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REVIEW ARTICLE

Effects of laparoscopic vs robotic-assisted mesorectal excision for rectal cancer: An update systematic review and meta-analysis of randomized controlled trials

Yan-Jiun Huang [a,b], Yi-No Kang [g], Yu-Min Huang [a,h], Alexander TH. Wu [f], Weu Wang [h], Po-Li Wei [a,b,c,d,e,i,*]

[a] *Department of Surgery, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[b] *Division of Colorectal Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan*
[c] *Cancer Research Center, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan*
[d] *Translational Laboratory, Department of Medical Research, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan*
[e] *Graduate Institute of Cancer Biology and Drug Discovery, Taipei Medical University, Taipei, Taiwan*
[f] *The PhD Program for Translational Medicine, College of Science and Technology, Taipei Medical University and Academia Sinica, Taipei, Taiwan*
[g] *Center for Evidence-Based Medicine, Department of Education, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan*
[h] *Division of General Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei, Taiwan*
[i] *Division of Colorectal Surgery, Department of Surgery, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*

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Summary Controversy still surrounds clinical benefits of robotic-assisted (RS) over laparoscopic surgery (LS) despite its popularity in clinical use in terms of outcomes and complication rates. The study aims to systematically review and provide the evidence concerning the risk of conversion to open laparotomy and oncological outcomes of LS vs RS rectal cancer surgery. The Cochrane Library (including the Cochrane Central Register of Controlled Trials),

* Corresponding author. Division of Colorectal Surgery, Department of Surgery, Taipei Medical University Hospital, 252 Wuxing Street, Sinyi District, Taipei, 11031, Taiwan.
E-mail address: poliwei@tmu.edu.tw (P.-L. Wei).

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EMBASE, PubMed, SCOPUS, and Web of Science were searched for randomized controlled trials (RCTs) comparing LS and RS. Eight RCTs including 1305 patients were identified. Pooled conversion rate was reported in 49 (11.89%) of 412 patients who underwent LS and in 23 (5.72%) of 402 patients who underwent RS (95% CI, 1.357 to 3.613; P = .001). However, shorter operative time was noted in LS group than RS group (95% CI, −43.106 to −3.876; P = .019). No significant difference in other outcomes was observed. Finally, in further analysis, the mean age in trial-level was found to be positively associated with operative time (point estimate = 2.598; 95% CI, 1.584 to 3.612; $P < .001$) and negatively with length of hospital stay. Robot-assisted surgery in rectal cancer showed lower conversion rate in comparison with that of laparoscopic surgery. Secondly, the laparoscopic surgery has shorter operative time compared with robot-assisted approach. The results also showed similar pathological outcomes between these two modalities. Future studies are needed to clarify the relationship between mean age and outcomes of surgery.

1. Introduction

Colorectal cancer is the third most common cancer in men and women in developed countries, with rectal cancer accounting for around 30% of the total colorectal cancer incidence.[1] It has long been technically challenging to perform laparoscopic total mesorectal excision (TME) for rectal cancer in the middle to lower position. With the introduction of minimal invasive surgery to the surgical field, results from several randomized controlled trials have demonstrated that the long-term oncological safety of laparoscopic approach is equivalent to that of open resection for rectal cancer, in terms of local recurrence and overall survival.[2–5] With increasing application of laparoscopic procedures using long and straight instruments, its native limitations for the surgical resection of rectal cancers have gradually being exposed through daily practices due to limited range of motion, loss of dexterity, and poor fulcrum effect of straight laparoscopic instruments in patients with large tumors or a narrow and deep pelvis. Conversely, robotic instruments may enable more meticulous TMEs because of the endo-wristed instruments, fixed third-arm retraction, and a magnified and controlled 3-dimensional view.

The surgical treatment of rectal cancer has always been more challenging, especially through a minimally invasive approach. With the development of robotic surgical system in the early 1990s, the first case series of robotic-assisted colectomies by Weber et al. was reported in 2002, various colorectal procedures have then been assisted by robotic system.[6] Robotic surgery using the Da Vinci surgical system (Intuitive Surgical Inc., Sunnyvale, CA) has been recognized among robotic surgeons to be able to break the limitations of laparoscopic surgery, especially in rectal surgery performed in confined space of pelvis. Many pros and recommendations of the small studies of using robotic Da Vinci S surgical system have seemed to show advantages towards practicing surgeons rather than focusing on the benefits of patients in terms of real oncological difference between insurance-covered traditional laparoscopic surgery and costly self-payed robotic surgery.[7,8]

Over the past decade, there has been an increased adoption of robotic surgery for pelvic procedures and its application to colorectal surgery. Many surgeons still remain concerned about oncological equivalence between robotic and laparoscopic rectal cancer surgery. However, little concrete evidence exists in support of robotic surgery for colorectal cancer. As nearly all countries are experiencing growth in the number and proportion of geriatric people in their populations. There were 901 million people aged 60 years or over in 2015 globally. The number is expected to grow to 1.4 billion in 2030.[9] The data on the types of surgical therapy for rectal cancer to be used in geriatric patients are limited. It is therefore important to find out which type of minimal invasive surgery best suits the aging population.[10] Major concern about robotic surgery remains on the capital cost and maintenance fees. Studies have even shown that the cost of robotic rectal cancer surgery is higher than for conventional laparoscopic surgery.[11,12] Inspite of this, robotic rectal cancer surgery has continued to gain acceptance worldwide. Many colorectal surgeons have expected that robotic surgery would resolve technical difficulties associated with laparoscopic surgery, such as steep learning curve.

Previous meta-analyses have failed to show superiority for robotic-assisted surgery over conventional laparoscopic surgery in short-term outcomes due to intrinsic design limitations of the included studies but recent reports from a few centers claim the outcome benefits with robotic approach.[13–15] With the latest study results coming out from kim's phase II open label prospective randomized controlled trial, and the multicenter, randomized ROLARR trial showing a reduced need to convert to open surgery with the robotic approach,[16–19] there is a need to include most recent and largest trial data in line with currently available randomized clinical studies to evaluate the safety and efficacy of rectal cancer surgery in adults through robotic surgery in comparison with traditional laparoscopic surgery, by short-term clinical and pathological outcomes. This will further explore the real benefits either solely to surgeons or to patients and also clarifying the role of robotic surgery in geriatric patients.

2. Methods

The flow diagram of evidence identification in this systematic review was presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] This systematic review was exempted from institutional review board approval, because it used published data.

2.1. Search and study selection

Relevant randomized controlled trials (RCTs) comparing LS and RS for rectal cancer resection were searched in the Cochrane Library (including the Cochrane Central Register of Controlled Trials), EMBASE, PubMed, SCOPUS, and Web of Science by using relevant keywords of rectal cancer, laparoscopic, robotic, and randomization. The comprehensive literature searches were conducted to identify RCTs published before March 2018 without language or publication date restrictions. The search strategy involved natural language, medical subject headings (MeSH in PubMed and Emtree in EMBASE), and truncation in appropriate Boolean algebras.

Two investigators (Y.J.H and Y.N.K) The flow diagram of evidence identification in this systematic review was presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] This systematic review was exempted from institutional review board approval, because it used published data.

2.2. Search and study selection

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Two investigators (Y.J.H and Y.N.K) screened potential citation records after comprehensive searches. Any disagreement during evidence identification was resolved by discussion with the third author (P.L.W.). The inclusion criteria were defined a priori and were as follows: (1) RCTs; (2) articles that recruited patients with rectal cancer; and (3) articles that compared laparoscopic surgery versus robotic surgery for mesorectal excision.

2.3. Quality assessment of included studies

The two investigators individually assessed the risk of bias of the included RCTs using the Cochrane risk of bias tool. This appraisal tool assesses selection, performance, detection, attrition, and reporting biases. The tool comprises seven evaluation items, and it assesses four methodologic bias. The seven items as follow: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. Disagreement of bias assessment were discussed with and resolved by the third author.

2.4. Data extraction and analysis

Two authors extracted and examined the data; they identified and verified data on the conversion rate, operative time, length of hospital stay, return to bowel function, circumferential resection margin, macroscopic mesorectal, distal resection margin, proximal resection margin, and lymph nodes harvested for meta-analysis.

Risk ratio (RR) was calculated for dichotomous data without zero-cell. Peto odds ratio (POR) was calculated for dichotomous data with zero-cell. Weighted mean difference (WMD) was calculated for continuous data. If the included RCT reported continuous data in mean and standard error (SE), we estimated the standard deviation (SD) based on the sample size ($SE = SD/\sqrt{N}$). If the included RCT reported continuous data in median with the minimum and maximum values, we estimated the mean and SD based on the sample size, median, and range. All meta-analysis except POR was conducted in random-effects model. Results were performed with 95% confidence intervals (CIs) and I-square. I-square presents the percentage of heterogeneity among the included RCTs in a meta-analysis. According to relevant literature, this study defined I-square of 25%, 50%, and 75% as low, moderate, and high heterogeneity, respectively.[21] This study set p-value < 0.05 for statistical significance in all analyses. Results of this study were expressed as forest plots that were generated by Comprehensive Meta-Analysis version 2 for Microsoft Windows in all analyses.

This study conducted meta-regression analysis by mean age in trial-level. Small study bias in this study was detected by funnel plot with Egger's regression intercept and Begg and Mazumdar rank correlation.

3. Results

3.1. Literature search and selection

The comprehensive searches of this systematic review identified 778 potential citation records, of which 533 were excluded based on the title and abstract screening. This systematic review retrieved and reviewed the full-text of the remaining 26 citation records, and the present study excluded 12 articles that met exclusion criteria. The remaining 14 articles were from eight RCTs. These eight RCTs were included for qualitative and quantitative synthesis.[18,19,22–27] The flow diagram of study selection is shown in Fig. 1 according to the PRISMA.

3.2. Characteristics of included studies

The included eight RCTs were published between 2008 and 2018. Among the included RCTs, one was conducted in

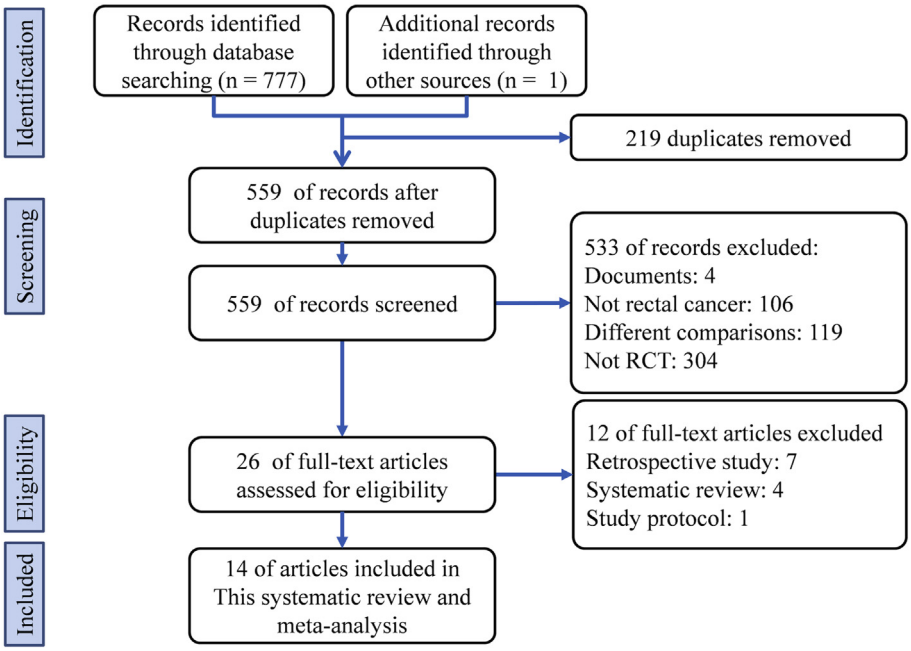


Fig. 1 Flowchart of this systematic review.

multi-area (United Kingdom, Italy, Denmark, United States, Finland, South Korea, Germany, France, Australia, and Singapore),[18] two in China,[13,27–29] one in Denmark,[25,30] another one in Italy,[24] two in South Korea,[19,22] and one in Spainbib23.[23] Overall, the quality of the RCTs was acceptable. The summary of risk of bias is shown in the eFigure 1. These RCTs randomized 1305 patients with rectal cancer into LS (n = 658) and RS (n = 647) groups for mesorectal excision from March 2004 through March 2017. The available data showed that the mean age of patients in each RCT was from 59.08 through 68.56. These available data included 679 (70.92%) male and 278 (29.08%) female. Further information is shown in Table 1.

3.3. Primary outcomes

Conversion rate was descripted in 6 of the included RCTs.[18,19,22–25] Pooled conversion rate was reported in 49 (11.89%) of 412 patients who underwent LS and in 23 (5.72%) of 402 patients who underwent RS; the POR was 2.215 (95% CI, 1.357 to 3.613; $P = .001$) with moderate heterogeneity ($I^2 = 50.134\%$) (Fig. 2A). No small study bias was observed in meta-analysis of conversion rate (Egger's regression intercept = 0.430; $P = .726$). Sensitivity analysis also showed similar trends when each study was removed from pairwise meta-analysis of conversion rate (eFile 1).

Operative time was descripted in 7 of the included RCTs[13,18,19,22–25] Pooled data showed shorter operative time (minutes) in LS comparing to RS (MD, −23.491; 95% CI, −43.106 to −3.876; $P = .019$) with high heterogeneity ($I^2 = 96.811\%$) (Fig. 2B). No small study bias was observed in meta-analysis of operative time (Egger's regression intercept = 1.997; $P = .451$). The pooled effect sizes in sensitivity analysis had similar trends with the effect size in overall pooling (eFile 2).

Length of hospital stay was descripted in 6 of the included RCTs.[18,22–25] Pooled data showed no significant difference in length of hospital stay (days) between LS and RS (MD, 0.677; 95% CI, −0.332 to 1.69; $P = .188$) with low to moderate heterogeneity ($I^2 = 42.853\%$) (Fig. 2C). No small study bias was observed in meta-analysis of length of hospital stay (Egger's regression intercept = −1.388; $P = .188$). Sensitivity analysis also showed similar trends when each study was removed from pairwise meta-analysis of Length of hospital stay (eFile 3).

Return of bowel function was descripted in 3 of the included RCTs.[19,22,23] Pooled data showed no significant difference in return of bowel function (days) between LS and RS (MD, 0.219; 95% CI, −0.095 to 0.533; $P = .172$) with very low heterogeneity ($I^2 = 8.005\%$) (Fig. 2D). No small study bias was observed in meta-analysis of return of bowel function (Egger's regression intercept = 6.302; $P = .30.14$). In sensitivity analysis, the trends of effect size were similar to overall pooling (eFile 4).

3.4. Pathological outcome

Circumferential resection margin was described in 3 of the included RCTs, but one of them reported no event in both LS and RS.[18,19,24] Therefore, there were only two RCTs contributed to the meta-analysis of circumferential resection margin. Pooled circumferential resection margin was reported in 18 (6.08%) of 296 patients who underwent LS and in 16 (5.33%) of 300 patients who underwent RS; the RR was 1.139 (95% CI, 0.592 to 2.191; $P = .697$) with very low heterogeneity ($I^2 = 0\%$) (Fig. 3A and eFile 5).

Macroscopic mesorectal was described in 2 of the included RCTs.[18,22] Pooled macroscopic mesorectal events was reported in 53 (22.18%) of 239 patients who underwent LS and in 56 (22.31%) of 251 patients who underwent RS; the

Table 1 Characteristics and risk of bias of included studies.

Study	Study size (RS)	Inclusion criteria	Age (year)		Gender (male)		TNM(I/II:III/IV)		Conversion To Open		Follow-up Period (mo)
			LS	RS	LS	RS	LS	RS	LS	RS	
Baik et al. 2008	36 (18)	Rectal cancer	62 ± 9	57.3 ± 6.3	14	14	9/9	9/9	2	0	1
Jimenez et al. 2011	56 (28)	Sigmoid/Rectal cancer	65.5 ± 15	68 ± 9.1	17	12	12/16	10/18	2	2	1
Patriti et al. 2009	66 (29)	Rectal cancer	69 ± 10	68 ± 10	25	18	25/12	20/9	7	0	24
ROLARR 2017	471 (237)	Rectal cancer	65.5 ± 11.9	64.4 ± 10.98	159	61	81/122	88/122	28	19	1
Wang et al. 2016	137 (71)	Rectal cancer	58.7 ± 8.7	60.3 ± 8	66	71	32/34	31/40	–	–	12
Kim et al. 2018	139 (66)	Rectal cancer	57.9 ± 11.7	60.4 ± 9.7	52	51	25/38	25/34	0	1	
China trial	349 (173)	Rectal cancer	–	–	–	–	–	–	4	0	–
Denmark trial	51 (25)	Rectal cancer	68 ± 9.9	63 ± 10.9	20	18	4/19	7/13	10	1	–

LS, laparoscopic surgery; RS, robotic-assisted surgery.

RR was 1.122 (95% CI, 0.485 to 2.595; $P = .788$) with low heterogeneity ($I^2 = 22.566\%$) (Fig. 3B and eFile 6).

Distal resection margin was described in 4 of the included RCTs.[19,22–24] Pooled data showed no significant difference in distal resection margin (cm) between LS and RS (MD, −0.581; 95% CI, −1.165 to 0.003; $P = .051$) with moderate to high heterogeneity ($I^2 = 60.262\%$) (Fig. 3C). No small study bias was observed in meta-analysis of distal resection margin (Egger's regression intercept = 2.489; $P = .161$). Sensitivity analysis also demonstrated similar trends when each study was removed from pairwise meta-analysis of distal resection margin (eFile 7).

Proximal resection margin was described in 2 of the included RCTs.[19,22] Pooled data showed no significant difference in proximal resection margin (cm) between LS and RS (MD, 0.209; 95% CI, −1.651 to 2.069; $P = .826$) with low to moderate heterogeneity ($I^2 = 46.908\%$) (Fig. 3D and eFile 8).

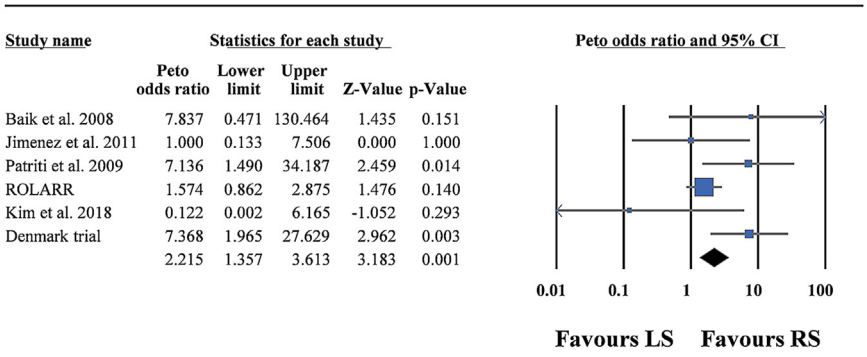
Lymph nodes harvested was described in 6 of the included RCTs [13, 18, 19,22−24]. Pooled data showed no significant difference in lymph nodes harvested between LS and RS (MD, −0.154; 95% CI, −1.398 to 1.090; $P = .808$) with low heterogeneity ($I^2 = 10.592\%$) (Fig. 3E). Although Egger's test detected small study bias in meta-analysis of lymph nodes harvested (Egger's regression intercept = −2.236; $P = .046$), Begg and Mazumdar rank correlation did not show the small study bias (Z, 0.751; $P = .452$). The most of pooled effect sizes in sensitivity analysis of lymph nodes harvested had similar trends with the effect size in overall pooling, but two effect sizes of sensitivity analysis differed from the overall pooing. However, the two effect sizes showed a favorable trend of RS in lymph nodes harvested without statistical significance (eFile 9). Moreover, funnel plot showed that adjusted pooled result was similar to unadjusted. Therefore, the pooled result of lymph nodes harvested was not seriously influenced by small study bias.

3.5. Further analysis

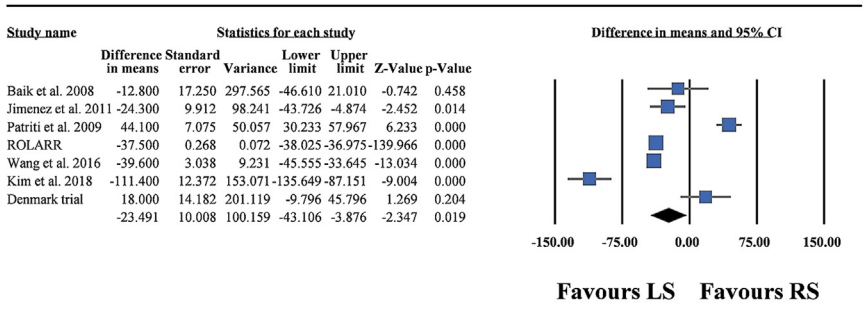
To explore the associations between mean age and our outcomes in trial-level, we applied meta-regression for further analysis. There were only two outcomes that were associated with mean age. One of these two outcomes was operative time, and the other one was length of hospital stay. Mean age in trial-level was positively associated with operative time (point estimate = 2.598; 95% CI, 1.584 to 3.612; $P < .001$) (eFile 2). In contrast, mean age in trial-level was negatively associated with length of hospital stay (point estimate = −0.277; 95% CI, −0.493 to −0.061; $P < .012$) (eFile 3).

4. Discussion

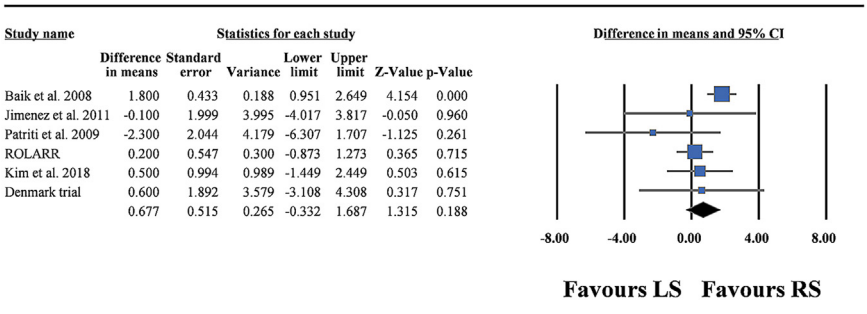
This study examines the outcomes of robotic surgery versus laparoscopic surgery for rectal cancer on the basis of evidence from only RCTs and includes the most recent 8 RCTs that randomized 1305 patients into the two mesorectal excision groups. Therefore, the sample size within this study is larger than the previous studies. Moreover, the present study also further explored the associations



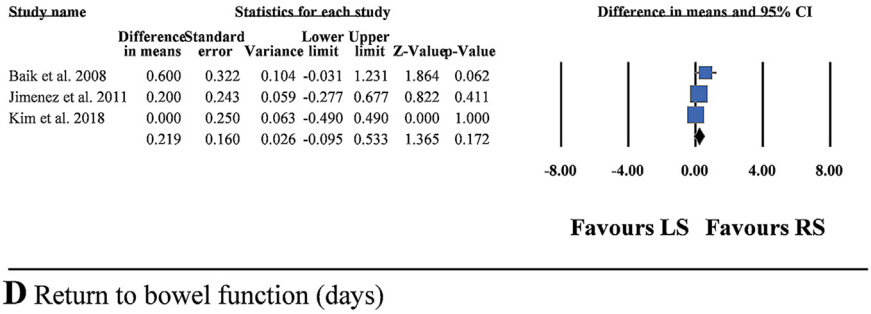
A Convert to open (Conversion rate)



B Operative time (minutes)



C Length of hospital stay (days)

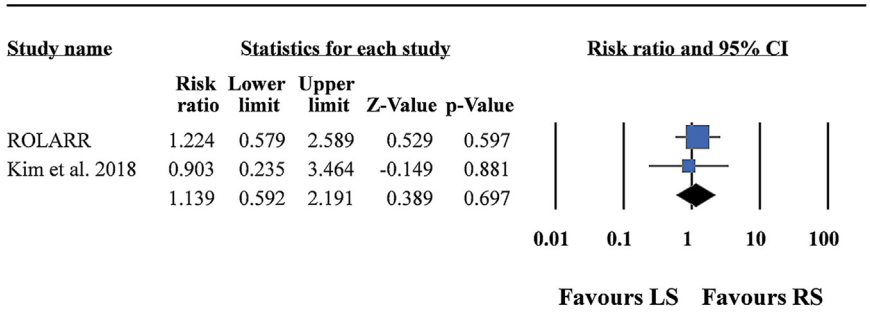


D Return to bowel function (days)

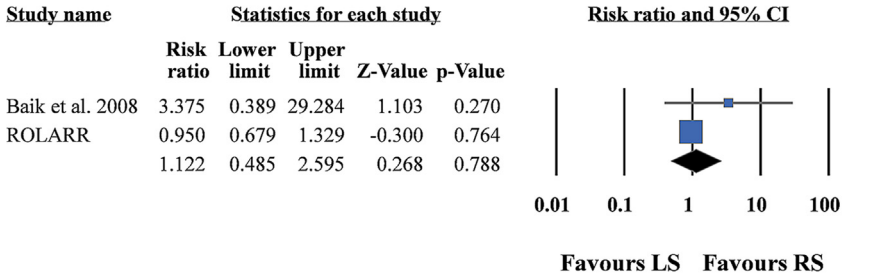
Fig. 2 Forest plots for primary outcomes.

between mean age and our outcomes in trial-level. For dichotomous data with any zero-cell, this meta-analysis used PORs rather than RRs. Therefore, the present findings seem to be more reliable for the use of clinical decision making.

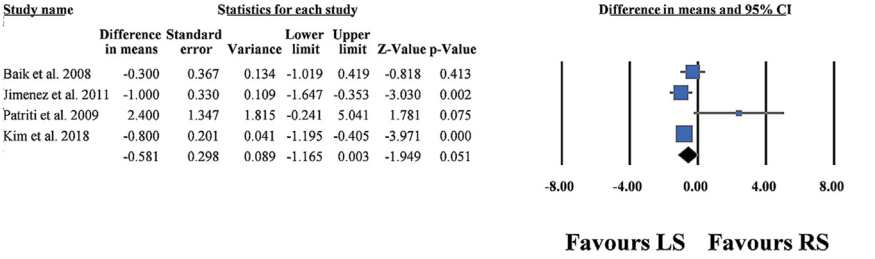
The present study has more advantages than previous systematic review and meta-analysis.[31–35] The advantages are the involvement of new RCTs, the subgroup of mean age, and adequacy of statistical methods. Two previous systematic reviews did not review RCTs.[32,35] Another group



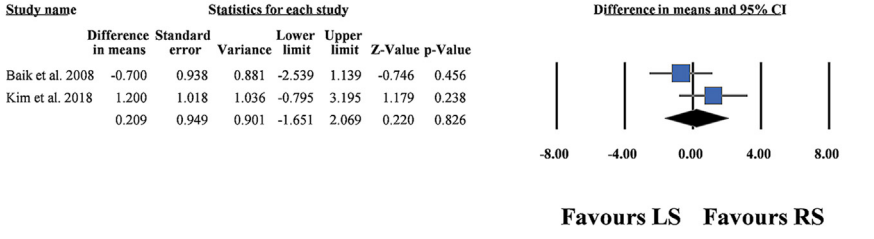
A Circumferential resection margin (rate)



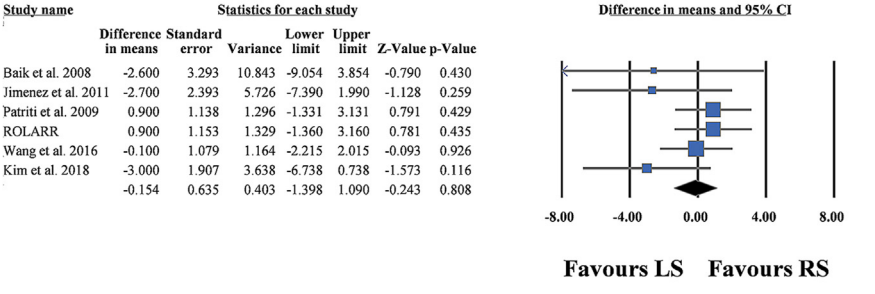
B Macroscopic mesorectal (rate)



C Distal resection margin (cm)



D Proximal resection margin (cm)



E Lymph nodes harvested (volume)

Fig. 3 Forest plots for pathological outcomes.

conducted meta-analysis of RCTs, but only estimated RRs in fixed-effect model.[31] Within that study 5 RCTs were included that randomized 671 patients into LS and RS reported similar effects on length of hospital stay, circumferential resection margin, macroscopic mesorectal, and lymph nodes harvested between LS and RS. These results did not take into consideration the difference between young-aged group and geriatric population.

With the released information from WHO, between 2015 and 2030, the number of geriatric people on earth is projected to grow by 56 per cent, from 901 million to more than 1.4 billion.[9] The present systematic review and meta-analysis focuses firstly on the conversion rate and secondly on the pathologic outcomes of laparoscopic versus robotic resections for rectal cancer.

The conversion rate is a valuable item to assess the its influence on early postoperative morbidity of rectal surgery.[36] The result demonstrates that the overall pooled conversion rate was significantly lower for patients who underwent RS than those undergoing LS. Pooled conversion rate was reported in 49 (11.89%) of 412 patients who underwent LS and in 23 (5.72%) of 402 patients who underwent RS; the POR was 2.215 (95% CI, 1.357 to 3.613; $P = .001$). Patients with rectal cancer over the age of 50 are reported to have more advanced disease when compared to patients younger than 50.[37] Many colorectal surgeons are reluctant to perform laparoscopic surgery in geriatric patients, due to poor cardiopulmonary function, unstable perioperative hemodynamics, hypercapnia during long-hour operation, and the steep Trendelenburg position. Seishima et al. reported that minimal invasive surgery in comparison with open surgery was significantly associated with a decreased risk of perioperative mortality and postoperative complications.[38] Robotic instruments designed to work best in confined spaces, have been reported as an option to provide more patients the advantages of minimally invasive surgery through a lower conversion rate.[39] Operative time was described in 7 of the included RCTs[13,18,19,22–25] Pooled data showed shorter operative time (minutes) in LS comparing to RS (MD, −23.491; 95% CI, −43.106 to −3.876; $P = .019$). Interestingly, mean age at trial-level was positively associated with operative time (point estimate = 2.598; 95% CI, 1.584 to 3.612; $P < .001$). This means as patients get older the operative time difference between laparoscopic and robotic approach diminishes. This finding may provide a direction to which clinicians may choose the best candidates for the high-cost robotic surgery and clearly in the best interest of patients. Adding to the maintaining costs of the robotic machine especially when occupation of operating room and personnel overtime is taken into consideration, how to put the robotic machine into its best use becomes an important topic of investigation. Recent review shows that the learning curve of both operative time and conversion rate in robotic surgery might decrease when 25 to 30 cases of experience has been reached.[40]

Under the theme of minimally invasive surgery, the superiority of laparoscopic surgery to open surgery, clinically as well as physiologically, has been reported.[41,42] Rectal cancer patients receiving either robotic or laparoscopic approach for surgery from this meta-analysis shows no significant difference in their hospital stay or return of bowel function. This corresponds well with the reported benefits of minimally invasive surgery.

From the pathological point of view, the completeness of the circumferential mesorectal excision (CRM) and distal resection margin are two essential items for assessing the oncological outcome of rectal surgery and an important predictor of recurrence in the pelvis.[43,44] Achieving negative CRM is challenging in surgical practice even through laparoscopic approach in the case of low rectal cancer, with a rate of CRM positivity reaching 15% of TME despite optimal resections.[45,46] However, the cutoff value for defining positive CRM remained controversial, with the threshold of 1 mm or less as the most frequently used in the literature. We found no significant difference between RS and LS with regarding to CRM involvement. Although this compares well with large laparoscopic trials,[47] lack of reporting CRM is an important issue, with only 3 out of 8 studies describing this outcome. As a matter of fact, unable to preserve the integrity of the posterior surface of the mesorectum was an important factor for local recurrence in patients with no CRM involvement. This was described in 2 of the included RCTs.[18,22]

Pooled macroscopic mesorectal events was reported in 53 (22.18%) of 239 patients who underwent LS and in 56 (22.31%) of 251 patients who underwent RS; the RR was 1.122 (95% CI, 0.485 to 2.595; $P = .788$) with low heterogeneity ($I^2 = 22.566\%$)

The importance of inability to obtain a distal margin of 1 mm is associated with worse oncologic results in rectal cancer surgery.[48] Distal resection margin was mentioned in 4 of the included RCTs.[19,22–24] Overall pooled data showed no significant difference in distal resection margin (cm) between LS and RS. The number of retrieved lymph nodes has a strong impact on prognosis but may be influenced by neoadjuvant CCRT or RT only, factors such as the difference in high or low vascular ligations of the mesentery or on the type of minimally invasive surgery.[49] Based on current literature, lymph nodes harvested was described in 6 of the included RCTs.[13,18,19,22–24] Final results showed no significant difference in lymph nodes harvested through either LS or RS approach.

Current evidence supporting a significantly faster recovery of bowel function in RS is pretty weak and mainly driven by a study conducted under enhanced recovery program.[26] The results came from our meta-analysis showed no significant difference in either duration of hospital stay nor early return of bowel function through either LS or RS approach.

4.1. Limitations

This meta-analysis collects solely RCTs; this type of study is currently considered to provide the best level of clinical evidence. However, potential bias cannot be completely ruled out, such as unstandardized protocols of neoadjuvant chemoradiotherapy of the included studies, different level of expertise in surgical procedures and various surgical procedures involved. The short-term follow-up (perioperative, 30 days) for the outcomes is also considered a limit for the conclusions of this review. Despite these limitations, the solidness and consistency of the analyzed results were

supported by our random-effect model analyses and the low heterogeneity observed.

5. Conclusions

Based on the available data pooled from the most recent RCTs, overall conversion rate seems to be statistically significant lower with robotic surgery. Shorter operative time was also observed in patients undergoing laparoscopic surgery but further analysis showed diminished trend of correlation as patients get older. There were no significant differences in immediate oncologic results between LS and RS group and they were comparable. The need for more randomized data is critical to determine the effect of age on operative time and hospital stay.

Competing interests

All authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.11.007.

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