlein et al. [35]	Germany, 1998–2005	Rectal cancer ≤16 cm from AV	NA	389	114	275	72/42	163/112	65.0 ± 9.9	65.5 ± 11.3	NA	NA	21.9
Koulas et al. [26]	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 et al. [24]	France, Lap: 2000–2006 Open: 1994–1996	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
Khaikin et al. [22]	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 et al. et al. [38]	USA	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
	Sept 2001–Sept 2005												
Randomized controlled trials													
Zhou et al. [17]	China, June 2001–Sept 2002	Rectal cancer with lowest margin under the peritoneal reflection and 1.5 cm above the dentate	1, 2, 8, 9, 11	171	82	89	46/36	43/46	44.0	45.0	NA	NA	NA

Study	Country and study period	Inclusion criteria	Exclusion criteria[a]	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	
		line											
Guillou et al. [2]	UK, July 1996–July 2002	Cancer of the colon and rectum	2, 3, 4, 5, 6	381	253	128	NA	NA	NA	NA	NA	NA	32.4
González et al. [32]	Spain, Jan 2003–April 2004	Rectal cancer <15 cm from AV	2, 9, 10, 12	40	20	20	11/9	8/12	66.6 ± 12.6	70.7 ± 9.2	26.0 ± 2.9	27.9 ± 5.1	10.0
Braga et al. [34]	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	NA	NA	7.2
Ng et al. [36]	Hong-Kong, July 1994–Feb 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	NA	NA	9.8
Lujan et al. [25]	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	NA	NA	7.9
Kang et al. [27]	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 et al. [23]	China, May 2004–Apr 2008	Rectal cancer	2, 11, 16, 17, 18, 19, 20	343	169	174	104/65	92/82	57.3[b]	57.4[b]	21.5[b]	22.3[b]	0.6

AV anal verge, Lap laparoscopic, BMI body mass index, NA not available

[a]Exclusion criteria are as follows: 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, American society of anesthesiology IV; 15 = familial adenomatous polyposis; 16 = presence of metastases; 17 = ongoing infections, low plasma neutrophil levels; 18 = BMI > 30 kg/m²; 19 = previous colon or rectal surgery and/or previous neoadiuvant chemotherapy; 20 = previous abdominal surgery

[b]Median value

Table 2 lists baseline patient characteristics comparing open and laparoscopic procedures. Table 3 lists characteristics of tumor location and stage, adjuvant therapy, and percentage of protective ileostomy.

Table 2

Comparison of baseline patient characteristics

RCT	No. of patients		Gender (M/F)[a]		Mean age (years)		Mean BMI (kg/m^2)	
	Lap	Open	Lap	Open	Lap	Open	Lap	Open
No	1,158	1,635	632/422	995/572	63.6	63.8	25.2	26.3
Yes	929	817	419/257	411/278	59.3	59.9	24.3	24.5
Overall	2,087	2,452	1,051/679	1,406/850	62.0	62.7	25.0	25.9

RCT randomized controlled trial, Lap laparoscopic, BMI body mass index

[a]The number of male and female subjects are not equal to the total number because gender data were not available in two studies (Guillou et al. [2] and Lelong et al. [33)

Table 3

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

RCT	No. of patients		Mean distance from anal verge (cm)		Tumor stage, T0–T2[a]		Tumor stage, T3–T4[a]		Neoadjuvant therapy		Protective ileostomy[b]	
	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open
No	1,158	1,635	7.22	6.35	520/852	670/1,240	332/852	570/1,240	538/842	720/1,405	553/968	774/1,308
Yes	929	817	6.50	6.47	175/342	153/341	167/342	188/341	267/425	268/426	208/400	200/406
Overall	2,087	2,452	6.75	6.43	695/1,194	823/1,581	499/1,194	758/1,581	805/1,267	988/1,831	761/1,368	974/1,714

RCT randomized controlled trial, Lap laparoscopic

[a]Tumor stage numbers are not equal to the total number because data were not available in all studies

[b]Percentages of protective ileostomy are calculated, when available, from the number of patients undergoing a surgical procedure involving a bowel anastomosis

Risk of bias of included studies

Assessment of quality according to the Cochrane collaboration's tool for assessing risk of bias for RCTs and to the Newcastle–Ottawa scale for prospective controlled clinical trials are 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 the risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome	Incomplete outcome data	Selective outcome reporting	Other source of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome	Incomplete outcome data	Selective outcome reporting	Other source of bias
Zhou et al. [17]	No	No	Unclear	Unclear	No	Yes
Guillou et al. [2]	Unclear	Yes[a]	Unclear	Unclear	Unclear	Yes
González et al. [32]	Unclear	Unclear	Unclear	Unclear	No	Yes
Braga et al. [34]	Yes[b]	Yes[a]	Unclear	Yes	Yes	Yes
Ng et al. [36]	Yes[b]	Yes[a]	Unclear	Yes	Yes	Yes
Lujan et al. [25]	Yes[b]	Yes[a]	Unclear	Yes	Yes	Yes
Kang et al. [27]	Yes[b]	Yes[a]	Yes[c]	Yes	Yes	Yes
Liang et al. [23]	Unclear	Yes[a]	Yes[c]	Yes	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

[a]In Guillou et al. [2] and Kang et al. [27], allocation concealment was done by telephone by the trial coordinator; in Braga et al. [34], Lujan et al. [25], and Liang et al. [23] by means of sealed envelopes; in and Ng et al. [36] by an independent operating theater coordinator

[b]In Braga et al. [34], Ng et al. [36], Lujan et al. [25], and Kang et al. [27], the randomization sequence was generated by a computer program

[c]In Kang et al. [27], pathologists who examined the resected specimen were masked to patients’ allocation; in Liang et al. [23], patients were assessed for postoperative complications by a reviewer unaware of patients’ allocation

Table 5

Quality assessment of the included prospective controlled clinical trials based on the Newcastle–Ottawa scale

Study	Selection[a]			Comparability[b]		Outcome assessment[c]		Score
	1	2	3	4	5	6	7	
Leung et al. [29]	*			*	**		*	5
Anthuber et al. [30]	*	*	*	*	*	*	*	7
Hu et al. [28]	*	*	*	*	**	*	*	8
Wu et al. [18]	*	*	*	**	**	*		8
Breukink et al. [19]	*	*	*	*	**	*	*	8
Morino et al. [25]	*	*	*	**	*	*	*	8
Law et al. [31]	*	*	*	**		*	*	7
Lelong et al. [33]	*	*	*	**	*	*	*	8
Staudacher et al. [37]	*	*	*	**	**	*	*	9
Veenhof et al. [21]	*	*	*	*	**	*		7
Ströhlein et al. [35]	*	*	*	*	**	*	*	8
Koulas et al. [26]	*	*	*			*	*	5
Laurent et al. [24]	*	*	*			*		4
Khaikin et al. [22]	*	*	*			*		4
Baik et al. [38]	*	*	*	**	**	*	*	9

[a]Selection: (1) assignment for treatment (if yes, one point). (2) How representative was the laparoscopic group in comparison to 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 to the general population undergoing rectal resections (if yes, one point; no points if the patients were selected or selection of group was not described)

[b]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). Comparability variables: 1 = age, 2 = gender, 3 = American Society of Anesthesiology score, 4 = neoadjuvant/adjuvant therapy, 5 = tumor location, 6 = stage, 7 = procedure

[c]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)

Figure 2 reports the potential sources of heterogeneity within all studies by a L'Abbé plot for morbidity outcome.

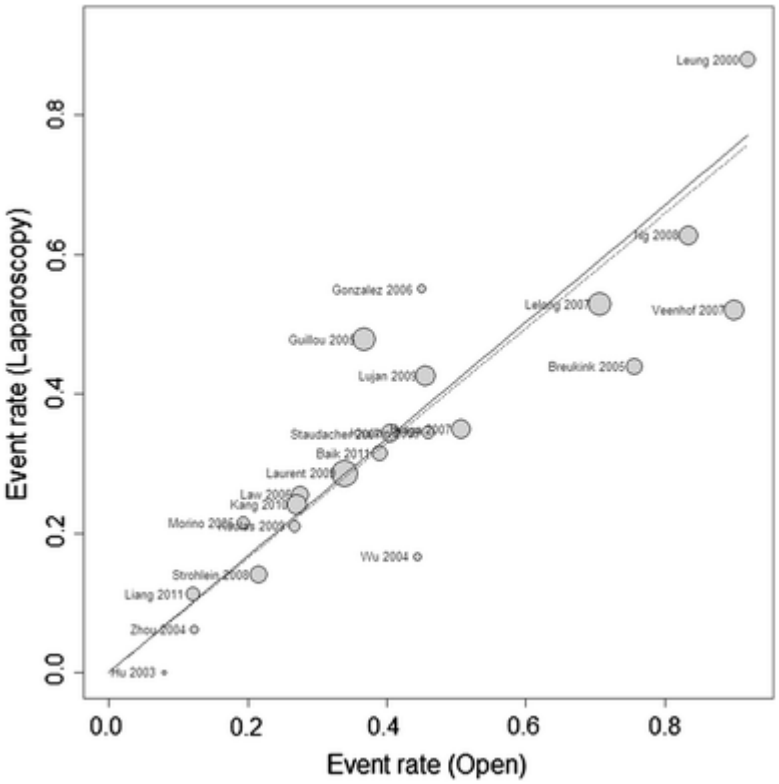

Fig. 2

L'Abbé plot for morbidity outcome for all trials to investigate potential sources of heterogeneity; the event rate in the laparoscopy group is plotted on the vertical axis and that in the open group on the horizontal one; circle dimension is proportional to the number of patients enrolled; the solid line is the overall RR line, representing the RR estimation by pooling the results of all studies. RR relative risk

Primary outcomes

The meta-analyses on the two primary outcomes investigated mortality and overall complications. For the first outcome, the raw incidence of mortality was lower in the laparoscopic group (1.0 %) compared to the open group I ^{2} 0.4 %). The overall RR was 0.46 (95 % confidence interval [CI] 0.21–0.99, p = 0.048), showing no differences between the RCT and prospective controlled clinical trial subgroups (RR 0.80 vs. 0.36, p = 0.327) (Fig. 3). No publication bias was found by the rank correlation test of funnel plot asymmetry (p = 0.579). When we performed a cumulative meta-analysis with these ten studies (three RCTs and seven prospective trials), adding one study at a time by publication date, the RR varied from 0.33 to 0.54; when we performed an influential meta-analysis by omitting one study in turn, the RR ranged from 0.42 to 0.55 for the entire time frame.

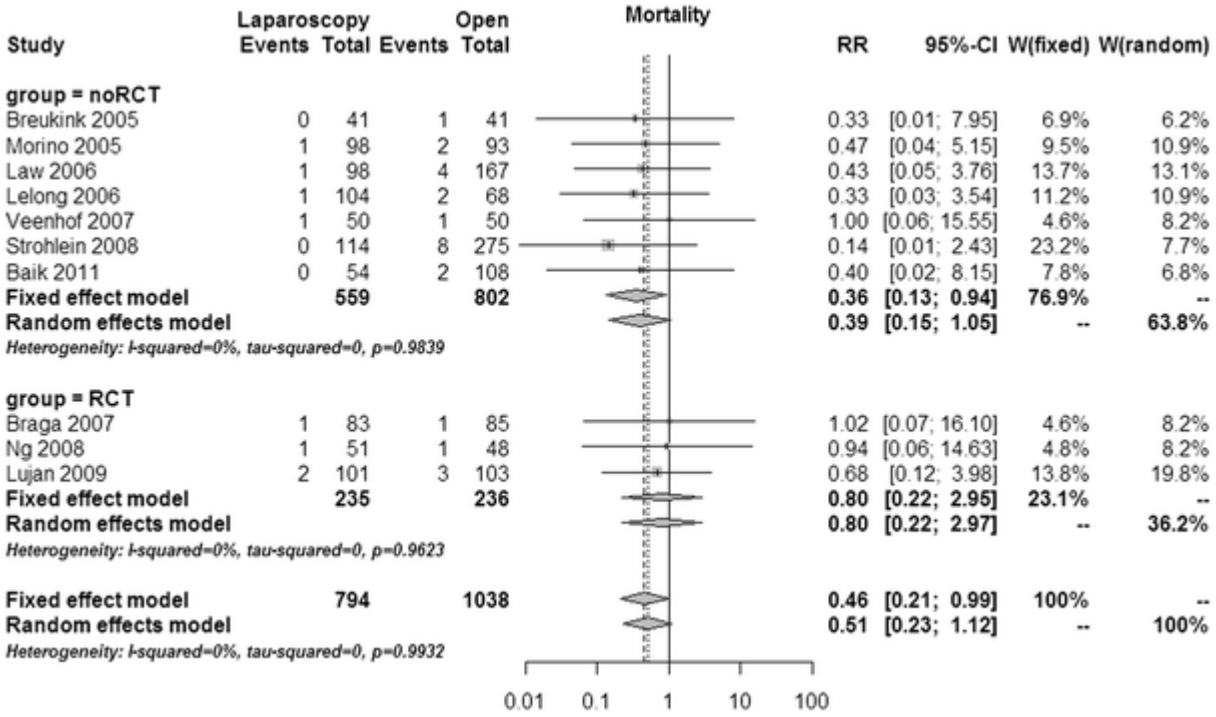

Fig. 3

Forest plot for 30-day mortality. RR relative risk, 95 % CI confidence interval, W weight of the single study

For the second outcome, the raw incidence of overall complications was lower in the laparoscopic group (31.8 %) compared to the open group (35.4 %). The overall RR was 0.83 (95 % CI 0.76–0.91, p < 0.001), with a statistically significant difference favoring prospective controlled clinical trials (RR 0.94 vs. 0.76, p = 0.021) (Fig. 4). Once again, no publication bias was found (p = 0.450). When we performed a cumulative meta-analysis with these 22 studies (eight RCTs and 14 prospective trials), the RR varied from 0.25 to 0.98, ranging only from 0.81 to 0.84 in the last period, 2007–2011; the main heterogeneity

source was represented by the study by Guillou et al. [2]. In the influential meta-analysis assessment, the RR that resulted was quite stable, ranging from 0.79 to 0.85 in the whole publication period and confirming the same trial as the cause of heterogeneity.

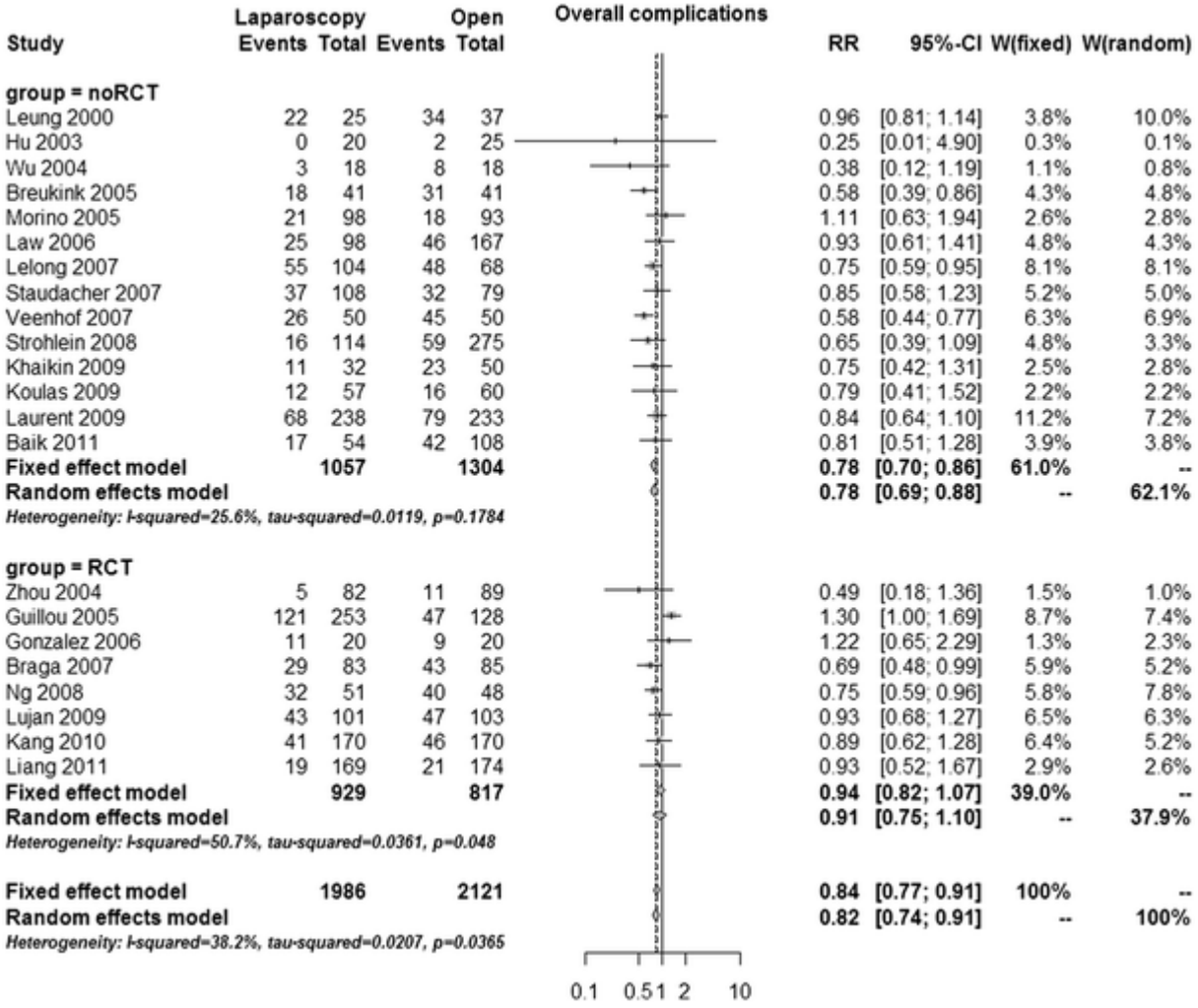

Fig. 4

Forest plot for 30-day overall morbidity. RR relative risk, 95 % CI confidence interval, W weight of the single study

Secondary outcomes

As secondary outcomes, the meta-analysis investigated medical and surgical complications in detail, such as number of patients with at least one medical or surgical complication, duration of surgery, mean blood loss, incidence injuries, bowel movement recovery, food intake recovery, blood transfusions, incidence of abscesses, incidence of wound complications, incidence of anastomotic leakages, incidence of reintervention, and length of hospital stay.

Percentages of patients with at least one medical or surgical complication was 31.9 % in the laparoscopic group and 35.4 % in the open surgery group; the overall RR was 0.83 (95 % CI 0.76–0.91, p < 0.001), without differences between RCTs and prospective controlled clinical trials (RR 0.94 vs. 0.76, p = 0.021).

The surgical complication rate was 16.6 % in the laparoscopic group and 19.0 % in the open group; the overall RR was 0.78 (95 % CI 0.68–0.89, p < 0.001) (Fig. 5), with no differences between subgroups (RR 0.84 vs. 0.74, p = 0.361).

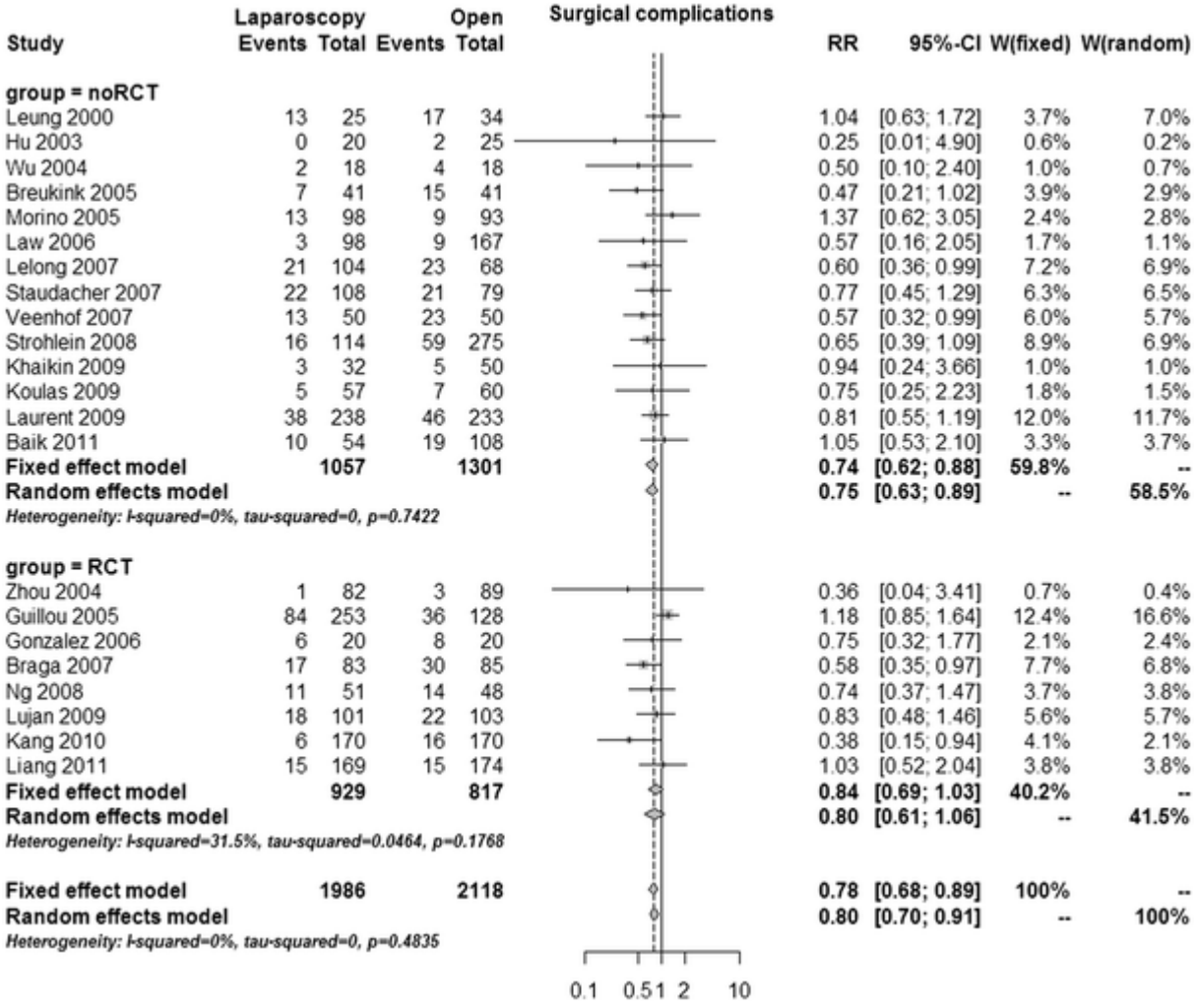

Fig. 5

Forest plot for 30-day surgical complications. RR relative risk, 95 % CI confidence interval, W weight of the single study

All but one study [17] provided the rate of conversion to open surgery. Overall, 13.0 % (260 of 2,005) laparoscopic cases were converted to laparotomy, 12.5 % (106 of 847) in the RCT studies and 13.3 % (154 of 1,158) in the prospective controlled clinical trials. Conversion rate ranged between 0.6 % [23] and 32.4 % [2] among RCT studies, and between 0 % [18,28] and 21.9 % [35] in the prospective trials. Among RCT studies,

reported conversion rates showed a strong time trend; this was not the case in the prospective trials (Table 1).

Medical complications rate was 16.6 % in the laparoscopic group and 19.1 % in the open group; the overall RR was 0.89 (95 % CI 0.78–1.02, p = 0.101) (Fig. 6), with a slight difference in the subgroup analysis (RR 1.06 vs. 0.79, p = 0.044).

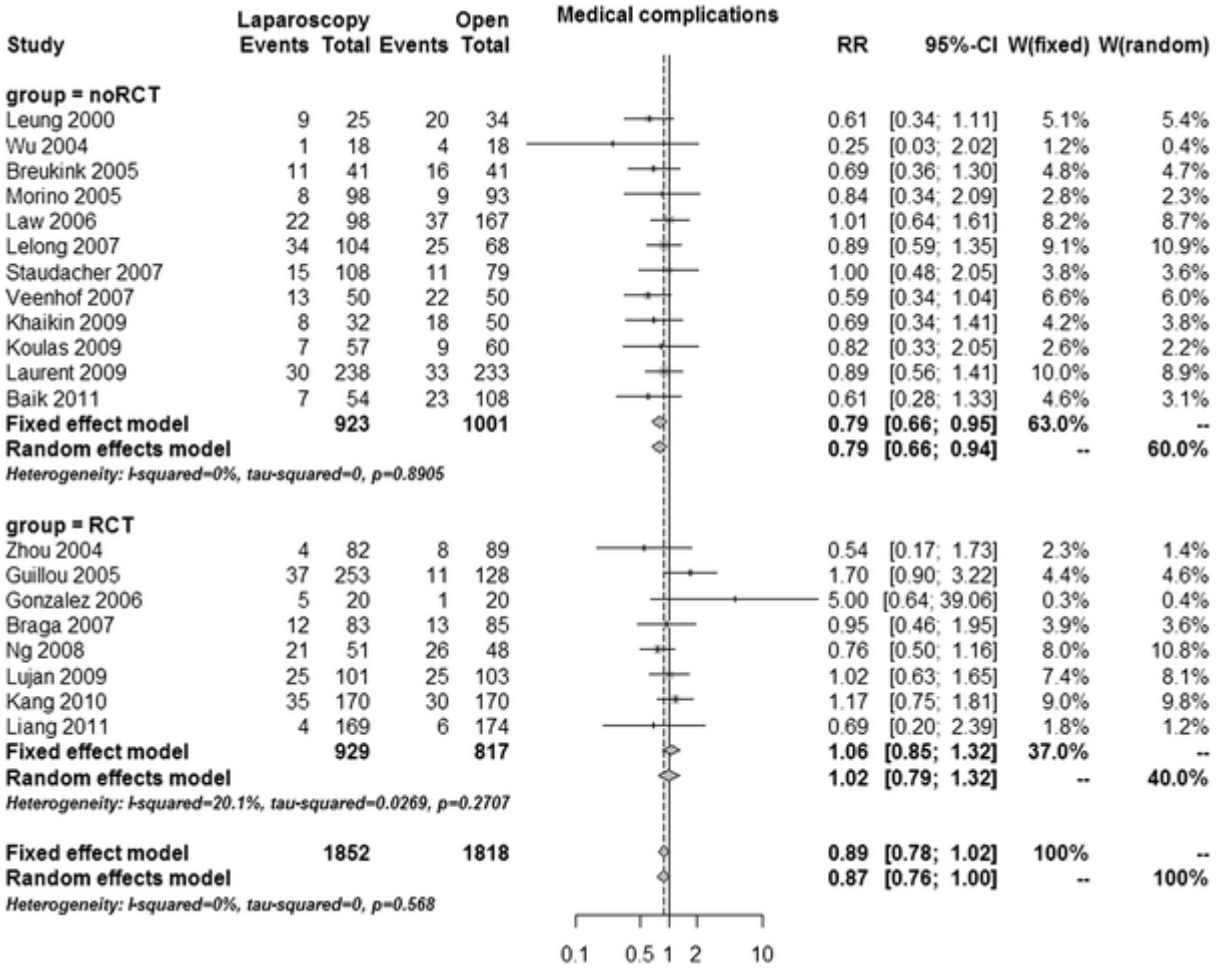

Fig. 6

Forest plot for 30-day medical complications. RR relative risk, 95 % CI confidence interval, W weight of the single study

The mean operative time was 219 min for laparoscopic surgery and 175 min for open surgery; the overall MD was 42.8 min (95 % CI 31.4–54.2, p < 0.001) (Fig. 7). Prospective trials had a significantly shorter duration (MD 30.0 vs. 52.0, p = 0.040), but with an extreme heterogeneity (I^2 92.9 %).

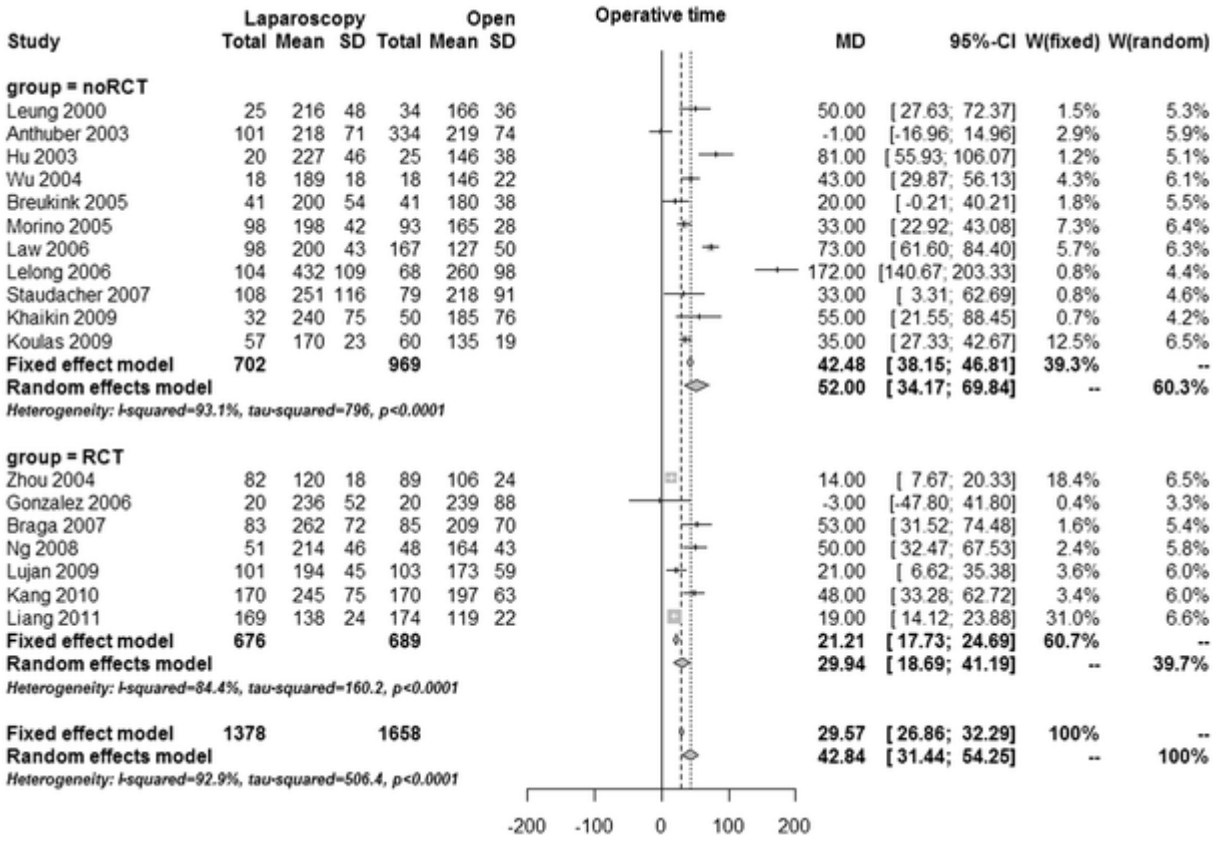

Fig. 7

Forest plot for mean operative time. MD mean difference, 95 % CI confidence interval, W weight of the single study

The mean blood loss was 307 ml in the laparoscopic group and 444 ml in the open surgery; the overall MD was −137 ml (95 % CI −199 to −75, $p < 0.001$) (Fig. 8), without subgroup differences (MD −103 vs. −146, $p = 0.360$) but with extreme heterogeneity (I^2 95.6 %).

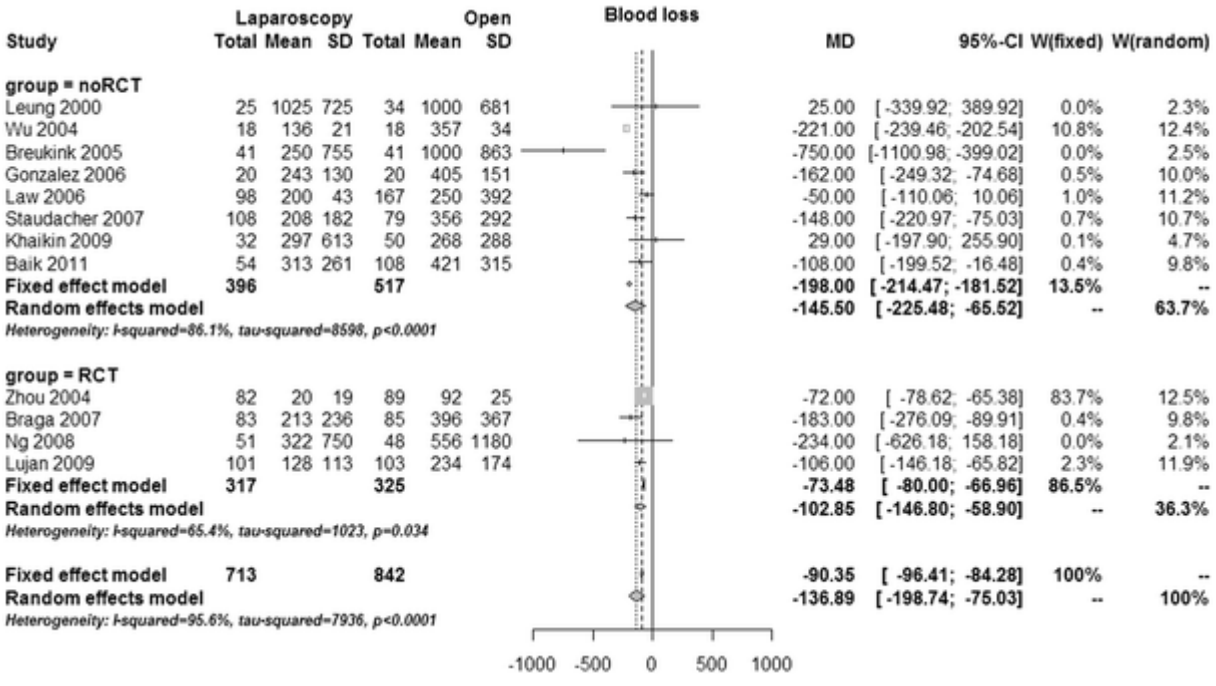

Fig. 8

Forest plot for mean blood loss. MD mean difference, 95 % CI confidence interval, W weight of the single study

The raw incidence of intraoperative injuries was 2.5 % among laparoscopic patients and 2.0 % among open patients; the overall RR was 1.11 (95 % CI 0.65–1.91, p = 0.701) (Fig. 9), without differences between RCTs and prospective trials (RR 1.36 vs. 0.93 p = 0.484).

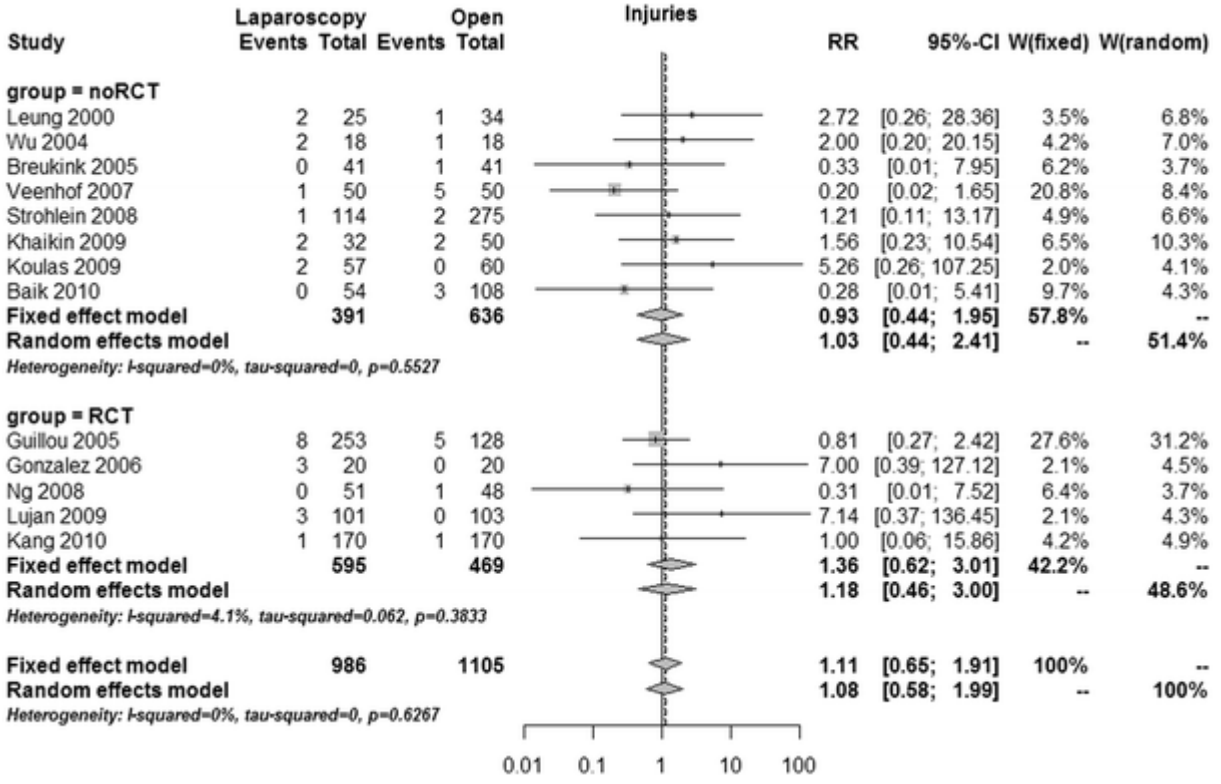

Fig. 9

Forest plot for incidence of intraoperative injuries. RR relative risk, 95 % CI confidence interval, W weight of the single study

The mean time for bowel movement recovery was 3.3 days in the laparoscopic group and 4.4 days in the open one; the overall MD was −0.96 days (95 % CI −1.3 to −0.6, p < 0.001) (Fig. 10), once again without differences between RCT and prospective controlled clinical trials (MD −0.94 vs. −1.04, p = 0.815), but with very high heterogeneity (I^2 81.4 %).

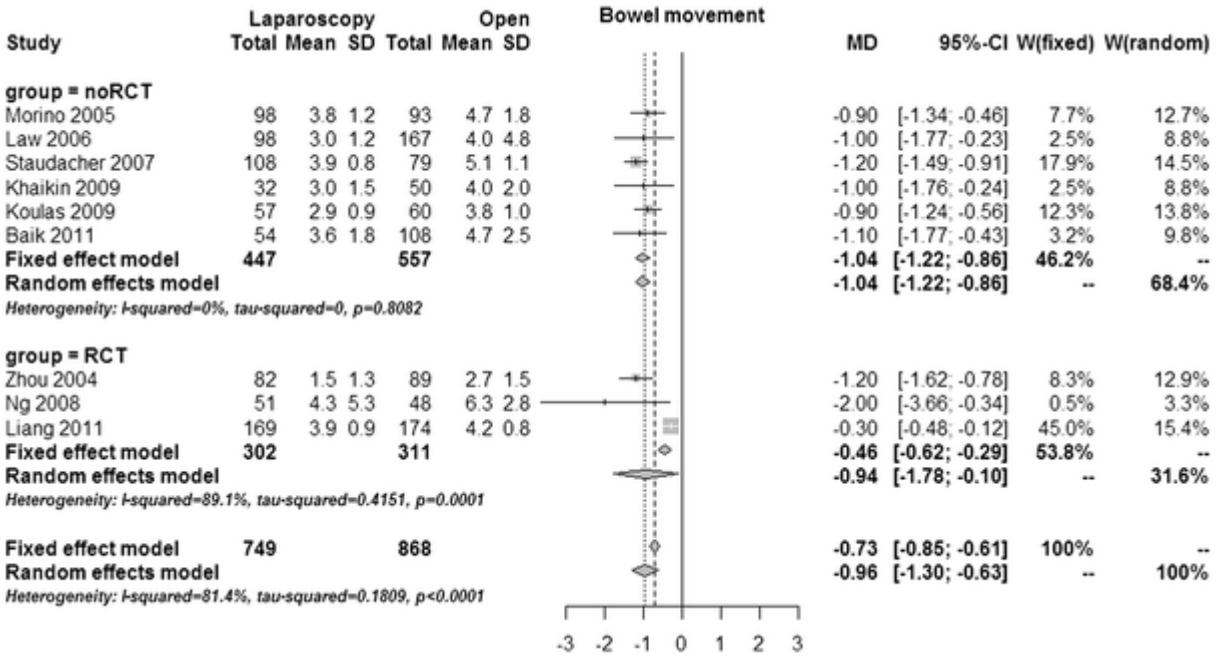

Fig. 10

Forest plot for bowel movement recovery. MD mean difference, 95 % CI confidence interval, W weight of the single study

The food intake recovery occurred after a mean of 3.8 days in the laparoscopic group and 4.8 days for the open surgery group; the overall MD was −1.0 days (95 % CI −1.4 to −0.7, $p < 0.001$) (Fig. 11), with no RCT versus prospective trials differences (MD −1.0 vs. −1.1, $p = 0.651$), and with very high heterogeneity (I^2 75.4 %).

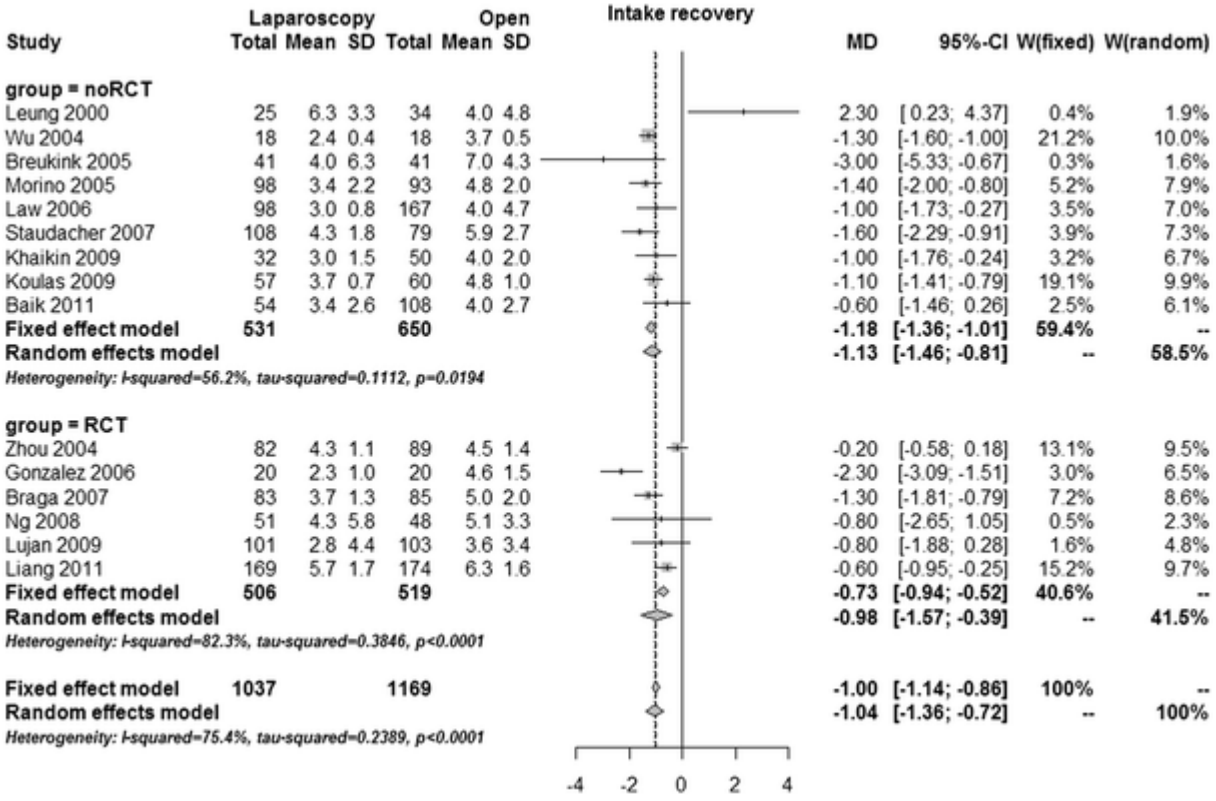

Fig. 11

Forest plot for food intake recovery. MD mean difference, 95 % CI confidence interval, W weight of the single study

Blood transfusions were needed by 5.1 % of laparoscopic and 16.6 % of open patients; the overall RR was 0.34 (95 % CI 0.24 to 0.49, $p < 0.001$) (Fig. 12), with no subgroup differences (RR 0.30 vs. 0.40, $p = 0.451$) and moderate heterogeneity (I^2 28.9 %).

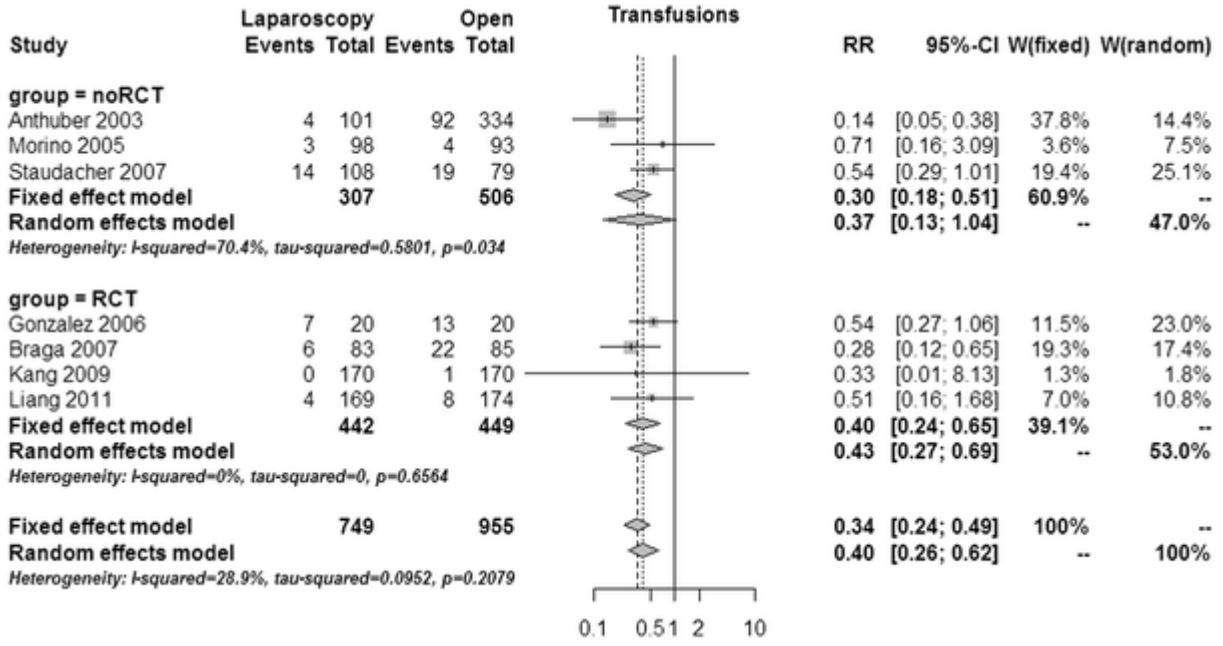

Fig. 12

Forest plot for incidence of blood transfusion. RR relative risk, 95 % CI confidence interval, W weight of the single study

Abscesses were observed in 2.7 % of patients in the laparoscopic group and 1.8 % of patients in the open group; the overall RR was 1.04 (95 % CI 0.66–1.63, $p = 0.862$) (Fig. 13), with no subgroup differences (RR 1.01 vs. 1.05, $p = 0.943$).

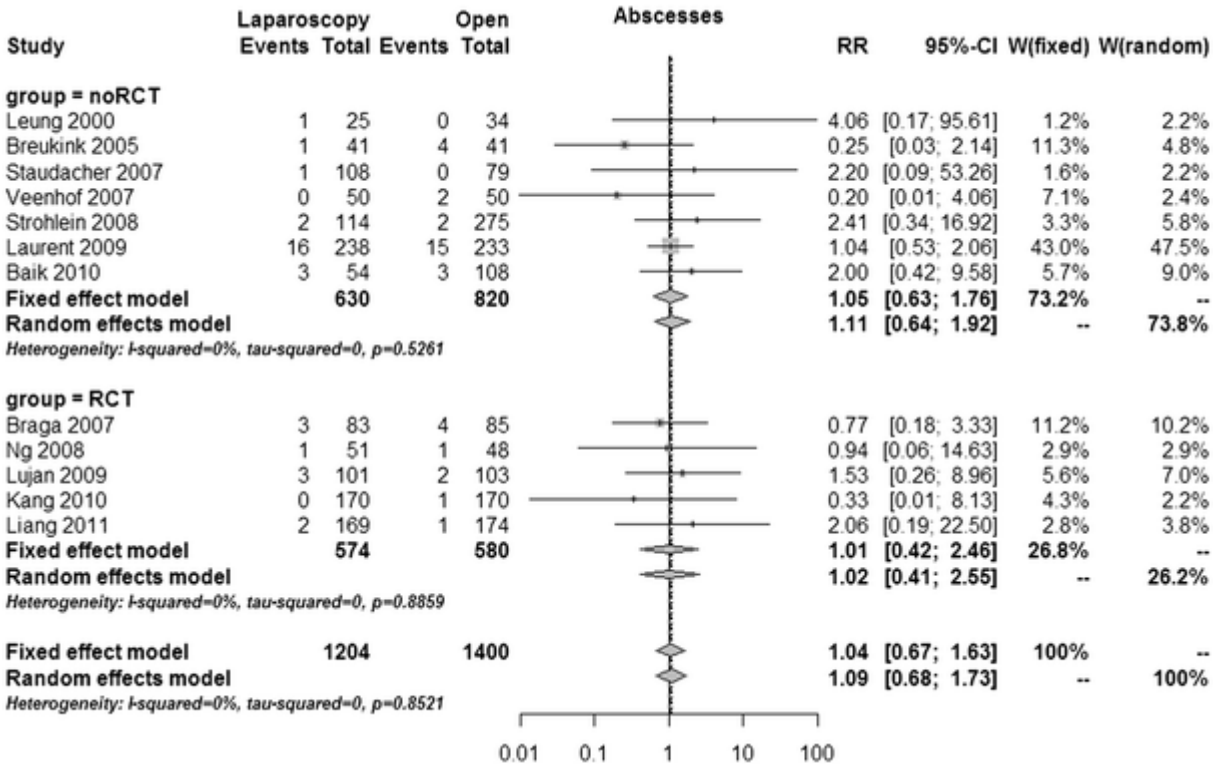

Fig. 13

Forest plot for incidence of abdominal abscesses. RR relative risk, 95 % CI confidence interval, W weight of the single study

On the other hand, wound complications were reported for 5.9 % laparoscopic patients and 8.1 % open patients; the overall RR was 0.66 (95 % CI 0.52–0.83, $p < 0.001$) (Fig. 14), with no subgroup differences (RR 0.58 vs. 0.74, $p = 0.285$).

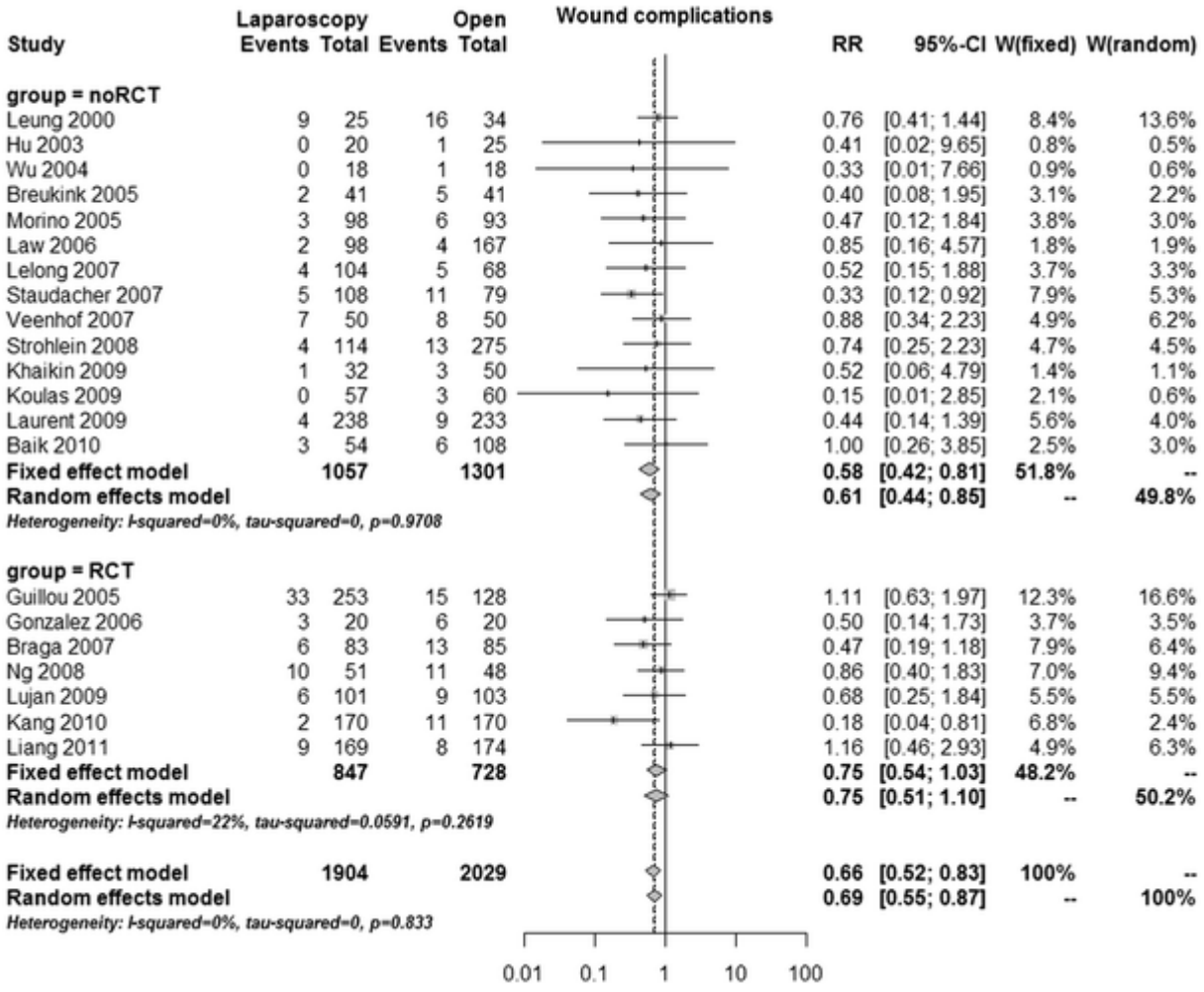

Fig. 14

Forest plot for incidence of wound complications. RR relative risk, 95 % CI confidence interval, W weight of the single study

Incidence of anastomotic leakage occurred in 7.6 % laparoscopic patients and 8.9 % open patients. The overall RR was 0.83 (95 % CI 0.65–1.06, p = 0.128) (Fig. 15), without differences between RCTs and prospective trials (RR 0.92 vs. 0.79, p = 0.556).

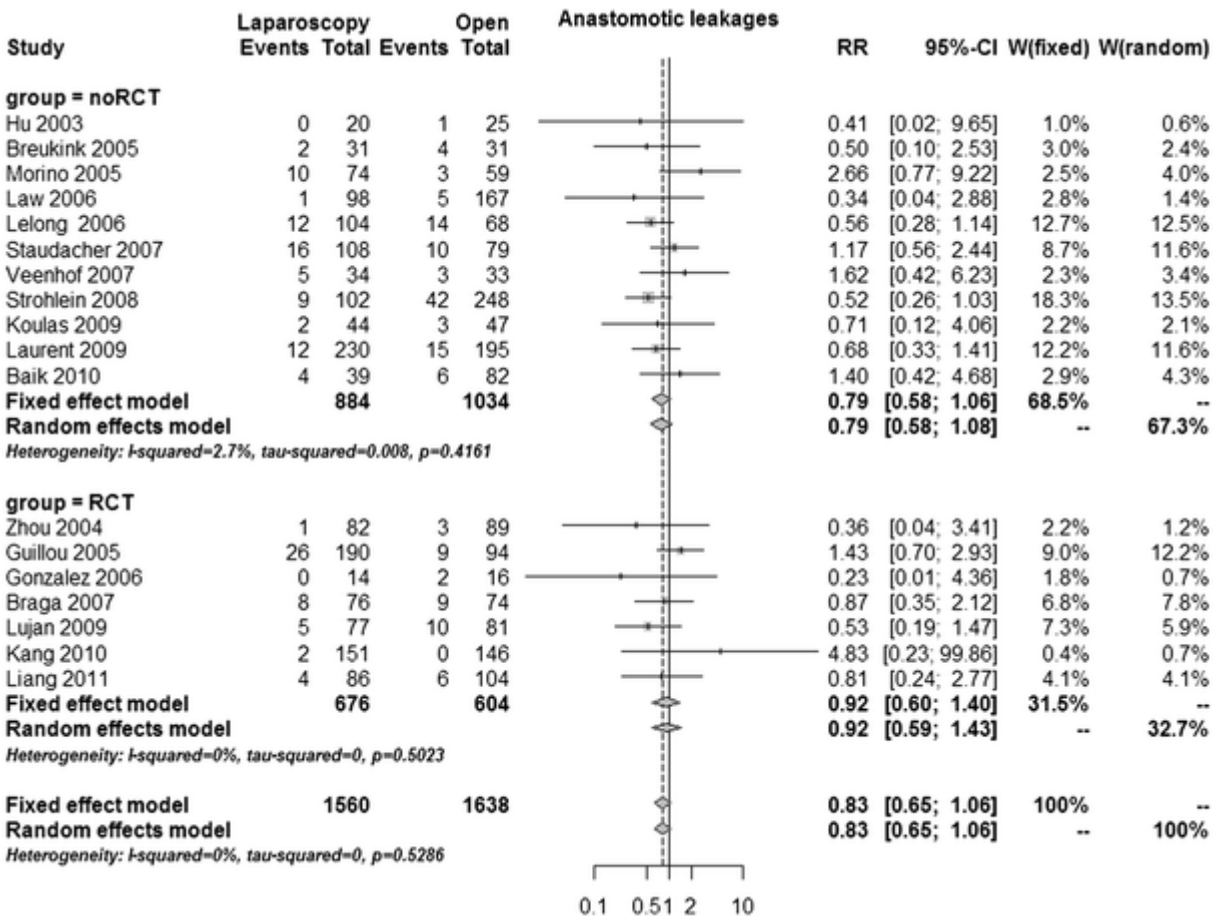

Fig. 15

Forest plot for incidence of anastomotic leakage. RR relative risk, 95 % CI confidence interval, W weight of the single study

The ratio of patients who needed a surgical reintervention within the first 30 postoperative days was 6.3 % for laparoscopic cases and 7.4 % for open cases; the overall RR was 0.84 (95 % CI 0.57–1.22, p = 0.357) (Fig. 16), again without RCT versus prospective trial differences (RR 0.72 vs. 0.89, p = 0.617).

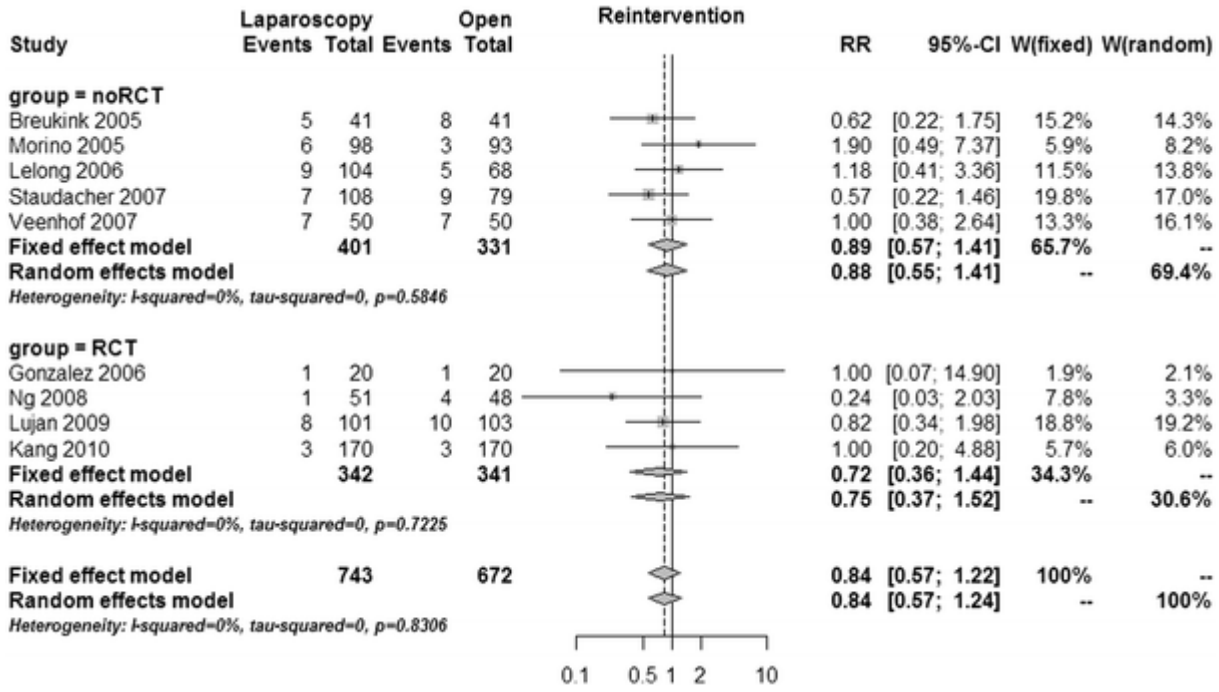

Fig. 16

Forest plot for incidence of reintervention. RR relative risk, 95 % CI confidence interval, W weight of the single study

The mean duration for hospital stay was 10.8 days in the laparoscopic group and 13.5 days for the open surgery group; the overall MD was −2.7 days (95 % CI −3.6 to −1.7, $p < 0.001$) (Fig. 17), with no differences in the subgroup analysis (MD −3.5 vs. −2.4, $p = 0.320$), and again with very high heterogeneity (I^2 77.4 %).

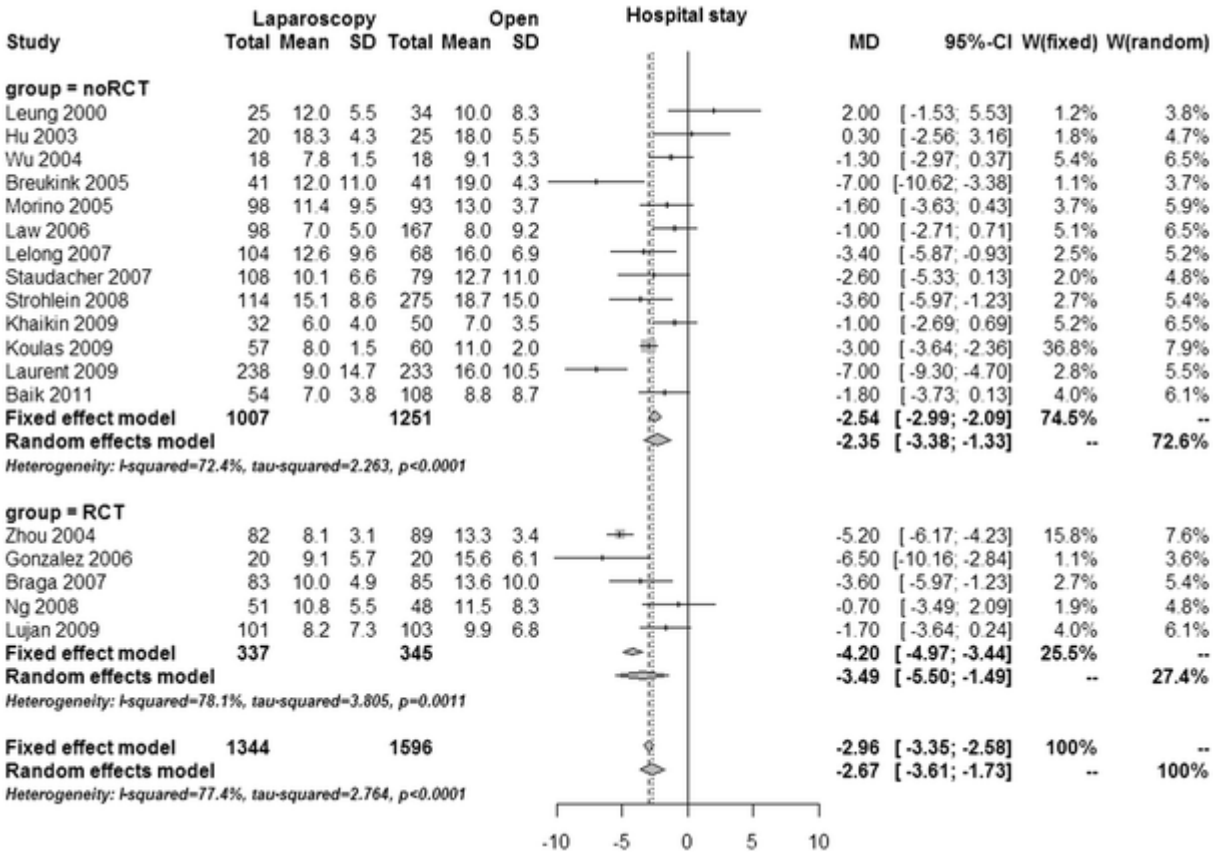

Fig. 17

Forest plot for length of hospital stay. MD mean difference, 95 % CI confidence interval, W weight of the single study

Discussion

Almost 20 years after the first report of laparoscopic colorectal surgery [39], laparoscopy has diffused widely to many fields, but its use in the treatment of colorectal diseases is still debated. Especially in the field of rectal surgery, where TME and systematic lymphadenectomy are considered the main step of curative therapy for rectal cancer [5], until now, available data have not permitted us to come to any reliable conclusions. Although long-term survival studies are awaited to focus on the oncologic adequacy of laparoscopic treatment of rectal cancer, a short-term analysis of safety can be performed on existing data.

Since 2000, a total of 23 studies [2,17-38] have been published comparing laparoscopic and open rectal resection in terms of safety. Although a meta-analysis of only RCTs would be ideal, we thought it wiser to extend the inclusion criteria to prospective nonrandomized matched series in order to increase the data to analyze while maintaining an acceptable level of evidence, as confirmed by risk of bias analysis and heterogeneity test. An analysis

of subgroups to verify the reliability of the RCT-only analysis was performed anyway. Because of these restrictions in the selections of articles, heterogeneity of results was kept reasonable, even though some of the study samples included in this analysis were relatively small and none of the included studies had made an estimate of what sample size was needed to detect differences between laparoscopic and open surgery on the basis of a well-defined primary outcome. The sensitivity analyses reveal that no study played an influential role on RR in the whole time frame studied, and that heterogeneity was reduced when including only articles published after 2005. This methodology has led to a more strict selection than the last Cochrane Review published on the topic [40], in which, as a result of lack of data, case series and case reports were also included, thus worsening reliability.

Although the initial purpose was to restrict our analysis to TME and other abdominal resections with primary anastomosis for rectal cancer, the analysis of data present in literature showed a majority of reports including abdominoperineal resections. Because it was not possible to separate data between the two groups, we decided to extend the analysis to both treatments and redesigned the study protocol accordingly, after verifying that the procedure was equally represented, with no selection bias in both groups in each of the studies. This way, we also included two reports entirely focusing on abdominoperineal resections [29,36]. We conducted two separate analyses, one including and one excluding these reports, only to find that the results substantially overlapped, so we opted to include them into the analysis. Finally, we verified, when available, that the tumor location and stage of cancer disease, neoadjuvant chemoradiotherapy, and protective ileostomy rates were comparable in the global analysis.

The main finding of the present meta-analysis was that the incidence of mortality showed a significant reduction in the laparoscopic group compared to open surgery. Furthermore, the overall incidence of postoperative complications was also significantly lower in the laparoscopic group, with a RR of 0.81. The analysis of all included studies showed a clear advantage for laparoscopy in the specific analysis of both surgical and medical complications. This was confirmed by the analysis of prospective controlled clinical trials, while the analysis of RCTs showed a significant advantage only for surgical complications. The most probable explanation of the lack of statistical significance in some of the analyses performed on RCT studies only is the insufficient number of patients randomized, which is about one third of the total number of patients compared. A further possible explanation might be the inclusion of the UK MRC CLASICC trial [2]. This has already

been recently argued by other authors [41], who have underlined that even though this is the only multicenter RCT published on rectal cancer, the results are probably influenced by the surgeons' short learning curve before entering the study. In fact, all the participating surgeons were required to have completed only 20 laparoscopic colorectal resections before entering the study. This could explain why in the initial phase the conversion rate was as high as 45 %, which declined to 15 % in the last year of the study. Different figures were reported when high-volume centers or single experience of highly trained and experienced colorectal surgeons were considered [20,24,37,42]. In fact, among all the studies analyzed, the CLASICC trial showed a clear discrepancy of results compared to the rest of the studies, although without affecting heterogeneity. Thus, the way in which these results will ultimately translate into common daily clinical practice remains unclear.

Another important finding of the present analysis was that no statistically significant difference in anastomotic leakage rate was observed. This represents an original finding, as the concern for a possible increase in anastomotic leakage in the laparoscopic group had risen in the past years. The high incidence of leakage was explained with the difficult access of laparoscopic linear staplers to the distal rectum in a narrow pelvis, the oblique transection from right to left or from anterior to posterior depending on the trocar of insertion for the stapler, and the difficulty of cephalad traction on the rectum. In recent years, the advent of new technologies, such as ultrasonic scalpel and articulated stapler, and better surgical experience resulted in a progressive optimization of the technique that most probably is reflected in the equivalence of leakage rates and the lower incidence of surgical complications with the laparoscopic approach.

Laparoscopy also confirmed, as it has already been demonstrated in the treatment of colon cancer [1-4], a clear advantage in terms of an earlier bowel activity restoration, time to oral intake, and duration of postoperative hospital stay, whereas the only clear disadvantages was the relatively longer operative time.

Further analyses would have been of extreme interest, such as sexual and urinary dysfunction, postoperative quality of life, and R0 achievement, but the lack of sufficient data on these topics did not permit us to analyze these factors further.

Nevertheless, the data analyzed in this meta-analysis suggest that laparoscopy has different clinical advantages in the perioperative period of rectal cancer surgery, in line with the well-described results of laparoscopic colon surgery [43]. Nevertheless, these results should be interpreted cautiously because our analysis has several limitations. First, most of the studies published were of relatively low quality according to acknowledged scientific

criteria such as the Cochrane collaboration's tool for assessing risk of bias scale and the Newcastle–Ottawa scale. Second, most of the studies did not have short-term complications as a primary outcome. Finally, scarce data regarding preoperative stage, patient selection, and neoadjuvant therapy were reported in the majority of the studies, so that a vast heterogeneity can be imagined among overall analyzed patients.

Good-quality RCTs comparing short-term outcome of laparoscopic TME are greatly needed. Although we have seen the results of the 5-year follow-up of the CLASICC trial [44], which confirms the oncological safety of laparoscopic surgery for both colonic and rectal cancer, we will be awaiting the long-term oncological outcome of the COLOR II trial to reassert this statement [9].

Notwithstanding the above-mentioned limitations, we can conclude that on the basis of evidence of both randomized and prospective matched series, laparoscopic rectal resection appears to have clinically measurable short-term advantages in patients with primary resectable rectal cancer. Although technically demanding, laparoscopic rectal resection is safe and results in faster recovery.

Disclosures

Drs. Arezzo, Passera, Scozzari, Verra, and Morino have no conflicts of interest or financial ties to disclose.

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