Robotic Versus Laparoscopic Minimally Invasive Surgery for Rectal Cancer

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Objective: The aim of this study was to evaluate the safety and efficacy of elective rectal resection for rectal cancer in adults by robotic surgery compared with conventional laparoscopic surgery.

Summary of Background Data: Technological advantages of robotic surgery favor precise dissection in narrow spaces. However, the evidence base driving recommendations for the use of robotic surgery in rectal cancer primarily hinges on observational data.

Methods: We searched MEDLINE, Embase, and CENTRAL for randomized controlled trials (until August 2016) comparing robotic surgery versus conventional laparoscopic surgery. Data on the following endpoints were evaluated: circumferential margin status, mesorectal grade, number of lymph nodes harvested, rate of conversion to open surgery, postoperative complications, and operative time. Data were summarized as relative risks (RR) or weighted mean differences (WMDs) with 95% confidence intervals (95% CIs). Risk of bias of studies was assessed with standard methods.

Results: Five trials were eligible, including 334 robotic and 337 laparoscopic surgery cases. Meta-analysis showed that RS was associated with lower conversion rate (7.3%; 4 studies, 544 participants, RR 0.58; 95% CI 0.35–0.97, $P = 0.04$, $I^2 = 0\%$) and longer operating time (MD 38.43 minutes, 95% CI 31.84–45.01: $P < 0.00001$) compared with laparoscopic surgery. Perioperative mortality, rate of circumferential margin involvement (2 studies, 489 participants, RR 0.82, 95% CI 0.39–1.73), and lymph nodes collected (mean 17.4 Lymph Nodes; 5 trials, 674 patients, MD −0.35, 95% CI −1.83 to 1.12) were similar. The quality of the evidence was moderate for most outcomes.

Conclusion: Evidence of moderate quality supports that robotic surgery for rectal cancer produces similar perioperative outcomes of oncologic procedure adequacy to conventional laparoscopic surgery. Robotic surgery portraits lower rate of conversion to open surgery, while operating time is significantly longer than by laparoscopic approach.

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BACKGROUND

Colorectal cancer is the third most common cancer in men and the second in women in developed countries,[1] with rectal cancer accounting for 28% to 35% of the total colorectal cancer incidence.[2]

The mainstay of treatment is radical resection by sphincter-preserving proctectomy [anterior resection (AR), low anterior resection (LAR), intersphincteric resection (ISR)] or abdominoperineal resection (APR).[2] Laparoscopic rectal resection (LS) is currently offered as the standard of surgical care.[3] LS has been credited with reducing surgical insult that could favor tumor progression and facilitating early postoperative recovery without compromising oncological outcomes,[4,5] an effect that might expedite the administration of chemotherapy and radiation therapy in advanced-stage cases.[6] Pathological analysis of surgical specimen has also supported that LS facilitates high-quality rectal cancer resection.[7,8]

However, laparoscopic pelvic dissection for rectal cancer is technically demanding with a very low margin for error.[9] The technical difficulties associated with laparoscopic proctectomy have been reflected by a higher conversion rate to open surgery and an increased rate of postoperative male sexual dysfunction.[4]

Conventional laparoscopic rectal surgery (LS) has been attributed limited dexterity with nonarticulating unstable instruments, unnatural hand-eye coordination, and flat 2-dimensional (2D) vision.[10]

"Robotic" or "robotic-assisted" laparoscopic surgery (RS) aims at eliminating many of the technical difficulties inherent to LS[11] by alleviating some of the manoeuvrability and visibility challenges that surgeons face in confined spaces as the pelvis, with an easier identification of the inferior hypogastric plexus, ureter, and gonadal vessels.[12,13]

Over the years, the use of RS has increased,[14] and patients appear to like it and request better access to it.[15] However, many of the perceptions of patients, caregivers, and administrators, that RS offers lower rate of complications and greater precision, do not appear to be substantiated by the current clinical evidence.[16]

A number of descriptive and comparative studies have reported favorable outcomes for robotic rectal resections,[17–19] though the quality of technical and oncological results still remains controversial in large retrospective studies,[20] and significant postoperative complication rates have also been reported.[21]

Two recent systematic reviews examining robotic and laparoscopic LAR for rectal cancer admitted intrinsic limitations for including studies of mixed design,[22,23] while the most recent literature search was completed over a year ago.[24]

We evaluate the safety and efficacy of elective rectal resection for the surgical treatment of rectal cancer in adults by robotic surgery (RS) compared with conventional laparoscopic surgery (LS), by short-term clinical, pathological, functional, and quality-of-life outcomes, based on the evidence from randomized clinical trials only.

METHODS

This review complies with the recommendations of the Cochrane Handbook for Systematic Reviews and Interventions,[25] is reported in line with the PRISMA statement,[26] and is AMSTAR[27] compliant. A protocol was developed a priori and published on PROSPERO: CRD42016046746.

We searched the following databases:

(1) Cochrane Central Register of Controlled Trials (CENTRAL) (from January 1950);
(2) MEDLINE (from January 1980);
(3) EMBASE (from January 1990).

We used medical subject headings (MeSH) and free-text words. The search strategy (appendix 1, http://links.lww.com/SLA/B328) was developed with a professional trial search coordinator to address the following research question:

(1) (Patients) adults with primary rectal cancer;
(2) (Intervention) robotic rectal resection;
(3) (Comparator interventions) laparoscopic rectal resection;
(4) (Outcomes) indicators of completeness of resection, conversion to open surgery, intra- and perioperative complications, functional outcomes, overall and disease-free survival (DFS), and quality of life;
(5) (Methods-Study design) randomized controlled trials (RCTs).

There was no restriction on language or publication status. The reference lists of all retrieved and relevant publications identified were searched for further studies.

We also searched the following databases for ongoing studies, scientific literature, conference proceedings, and abstracts: ClinicalTrials.gov, Current Controlled Trials, The WHO Clinical Trials Search Portal, ISRCTN registry, UMIN Clinical Trial Registry, EU Clinical Trials Register, CRSA (Clinical Robotics Surgical Association). Grey literature databases were examined: Grey Literature Report, OpenGrey, PubliCat, and ScienceDaily.com. Google Scholar was explored and a comprehensive search of the Conference Proceedings Citation Index (CPCI) was also carried out. Open access theses and dissertations were retrieved from the ProQuest Dissertation Thesis Database and thesis.com. The Science Citation Index (SCI) was used to scan and track study titles. The last search was done on August 11, 2016.

Selection of Studies

Selection of relevant articles was performed in stages. Two independent reviewers (FPP, RM) screened the articles retrieved from the initial literature search. Duplicate studies were removed and studies considered irrelevant were discarded. Two reviewers (FPP, FP) further reviewed independently the eligibility of studies in an abstract form, or if appropriate, in full text, by assessing if the inclusion criteria and outcome measures were met.

Each author decided on trial inclusion using predetermined eligibility criteria:

(1) RCTs;
(2) Comparison between elective robotic-assisted or totally RS and conventional laparoscopic or laparoscopic-assisted surgery (LS) for resection of rectal cancer: AR, LAR, ISR, Hartmann resection, or APR, with partial mesorectal excision (PME) or total mesorectal excision (TME).
(3) Adult participants (>18 years of age) diagnosed with rectal adenocarcinoma (0 to 15 cm from the anal verge[28]), with an indication to elective rectal resection. Melanomas, sarcomas, and nonadenocarcinomas were excluded, as treated differently.
(4) Studies including colorectal cancer were eligible only if outcomes for rectal carcinoma only could be obtained.

We extracted data on the following outcomes in all included studies:

(1) Primary outcomes
- Macroscopic mesorectal grade (rate of macroscopically intact mesorectal sheath at the end of TME)(intact/nonintact mesorectum);
- Rate of positive circumferential resection margin (CRM, yes/no);
- Number of harvested lymph nodes;
- Conversion rate to open surgery or LS (yes/no);
- Incidence of anastomosis leakage (yes/no);
- Incidence of peri-operative mortality (within 30 days of operation) (yes/no);
- Perioperative complications (yes/no);
- Estimated blood loss (EBL, mean, mL).

(2) Secondary outcomes
- Overall survival (OS, months);
- DFS (relapse-free survival and local recurrence-free survival) (months);
- Incidence of nerve injury leading to possible urinary and sexual dysfunction (yes/no);
- Overall operation time (mean, min.);
- Instrument set-up time (mean, min.);
- Day to return of normal bowel function (mean, days);
- Duration of hospital stay (mean, days);
- Quality of life up to 1 year postoperation (as measured with validated questionnaires);
- Economic cost of hospital stay per surgical modality (US dollars).

At each stage, reasons for excluding studies were documented. Disagreement regarding article selection was resolved by discussion and consensus or by consulting a third member of the review team (GFMS). All identified studies were saved in an EndNote database.[29]

A custom data form (Appendix 2, http://links.lww.com/SLA/B328), pilot-tested on 10 random studies and approved by agreement between 2 data abstractors (FPP and FP), was independently used to extract data. Data were recorded onto 2 Microsoft Excel databases (Version 2010-Windows) that were then compared and any disagreements were reconciled.

Non-English articles were translated before data extraction. In case of publications with partially overlapping data from the same Author/Institution, that of higher methodological quality was included.

Two researchers (FPP and RM) independently assessed the eligible studies for bias according to the Cochrane Collaboration tool for assessing risk of bias.[30]

Seven distinct domains were identified and evaluated as "Low risk of bias" or "High risk of bias" or "Unclear": sequence generation,

allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential threats to validity.

Disagreement regarding data extraction and quality assessment between reviewers was resolved by consensus or consultation with a third party (GFMS).

Measures of Treatment Effect

For dichotomous outcomes, we extracted the number of patients who experienced the outcome of interest in each group and the number of patients assessed at endpoint, in order to estimate a relative risk (RR) and its 95% confidence interval (95% CI).

For continuous outcomes, we extracted the final value and standard deviation of the outcome of interest and the number of patients assessed at the endpoint in each treatment arm. Then, where appropriate, a pooled estimate of treatment effect was calculated by the mean difference (MD) and 95% CI.

For trials with missing data or in case of doubt, we contacted the study authors to request data or information, to ensure accuracy. We contacted 5 Authors: 3 of them responded, and 2 provided numerical data for subsets of eligible participants to trials.

Statistical Analysis

All end-points were qualitatively summarized. Where clinically similar studies were available, we pooled their results in meta-analyses by using review manager (Revman version 5.3; Nordic Cochrane Center, Cochrane Collaboration, 2011).

For dichotomous data (eg, incidence of complications), we used both a fixed and random effects model to calculate a pooled RR.

For continuous data (eg, mean operating time), we used both a fixed and random effects model to calculate a weighted MD (WMD). In case of continuous data presented as median and range, we estimated the mean and standard deviation according to the method described by Higgins.[25,31]

Heterogeneity was investigated by the use of X^2 test and I^2 statistics. For I^2 of between 0% and 30%, heterogeneity was considered as probably not important, between 30% and 60% moderate, between 50% and 90% (or if the P value of X^2 was <0.10) substantial, and between 75% and 100% considerable.[32] If heterogeneity existed (>30%), we analyzed data using a random effects model. If heterogeneity was not important, a fixed effects model was used. $P < 0.05$ was considered statistically significant. Missing standard deviations were reconstructed from other statistics, such as P values. Possible reasons for substantial heterogeneity were investigated and reported.

We attempted subgroup analysis considering factors such as sex, age, comorbidities, stage, neoadjuvant therapy, and type of procedure (where sufficient information was available).

Sensitivity analysis was performed by excluding studies of the lowest quality, to explore the degree to which the main findings were affected by the data from individual studies. Only studies that were assessed as having a low risk of bias in all key domains (adequate random sequence generation, allocation concealment, and blinding of outcome assessor) entered sensitivity analysis.

Risk of bias was assessed by standard methods and confidence in the evidence assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE),[33] starting at high quality and downgrading for risk of bias, imprecision, inconsistency, indirectness, and publication bias.

We rated the quality of the evidence for the following main outcomes:

(1) CRM positivity;
(2) Mesorectal grade;
(3) Lymph nodes retrieved;
(4) Conversion rate;
(5) 30-day morbidity;
(6) 30-day mortality;
(7) Operating time.

RESULTS

Literature Search

The results of our literature searching are presented in Fig. 1. After exclusion of duplicates, we screened 2251 references and identified 20 eligible references; from these 20, we identified 6 references for 5 published clinical trials.

A large randomized clinical trial[34] published short-term data as conference proceedings,[35] accounting for 2 references. The remaining 4 single-center clinical trials have 1 reference each.[36–39]

In 1 trial,[37] randomization was interrupted during the study and surgical procedures were assigned according to surgeon's preference thereafter; Authors provided complete data and methodological information on the randomized portion of the study, to which we will refer from now on.

Of another study including colon and rectal cancer patients,[38] Authors provided complete data on the subset of patients with rectal cancer, to which we will now refer.

Characteristics of Interventions and Populations in the Included Studies

The included studies involve 681 patients (range 12 to 471 per trial) from 12 countries (Australia, China, Denmark, Finland, France, Germany, Korea, Italy, Singapore, Spain, the UK, and the US). Similar exclusion criteria across studies were T4 rectal cancer and metastatic disease (with the exception of Patriti et al[37]) and no consent (Table 1).

The majority of single-center trials described the surgical technique of rectal resection,[36–39] defining both PME and TME—where performed—and used a hybrid approach.[36–38] The ROLARR study included hybrid or totally robotic procedures, depending on the trial site.[35] The outcomes reported by the included studies are summarized in Table 2.

Excluded Studies

Seven ongoing randomized clinical trials were excluded as either still recruiting patients[40–45] or not recruiting yet.[46]

Seven published trials were excluded, all by study design[19,36,47–52] (Fig. 1).

Risk of Bias

We assessed the risk of bias and quality of the evidence of the ROLARR trial (published as conference proceedings) as in a fully published study: sufficient methodological details were available from the published protocol[53] and Authors (contacted) confirmed that no deviations from the protocol had occurred in the conduct of the study.

Of the included trials, none had a low risk of bias on all items, while 2 scored low on 6 out of 7 domains. Three trials were of unclear or low quality, with a high or unclear risk in at least 1 of 7 domains (Fig. 2).

Allocation

The method of randomization was clarified in all trials. In studies by Patriti et al[37] and Jimenez Rodriguez et al,[38] allocation concealment was explained by contacting Authors. Only 2 trials[36,38] presented an adequate inclusion and randomization flow diagram,

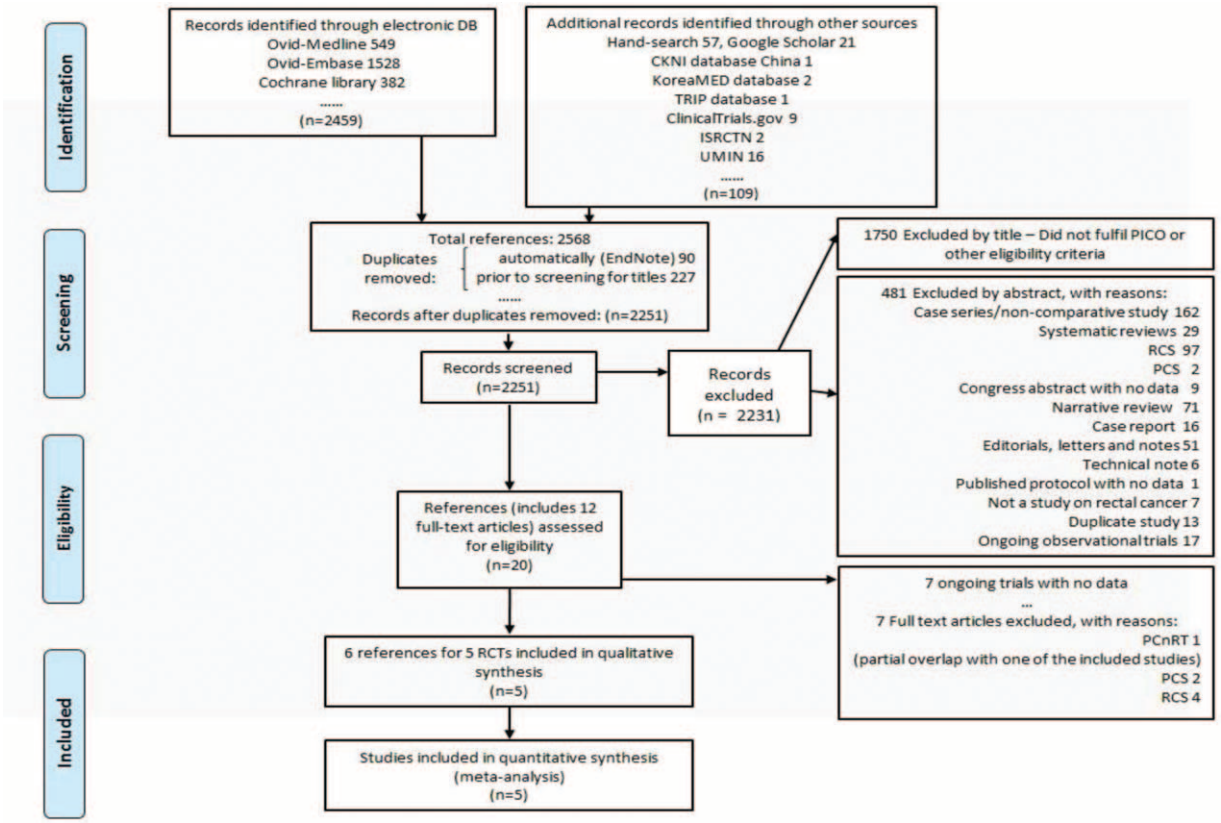

FIGURE 1. PRISMA flow chart of studies selection.

including a description of the loss to follow-up. All trials described reasons for patient inclusion.

Blinding

Because surgeons cannot be blinded to the type of surgery performed, we assessed whether operative technique and postoperative care were standardized, and how outcome data and pathological data were recorded.[54] Standardization of operative technique, postoperative protocols, and criteria for discharge was adequate in all 4 single-center trials and unclear in the multicenter trial (Appendix 3, http://links.lww.com/SLA/B328).

All single-center trials provided published details of postoperative care including feeding policy[36] or enhanced recovery protocol[39,55] or used a local standardized perioperative (Authors contacted).[37,38] In the ROLARR trial, perioperative care depended on each participating Institution protocol.

Criteria for discharge, described in the article[36–38] or in previous publications,[55] were similar across studies (recovery of bowel function, tolerance to oral diet, adequate analgesia, no surgical complication, ambulation, and acceptance of discharge).

As blinding of outcome assessors is possible for pathological and quality of life outcomes, we considered all clinical outcomes other than mortality (hospital stay, postoperative recovery outcomes, adverse events) to be at an unclear or a high risk of bias, respectively, if information available was insufficient for judgment or there was lack of blinding of personnel/outcome assessors.

Selective Reporting

In 4 studies, we found no evidence of selective reporting[35–38]; 1 study did not report exact data on statistically significant results.[39]

Other Potential Sources of Bias

All surgical teams appeared experienced in both LS and RS. In single-center trials, surgeons' experience was stated or previously published. The ROLARR[35] defined the surgical experience necessary for surgeons to participate (Appendix 3, http://links.lww.com/SLA/B328).

Primary Outcomes

Mesorectal Grade

The macroscopic grade of completeness of mesorectal excision after TME was reported in 2 trials, 505 participants. There was no significant difference in the rate of incomplete mesorectal sheath for RS compared with LS (RR 0.92; 95% CI 0.68–1.25; $P = 0.60$) with no heterogeneity ($I^2 = 10\%$). The quality of evidence was moderate (Fig. 3A, Table 3A).

Rate of Positive Circumferential Resection Margin

There was no significant difference in the risk of circumferential margin involvement in RS (2 studies, 489 participants, RR 0.82, 95% CI 0.39–1.73). Moderate quality of evidence supported the summary estimate (Fig. 3B, Table 3A).

TABLE 1. Characteristics of the Included Studies

			Participants												Interventions					
			Male Sex		Age (Mean y)			TNM Stage (II:III)		ASA I-II/III		Neoadiuv. Treatment		AR/LAR/APR (%)		Causes of Conversion			
Ref.	Study Size Total n. (RS)	Inclusion Criteria	RS	LS	RS	LS	Rectal Cancer Definition (cm from Anal Verge	RS	LS	RS	LS	RS	LS	RS	LS	RS	LS	Procedure - Robotic Technique	Follow-up, mo
Baik et al[36]	36 (18)	Rectal cancer -(colonoscopy CT/MRI) -consent	14	14	57.3±6.3	62.0±9.0	0-15	4:9	4:9	18/0	15/1	—	—	Unkn/ Unkn/0	Unkn/ Unkn/0	No conv	Hemorrhage, difficult pelvic dissect.	AR, LAR - Hybrid	1
Jimenez Rodriguez et al[38]	56 (28)	Sigmoid or rectal cancer	12	17	68 ± 9.1	65.5 ± 15.0	Sigmoid and rectal	—	—	14/14	20/8	—	—	—	—	Obesity, advanced cancer	Difficult pelvic dissect., advanced cancer	AR, LAR, APR - Hybrid	1
	12* (6*)		4*	2*	63 ± 5.9*	56.2 ± 16.5*	0-15	2:2	0:1	3/1	3/2	—	—	83/17/0	50/17/33				
Patriti et al[37]	66 (29)	Rectal cancer -any tumor size -resectable liver M1	18	25	68 ± 10	69 ± 10.0	0-15	9:7	8:10	16/21	15/14	7	2	—	—	(No conv)	—	AR, LAR, APR - Hybrid	24
	30‡ (13‡)		10‡	9‡	71 ± 8.8‡	71.6 ± 9.7‡		6:5‡	5:6‡	6/7‡	5/12‡	5	0	8/77/15	35/47/18				32.5
ROLARR[35]	471† (237)	Solitary rectal cancer -AR/LAR/APR -M0 on imaging -≥18 years -ASA ≤ 3 -fit for RS or LS - question sheet at consent	161	159	—	—	0-15	146: 88	150: 79	—	—	109	103	12/65/22	8/72/20	Hemorrhage, difficult pelvic dissect., advanced cancer	Hemorrhage, difficult pelvic dissect., advanced cancer, obesity	AR, LAR, APR - Hybrid + Totally robotic	1
Wang et al[39]	137 (71)	Rectal cancer	71	66	60.3 ± 8	58.7 ± 8.7	0-12	22:40	24: 34	—	—	13	11	97	96	-	-	LAR - Unknown	12

Light grey data rows: data as originally published (Jimenez Rodriguez et al[38]: colon and rectal cancers; Patriti et al[37]: study with both randomized and nonrandomized components).
APR indicates abdominoperineal resection; AR, anterior resection; LAR, low anterior resection.
*Data from the rectal cancer subset of the published study.
†RS: 93 pts normal/underweight, 90 overweight, 54 obese; LS 87 pts normal/underweight, 92 overweight, 55 obese.
‡Data from the randomized component of the published study.

TABLE 2. Outcomes Reported by the Included Studies, by Endpoints of This Review

	Primary Outcomes														Secondary Outcomes									
	Operative			Postoperative Complications					Pathological					Operative		Postoperative Clinical		Oncological		Functional/ Quality of Life			
Study ID	Conversion to Open Surgery	Estimated Blood Loss	Anastomotic Leakage	Bleeding	Wound Infection	Gastrointestinal	Respiratory	Urinary	Other	All	Mesorectal Grade	Circumferential Resection Margin	Lymph Nodes	Operating Time	Instruments Setup Time	Recovery of Bowel Function	Length of Stay	Overall Survival	Disease -free Survival	Urinary Dysfunction	Sexual Dysfunction	Cost	30-day Mortality
Baik et al[36]	•	*		•					•	•	•		•	•		•	•						•	•
Patriti et al[37]	•	•	•		•		•	•	•	•		•	•	•			•	•			•		•	•
Jimenez et al[38]	•			•		•				•			•	•	†	•	•		‡	‡	‡	‡	•	•
ROLARR[35]	•				•	•	•	•		•	•	•	•	•										
Wang et al[39]				•	•	•	•	•		•			•	•		•				‡	•		•	•

•Extracted from study.
Blank: Not recorded or not occurred.
*Difference between preoperative and postoperative Hb.
†Total theatre time (contains anaesthesia/emergence time).
‡Ongoing study, long-term endpoints.

Harvested Lymph Nodes

There was no significant difference for the mean number of lymph nodes harvested in RS (5 trials, 674 patients, MD −0.35, 95% CI −1.83 to 1.12, $I^2 = 0$). The quality of evidence was moderate (Fig. 3C, Table 3B).

Conversion Rate to Open Surgery or Laparoscopic Surgery

There was significant difference in the RR of intraoperative conversion to open surgery, the risk being lower in RS than LS (4 studies, 544 participants, RR 0.58; 95% CI 0.35–0.97; $P = 0.04$, $I^2 = 0\%$). The quality of evidence was moderate (Fig. 3D, Table 3A).

Sensitivity analysis by removing the study of lowest quality[38] did not modify results (RR 0.57; 95% CI 0.34–0.97; $P = 0.04$, $I^2 = 0\%$). Subgroup analysis showed a significantly lower risk of conversion rate in men undergoing robotic proctectomy (Fig. 3E).

Incidence of Anastomosis Leakage

The rate of anastomotic leakage was reported by 3 studies, 174 participants. There was no significant difference in the risk of leakage in RS (RR 1.26; 95% CI 0.39–4.10; $P = 0.70$, $I^2 = 0\%$) (Fig. 3F).

Incidence of Perioperative Mortality (Within 30 Days of Operation)

All studies reported on perioperative mortality, 681 patients. With 2 perioperative deaths in either arm of the ROLARR trial and none in the other trials, pooled overall mortality was similar, 0.58% for RS and 0.59% for LS; the quality of evidence was moderate (Fig. 4A, Table 3A).

Perioperative Complications (30-day Postoperative Morbidity)

The overall rate of perioperative complications (5 trials, 681 patients) was similar, 27.3% RS and 26.7% LS, with a similar rate of wound infections, urinary infection or retention, and respiratory complications. Quality of evidence was low (Fig. 4B–E, Table 3A).

Estimated Blood Loss

Four studies analyzed EBL, but definitions, measures, and reporting varied widely. Baik et al[36] used the perioperative variation of hemoglobin concentration, not significantly different between RS (0.6 ± 0.6 g/dL) and LS (0.8 ± 1.0 g/dL). Patriti et al[37] reported mean EBL 158.3 (±219.3) mL for RS and 162.5 (±197.4) mL for LS. No transfusions were required in studies by Jimenez Rodriguez et al[38] and Patriti et al.[37] Wang et al[39] only reported the overall range of EBL across both RS and LS procedures (20 to 1545 mL).

Secondary Outcomes

Overall Survival and Disease-free Survival

Only Patriti et al,[37] 30 participants, reported on OS and DFS. At a median FU of 32.5 (±14.6) months, OS was 100% and 94.1% in the RS and LS group, respectively, and DFS was 100% and 88.2%, respectively. There was no local recurrence in the RS group, while 1 patient was alive with local recurrence (5.8%) in the LS group 47.4 months from the operation.

Incidence of Nerve Injury Leading to Possible Urinary and Sexual Dysfunction

Two trials analyzed erectile dysfunction (ED), but at different follow-up intervals. In the study by Patriti et al[37] (9 patients), ED was 11.1% for RS versus 0 for LS at a median follow-up of 32.5 (±14.6) months. In the study by Wang et al,[39] 137 participants, 12 months

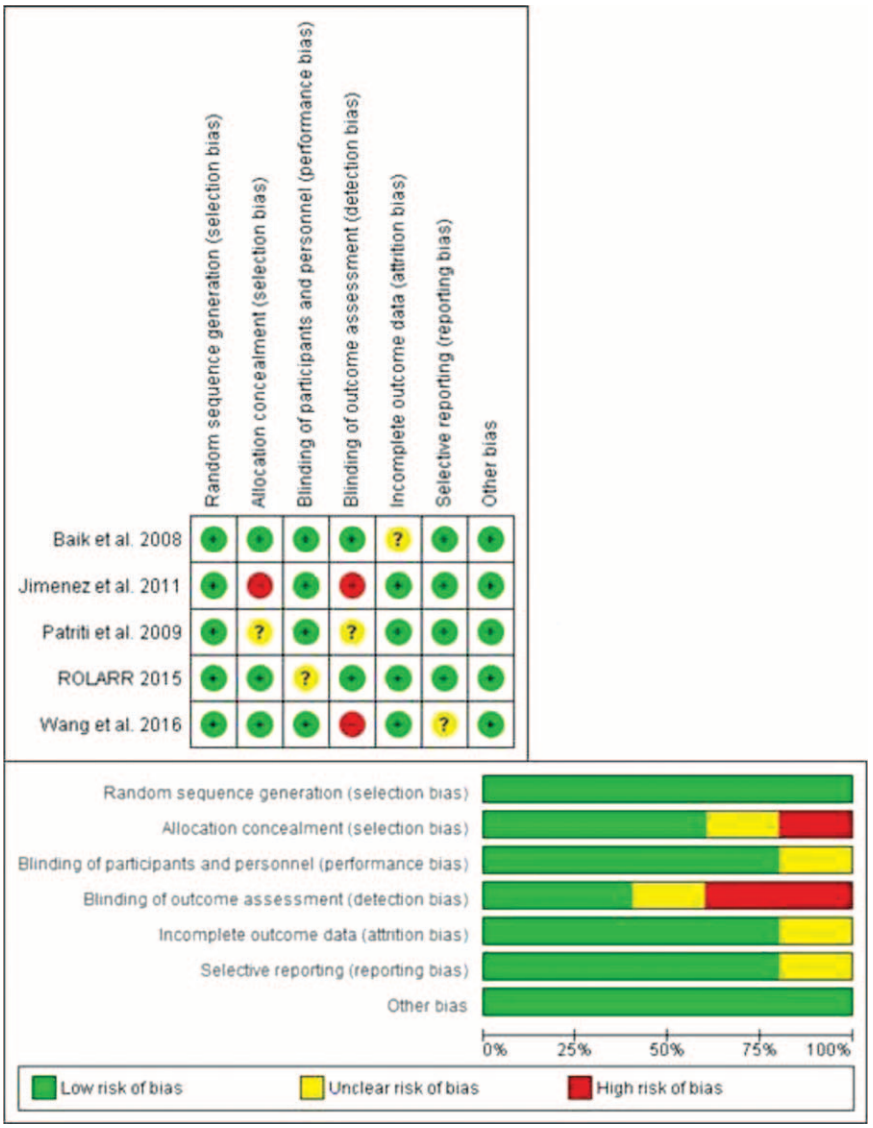

FIGURE 2. Risk of bias summary: review authors' judgment about each risk of bias item for each included study.

partial and complete ED was 37.3% (RS) and 62.7% (LS), while sexual dysfunction was less frequent in RS (18.3%) than in LS (34.8%).

Overall Operation Time

The duration of surgery was significantly longer in RS (all trials, 681 participants), with a pooled MD of 38 minutes to LS (MD 38.43; 95% CI 31.84–45.01: $P < 0.00001$, $I^2 = 4\%$). The quality of evidence was moderate (Fig. 4F, Table 3B).

Instrument Set-up Time

Only Jimenez Rodriguez et al[38] defined and measured instrument setup time, 96.6 (±15) minutes for RS and 91.7 (±27.1) minutes for LS.

Day to Return of Normal Bowel Function (RBF)

Time to return of bowel function (RBF) was given in 2 studies,[36,39] 173 participants, and showed an earlier RBF of about half a day for the RS group (MD −0.59; 95% CI −0.95 to −0.23; $P = 0.001$, $I^2 = 0$). Quality of evidence was very low (Fig. 4G, Table 3B).

Duration of Hospital Stay

Length of hospital stay, reported in 4 studies (522 participants), was similar between RS and LS (MD −0.61; 95% CI −2.23 to 1.02), with significant heterogeneity ($I^2 = 66\%$). The quality of evidence was low (Fig. 4H, Table 3B).

Quality of Life up to 1 Year Postoperation

Wang et al[39] analyzed urinary and sexual function by both telephone interview and questionnaires for International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) score at 12 months.

IPSS is a subjective scoring system measuring voiding function in 7 categories (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, nocturia score range 0 to 35); higher scores correspond to greater dysfunction (mild ≤7, moderate 8 to 19, severe 20 to 35).[56]

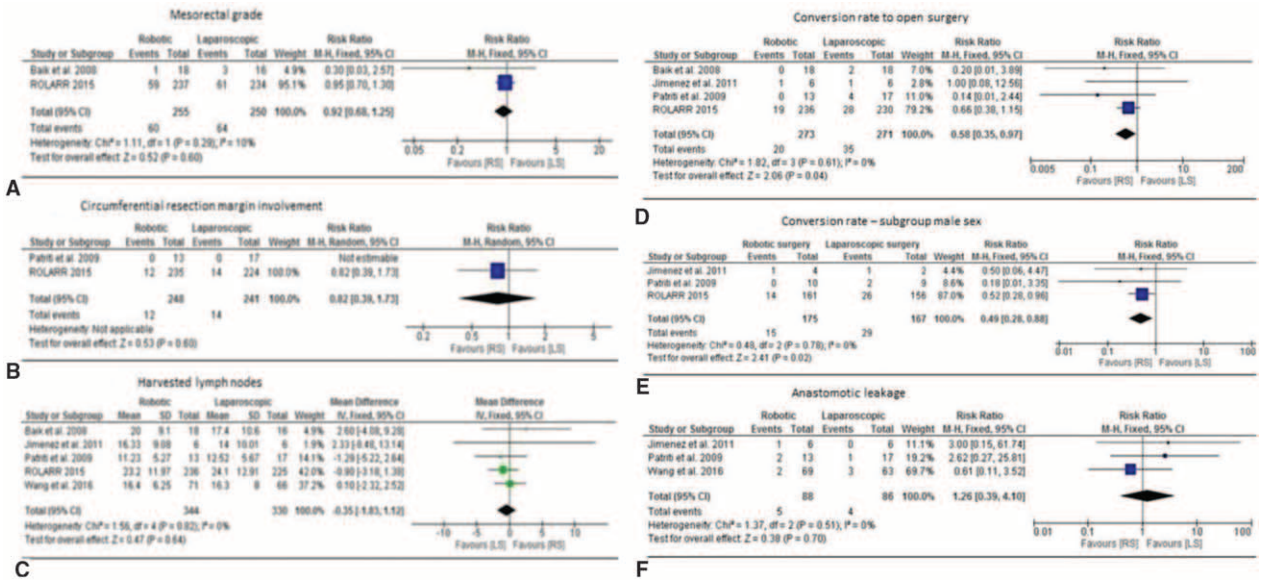

FIGURE 3. Forest plot, meta-analysis, and funnel plot for (A) Mesorectal grade, (B) Circumferential resection margin involvement, (C) Harvested lymph nodes, (D) Conversion rate to open surgery, (E) Conversion rate-subgroup male sex, (F) Anastomotic leakage. CI indicates confidence interval; df, degree of freedom; LS, laparoscopic surgery; M-H, Mantel-Haenszel; RS, robotic surgery.

IIEF is a self-administered scoring system including a questionnaire exploring 5 domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction- score range: 0 to 75); higher score is related to better erectile function.[57]

Preoperative IPSS scores were similar for RS and LS (mean IPSS 4.07), while scores at 12 months increased in the LS group (9.66 ± 5.74), significantly more than in RS (6.79 ± 5.69).

Starting from similar preoperative baseline IIEF scores between RS and LS (mean IIEF 57.15), postoperative total IIEF scores for RS (46.2 ± 29.4) were significantly lower than LS (40.1 ± 30.1).

Economic Cost of Hospital Stay

None of the included studies reported on costs involved in RS or LS for rectal cancer.

DISCUSSION

This study examines the outcomes of RS for rectal cancer on the basis of evidence from only RCTs and includes the most recent RCTs. All previous reviews included studies of mixed design. Since 2008, 5 RCTs have been published to answer the question whether RS shows better short-term results and is at least as safe as LS. All studies reported on at least one of the short-term clinic-pathological outcomes of interest.

Key Findings

Meta-analysis showed similar 30-day overall perioperative mortality and morbidity rates after RS rectal resections and LS. The rates of involvement of CRM, incomplete mesorectum, and mean number of harvested lymph nodes were also similar between RS and LS.

CRM involvement in surgical specimens is the independent pathological factor that is most strongly associated with local recurrence and distant metastases in rectal cancer.[58] The most commonly accepted definition of a positive CRM is the tumor extension (either continuous or discontinuous) or the presence of a positive lymph node within 1 mm of the radial, nonperitonealized soft tissue edge of rectal wall.[59] We found a CRM involvement less than 5%, with nonsignificant difference between RS and LS. Although this compares well with large laparoscopic trials,[8] lack of reporting CRM is an important issue, with only 2 out of 5 studies describing this outcome.

Adequate TME, or the grade of macroscopic completeness of the mesorectal sheath at the end of pelvic dissection,[60] has been indicated to represent TME quality more precisely than CRM involvement.[47] Many authors have been imputing much of the technical challenge of performing minimally invasive TME to the technical limitations of the laparoscopic technology, while improvements in ergonomics, stability, flexibility of instruments, and control with robotic technology have been indicated as likely conducive of a better dissection of rectal cancer.[18]

In our review, LAR with TME was the most frequently performed procedure across groups. Male patients (narrow pelvis) were equally balanced among pooled groups of RS and LS; average body mass index (BMI) was below 28 across all trials; the proportion of stage II and III cancers was equally balanced across trials, and specimens were reviewed by expert pathologists: with cases well matched under these parameters, a meta-analysis showed a nonsignificant difference for a lower risk of incomplete mesorectum in robotic TME. However, despite the fact that patients were also all operated on by skilled surgeons, the rate of incomplete mesorectal excision was 23.5% RS and 25.6% LS, compared with a rate of incomplete mesorecta of 12% in LS group in a recent large RCT.[61] This shows that TME is still a challenging operation even in expert hands and suggests that other reported factors may possibly be responsible for surgical performances, as the presence of bulky or fixed tumors within the same stage group, differences in the scheme of preoperative treatments, or other surgeon-related variables, including a longer learning curve for both LS and RS.[62]

The number of retrieved lymph nodes has a strong impact on prognosis but may be influenced by preoperative radiation therapy[63]

TABLE 3. Effects of Interventions: (A) Summary of Findings Table for Dichotomous Outcomes; (B) Summary of Findings Table for Continuous Outcomes

Robotic Surgery (RS) Compared with Laparoscopic Surgery (LS) for Rectal Cancer

Patient or Population: Rectal Cancer
Setting: Hospital
Intervention: Robotic Surgery (RS)
Comparison: Laparoscopic Surgery (LS)

	Anticipated Absolute Effects* (95% CI)					
Outcomes	**Risk with Laparoscopic Surgery (LS)**	**Risk with Robotic Surgery (RS)**	**Relative Effect (95% CI)**	**No. of Participants (Studies)**	**Quality of the Evidence (GRADE)**	**Comments**
Macroscopic mesorectal grade (rate of nearly complete/incomplete mesorectal sheath)	256 per 1000	236 per 1000 (174–320)	RR 0.92 (0.68–1.25)	505 (2 RCTs)	⊕⊕⊕◯ MODERATE†	Lower score indicates higher quality and completeness of pelvic surgical dissection
CRM (circumferential resection margin) involvement	58 per 1000	48 per 1000 (23–100)	RR 0.82 (0.39–1.73)	489 (2 RCTs)	⊕⊕⊕◯ MODERATE†	Lower score indicates lower risk of local recurrence
Conversion to open surgery - overall	129 per 1000	75 per 1000 (45–125)	RR 0.58 (0.35–0.97)	544 (4 RCTs)	⊕⊕⊕◯ MODERATE†,‡	Lower score indicates lesser degree of difficulty faced during surgery
Conversion to open surgery - subgroup male pts only	174 per 1000	85 per 1000 (49–153)	RR 0.49 (0.28–0.88)	342 (3 RCTs)	⊕⊕⊕◯ MODERATE§,¶	Lower score indicates lesser degree of difficulty faced during surgery
Incidence of anastomotic leakage	47 per 1000	59 per 1000 (18–191)	RR 1.26 (0.39–4.10)	174 (3 RCTs)	⊕⊕◯◯ LOW†,‖	Lower score indicates lower incidence of leakage from intestinal anastomosis
30-day mortality	6 per 1000	6 per 1000 (1–41)	RR 0.97 (0.14–6.86)	681 (5 RCTs)	⊕⊕⊕◯ MODERATE†	Lower score indicates lower mortality rate
Overall 30-day morbidity (overall perioperative complications)	267 per 1000	272 per 1000 (214–350)	RR 1.02 (0.80–1.31)	681 (5 RCTs)	⊕⊕◯◯ LOW‖,**,††	Lower score indicates fewer postsurgical complications **
Lymph nodes harvested	The mean lymph nodes harvested was 16.86 lymph nodes	The mean lymph nodes harvested in the intervention group was 0.35 lymph nodes lower (1.83 lower to 1.12 higher)	—	674 (5 RCTs)	⊕⊕⊕◯ MODERATE†,‡‡	Higher score indicates higher lymph node yield
Overall operation time	The mean overall operation time was 197.8 min	The mean overall operation time in the intervention group was 38.43 min higher (31.84 higher to 45.01 higher)	—	681 (5 RCTs)	⊕⊕⊕◯ MODERATE†,§§	Higher score indicates a longer lasting operation
Days to return of peristalsis	The mean days to return of peristalsis was 2.26 days	The mean days to return of peristalsis in the intervention group was 0.59 days lower (0.95 lower to 0.23 lower)	—	173 (2 RCTs)	⊕◯◯◯ VERY LOW†,‖,¶¶,‖‖‖	Lower score indicates earlier return of bowel function
Duration of hospital stay	The mean duration of hospital stay was 8.9 days	The mean Duration of hospital stay in the intervention group was 0.61 days lower (2.23 lower to 1.02 higher)	—	522 (4 RCTs)	⊕⊕◯◯ LOW†,***	Lower score indicates shorter postoperative stay in hospital

GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
CI indicates confidence interval; MD, mean difference; OR, odds ratio; RR, risk ratio.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Statistical inaccuracy with wide confidence intervals at both sides.
‡The only trial showing high risk of bias in critical areas weighs <3% in the overall best estimate of effect.
§The only clinical trial showing high risk of bias in critical areas weighs <4.5% in the overall best estimate of effect.
¶Confidence intervals do not cross null effect and narrow confidence intervals but few events.
‖More than 50 percent high or unclear risk of detection bias for an outcome with a degree of subjectivity.
**Definitions of perioperative complications varied or were unclear.
††The confidence intervals of the pooled estimate of effect include the null effect but do not include appreciable harm or benefit (RR 0.75—clinical action would not differ if the upper or the lower boundary of the CI represented the truth).
‡‡Objective outcome.
§§The only trial showing high risk of bias in critical areas weighs <1% in the overall best estimate of effect.
¶¶The study that weighs most in calculating the best estimate of effect includes only male participants.
‖‖‖Only 2 studies provided data on return of bowel function with less than 200 patients.
***There is substantial, unexplained heterogeneity.

or depends on technical factors as the difference in high and low vascular ligations of the mesentery or on the technology assisting minimally invasive surgery.[64] The number of patients receiving neoadjuvant treatment is not known for 3 trials, and with a tumor localization between 15 cm and the anal verge, there is a fair amount of clinical heterogeneity among the included studies. However, the average number of retrieved lymph nodes, reported by all studies, has been in both RS and LS beyond the recommended minimum of 12 nodes for adequate assessment of a colorectal resection.[65]

RS, devised to work best in constrained spaces, has also been seen as an option to afford to more patients the benefits of minimally invasive surgery through a lower conversion rate.[66] We found that conversion rate was significantly lower in RS, with 18 rectal resections needed to see one less conversion, an effect that can be seen in large-volume clinical practice. Because converted patients have higher complication rates and worse oncological outcomes, the low conversion rate for robotic rectal cancer surgery may support better postoperative courses and improved oncological outcomes.[67,68] Only the ROLARR trial gave a definition of conversion to open surgery. The most commonly reported reasons for conversion were difficulties in the completion of rectal or pelvic dissection, obesity, and intraoperative hemorrhage, while from our analysis male sex, usually surrogate for a narrow pelvis, emerged as a significant factor for conversion, possibly contributing to the complexity of pelvic dissection: conversion has been shown to be highly dependent on the location of the tumor and the experience of the surgeon.[67]

In our meta-analysis, RS proctectomy has also been consistently showing a significantly longer operating time than LS, on average almost 40 minutes more,[69–71] adding to the running costs of the robotic technology especially when theater overtime and extra personnel is concerned. Recent review of studies on learning curve in RS suggests that both operative times and conversion rates might decrease when experience in RS prolongs beyond the 25 to 30 cases generally believed to be necessary to achieve competency.[72]

Excepting the ROLARR trial, we found no definition of overall perioperative complications, contributing to indirectness of the evidence. Moderate and low quality of evidence supported similar morbidity and mortality between RS and LS, respectively, comparable to the figures reported in the COLOR II trial (40% and 1%, respectively), showing that RS compares well with the most recent results of LS in selected centers.[8]

Given that most trials shared similar criteria for discharge, the heterogeneity found analyzing the length of hospital stay might be contributed to different compositions of the study populations among different Centers in different Countries, to the different proportion of AR/LAR/APR, or to differences in surgical skills or perioperative recovery protocols. Because it was not possible to match all the patient characteristics for all the included studies, we applied a random model to reflect between-study variation.

The evidence supporting a significantly earlier recovery of bowel function in RS was very low and mainly driven by a study that was running an enhanced recovery program.[39] LS in combination with fast track recovery has resulted in the fastest recovery and hospital discharge compared with regular care and open surgery in previous trials.[73]

The quality of these studies varied, as did the number of included participants. The quality of the evidence for the most important outcomes was moderate (Table 3), the main reason being imprecision of CIs. This means that further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates.

Comparison with Existing Knowledge

As the most recently published systematic reviews found, intraoperative and short-term results show significantly lower rate of conversion to open surgery[22,23,69,70] (in our case benefitting only the subgroup of male patients), longer operating time,[70,71] and comparable perioperative complications[24] between the 2 approaches. Our review did not show lower incidence of positive CRM as in refs.[22,23] Previous systematic reviews on RS for rectal cancer identified by our literature search[22–24,70–72,74] included nonrandomized or mixed studies, and few examined the quality of included studies (Appendix 4, http://links.lww.com/SLA/B328).

Strengths

To avoid publication bias, we performed an extensive, systematic literature search that is likely to have identified all the available RCTs comparing RS to LS in proctectomy for rectal cancer. Also, this review is fully compliant with AMSTAR criteria, while none of prior systematic reviews scored for all 11 items (appendix 4, http://links.lww.com/SLA/B328). Contact with Authors provided data for comparison of outcomes that no previous other reviews made use of. Complete data were obtained for judging the quality of the evidence in included studies, while participants to the trials represent almost all of the world regions.

Limitations

The majority of included studies are small studies. In 2 of them,[37,38] the subset of participants with rectal cancer is smaller than the originally planned sample size, with consequences on statistical power. We took every step to capture all relevant studies and data; however, some records might have been missed despite best efforts; it was not possible to obtain data for a number of key comparisons (conversion, complications, leakage) from the larger studies. The short follow-up (perioperative, 30 days) for the outcomes considered is a limit for the conclusions of this review. All of the examined studies were not blinded, and observer bias is an important limitation when clinical and functional outcomes are considered. Less than half of the studies defined their outcomes a priori in or published a protocol. The lack of information on the cost of the 2 technologies is an important limitation to the applicability of the evidence from this review, with respect to cost-effectiveness of RS versus standard LS.

Implications for Research

In this study, the quality of evidence was moderate but sufficient to establish the safety and efficacy of RS for rectal cancer; however, further studies could significantly change the results presented. Framing the trials that were identified by our searches through the recommendations of the IDEAL collaboration[75]—the majority of studies presented as feasibility and explanatory RCTs—RS positions in an assessment stage. However, analysis also suggested the need for defining agreed reporting standards and definitions for key outcomes of efficacy and quality in robotic rectal cancer surgery: aspects of an earlier, development stage. This review supports further research by RCTs of adequate power and size calculation, comparing clinical, pathologic, quality of life outcomes, and cost of RS for rectal cancer.

Implications for Clinical Practice

There is currently moderate quality of evidence that RS for resection of rectal cancer portrays low perioperative mortality, similar to LS. RS also has similar effects to conventional LS on markers of adequate oncological resection as CRM, harvested lymph nodes, and integrity of the mesorectal sheath at the end of resection for the treatment of rectal cancer.

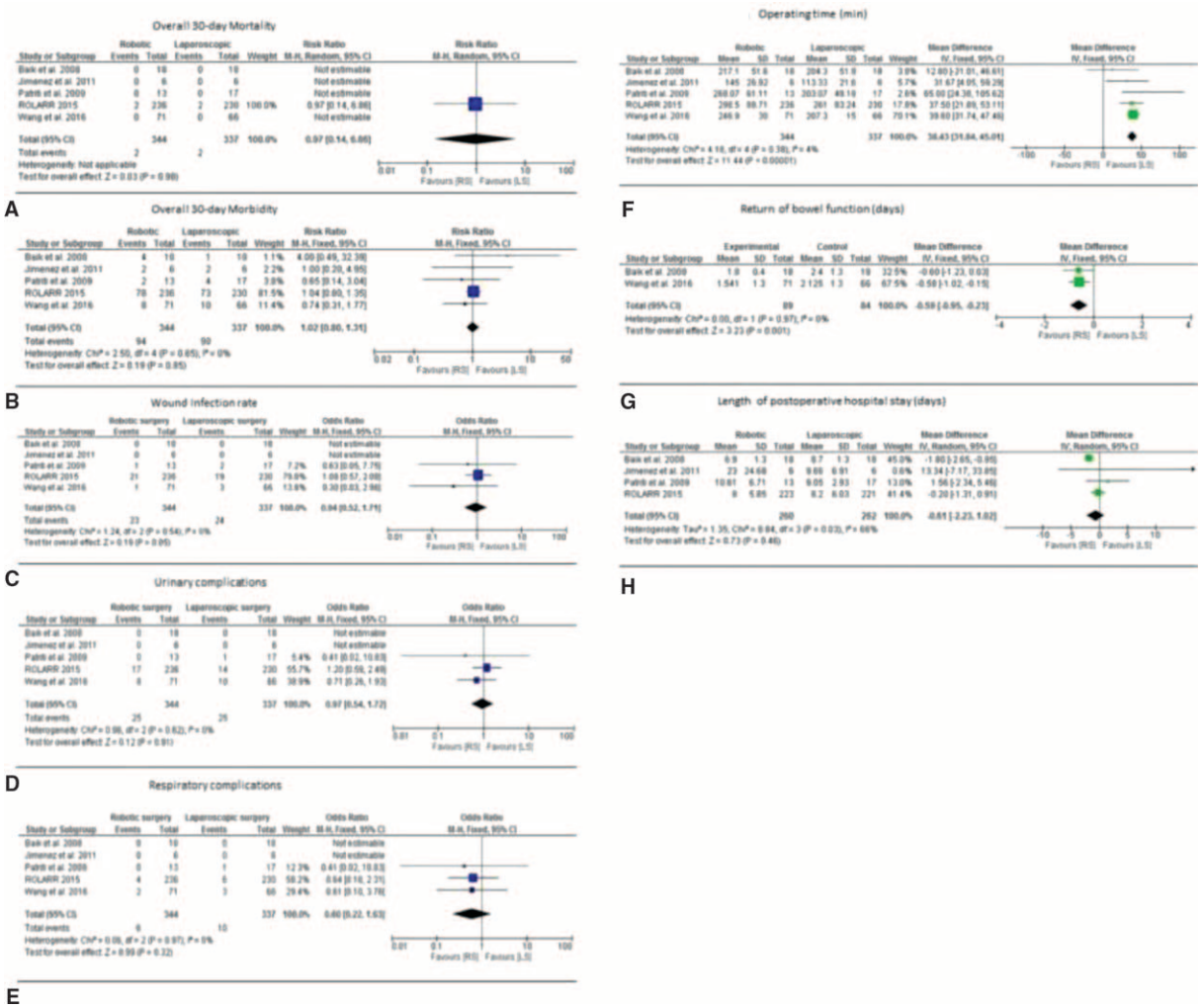

FIGURE 4. Forest plot, meta-analysis, and funnel plot for (A) Perioperative mortality, (B) Perioperative morbidity, (C) Wound infections, (D) Urinary complications, (E) Respiratory complications, (F) Operating time, (G) Return of bowel function, (H) Length of postoperative hospital stay. CI indicates confidence interval; df, degree of freedom; LS, laparoscopic surgery; M-H, Mantel-Haenszel; RS, robotic surgery.

Due to the quality of evidence, we cannot rule out either approach being superior.

There is also moderate quality of evidence that RS is associated with a lower risk of conversion to open surgery, which is a significant benefit for recovery and oncological outcomes, but it is tied to significantly longer operating times.

There is low-quality evidence that RS leads to similar perioperative complications and hospital stay as LS, and very low quality evidence that results in earlier recovery of bowel function.

Considering the moderate quality of evidence for most primary outcomes but partly different inclusion criteria between studies, the selected offer of surgical skills, differences in postoperative regimens between studies, unclear definition of some of the outcomes, short follow-up, and some uncertainty with the estimates of benefits, closely balanced with burdens, the conclusion of this study is that of a substantial equivalence of the 2 surgical approaches, with a weak recommendation for using RS in a research setting; other approaches might be better for some patients under some circumstances.

We await long-term data from a number of ongoing studies to contribute to a more robust analysis of long-term DFS, OS, local recurrence, quality of life, and cost.

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