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SCIENTIFIC REVIEW

Robotic Versus Conventional Laparoscopic Surgery for Colorectal Cancer: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

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Abstract

Background Minimally invasive surgery has been considered as an alternative to open surgery by surgeons for colorectal cancer. However, the efficacy and safety profiles of robotic and conventional laparoscopic surgery for colorectal cancer remain unclear in the literature. The primary aim of this review was to determine whether robotic-assisted laparoscopic surgery (RAS) has better clinical outcomes for colorectal cancer patients than conventional laparoscopic surgery (CLS).

Methods All randomized clinical trials (RCTs) and observational studies were systematically searched in the databases of CENTRAL, EMBASE and PubMed from their inception until January 2018. Case reports, case series and non-systematic reviews were excluded.

Results Seventy-three studies (6 RCTs and 67 observational studies) were eligible (n = 169,236) for inclusion in the data synthesis. In comparison with the CLS arm, RAS cohort was associated with a significant reduction in the incidence of conversion to open surgery ($\rho < 0.001$, $I^2 = 65\%$; REM: OR 0.40; 95% CI 0.30,0.53), all-cause mortality ($\rho < 0.001$, $I^2 = 7\%$; FEM: OR 0.48; 95% CI 0.36,0.64) and wound infection ($\rho < 0.001$, $I^2 = 0\%$; FEM: OR 1.24; 95% CI 1.11,1.39). Patients who received RAS had a significantly shorter duration of hospitalization ($\rho < 0.001$, $I^2 = 94\%$; REM: MD − 0.77; 95% CI 1.12, − 0.41; day), time to oral diet ($\rho < 0.001$, $I^2 = 60\%$; REM: MD − 0.43; 95% CI − 0.64, − 0.21; day) and lesser intraoperative blood loss ($\rho = 0.01$, $I^2 = 88\%$; REM: MD − 18.05; 95% CI − 32.24, − 3.85; ml). However, RAS cohort was noted to require a significant longer duration of operative time ($\rho < 0.001$, $I^2 = 93\%$; REM: MD 38.19; 95% CI 28.78,47.60; min).

Conclusions This meta-analysis suggests that RAS provides better clinical outcomes for colorectal cancer patients as compared to the CLS at the expense of longer duration of operative time. However, the inconclusive trial sequential analysis and an overall low level of evidence in this review warrant future adequately powered RCTs to draw firm conclusion.

PROSPERO Registration: CRD42018085903

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Introduction

Colorectal cancer is one of the leading causes of cancer-related death in men and women worldwide [1]. Minimally invasive surgery (MIS) has recently been considered in the management of colorectal cancer due to its technical advantages and long-term favorable postoperative outcomes [2–7]. Laparoscopic radical resection of colorectal tumor is believed to offer high-quality colorectal resection and minimizes surgical insult on the surrounding tissues and organs [8–11]. In the recent years, many researchers have shifted their interests to compare the postoperative and oncological outcomes between the robotic and conventional laparoscopic surgery for colorectal cancer [12–14].

The utilization of robotic technology in laparoscopic surgery is believed to overcome the technical limitations of a conventional laparoscopic method, namely limited dexterity, flat two-dimensional vision and unnatural hand–eye coordination. Despite many observational studies (OS) reporting on the safety and feasibility of the robotic-assisted laparoscopic surgery (RAS) for colorectal cancer, there were only several OS [4, 7, 15–17] that concluded the superiority of it over conventional laparoscopic surgery (CLS). A meta-analysis [18] based on five OS concluded that both RAS and CLS had no significant difference in oncological outcomes in colorectal cancer. Another meta-analysis [19] based on four randomized controlled trials (RCTs) reported that RAS is safe and effective for colorectal cancer but it did not affirm the superiority of RAS over CLS. However, in the two recent meta-analyses [20, 21], it suggested that RAS might be a promising treatment than CLS for patients with colorectal cancer. In view of several recent published RCTs [12–14] investigating the benefits of robotic and conventional laparoscopic surgery for colorectal cancer, a systematic review and meta-analysis are timely warranted to summarize the current evidence in the literature.

To date, there is no consensus whether the RAS is superior to the CLS for colorectal cancer. We hypothesized that colorectal cancer patients may receive greater clinical benefits from the RAS than the CLS. The primary aim of this review was to determine whether RAS has an effect on mortality and incidence of conversion rate (laparoscopic to open surgery) for patients with colorectal cancer. Secondary aim was to update the previous meta-analyses [18–21] by including all recently published RCTs and OS to summarize the current evidence of RAS versus CLS for colorectal cancer. Subgroup analysis was performed based on study design (RCTs vs OS) for all the measured outcomes to overcome the potential bias of observational studies. We also performed trial sequential analysis to determine whether all the measured outcomes in this meta-analysis are conclusive for their statistical findings after adjusted for random error and multiplicity phenomenon due to repeated significant testing in meta-analyses.

Methods

This meta-analysis was conducted and reported according to the "Preferred Reporting Items for Systematic Review and Meta-analysis" (PRISMA) statement 2015 [22] and the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The review protocol was registered on PROSPERO (CRD42018085903). The research questions were formulated using a population, intervention, control, outcomes (PICO) approach (eTable 1 in the online supplement).

Search strategy

PubMed, EMBASE and CENTRAL were systematically searched from its inception until January 2018. The search strategy and terms used are provided in eTable 2. No language restriction was applied to the search. Articles not written in English language were included if the journal provided English-translated version. Inclusion criteria were adults (≥18 years old), robotic-assisted laparoscopic surgery versus conventional laparoscopic surgery for colorectal cancer (colon cancer, rectal cancer, colon + rectal cancer), RCTs and observational studies (prospective/retrospective cohort studies, case-controlled studies) only.

Case reports, case series, non-systematic reviews and trials published as abstract were excluded. Other exclusion criteria were studies that involved hand-assisted laparoscopic surgery for colorectal cancer [23, 24]. The bibliographies of included papers and relevant systematic reviews were hand-searched for additional papers. Experts and authors of papers identified in the search strategy were attempted to be contacted on two occasions for any missing data.

Measured outcomes

Co-primary outcomes were incidence of conversion to open surgery and all-cause mortality. In term of the incidence of all-cause mortality, the longest follow-up data (30 days, 90 days, 180 days) were selected for data analysis. If multiple studies were published based on the same trials, the outcomes with the longest duration of follow-up were included. Secondary outcomes were incidence of surgical site infection (SSI), local recurrence rate, distant recurrence rate, anastomotic leak, operative time,

intraoperative estimated blood loss, length of hospital stay and time to oral diet.

Study selection and data extraction

Titles and abstracts were independently screened against eligibility criteria by two authors (AT and VC). If both authors were confident that a study was unsuitable, based on the titles and abstracts, this study was excluded. Any disagreements or different opinions at this stage were resolved by the third author (KN). Two reviewers (AT and VC) independently screened full texts of qualifying papers. If both were certain that a study was unsuitable, it was excluded. Any discrepancies at this stage were discussed with the third author (KN) to reach a final decision. Selection of the final included articles was based on the final consensus among all authors (AT, VC and KN).

All the included RCTs and observational studies were assessed for risk of bias by two authors (AT and VC) independently using the Cochrane Collaboration Risk of Bias Assessment Tool (https://handbook.cochrane.org) and the Newcastle–Ottawa Scale [25], respectively. The Newcastle–Ottawa Scale less than 7 was considered as high risk of bias, while those with 7 or more were considered as low risk [26]. Any disagreements were resolved by a discussion with the third author (KN). In addition to the measures of outcomes, the following fields, namely citation, year of publication, study design, country, population, sample size and location of colorectal cancer, were extracted. When the data were presented as median (range/interquartile range), it was converted to mean (± standard deviation) [27].

The GRADE assessments of the evidence and summary of findings tables were independently performed by two authors (AT and VC) using the GRADEpro/GDT software (https://gradepro.org/). Based on the Cochrane handbook, we downgraded a starting rating of "high-quality" evidence of RCT based on the five criteria (risk of bias, inconsistency, indirectness, imprecision and publication bias) by one level for serious concern or by two levels for very serious concerns [28]. Any disagreements were resolved by the third author (KN).

Statistical analysis

Statistical analyses were carried out using RevMan Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). I^2 test was used to assess the heterogeneity of studies. The values of less than 40%, 40–60% and more than 60% were used to determine low, moderate and substantial heterogeneity, respectively [28]. A two-sided p-value of <0.05 was considered to denote the statistical significance of heterogeneity. If no substantial heterogeneity was noted, a fixed-effects model (FEM) analysis (Mantel–Haenszel method) was used to pool estimates. If evidence of substantial heterogeneity ($I^2 > 60\%$) was observed, a random-effects model (REM) analysis (DerSimonian–Laird method) was used. Findings were reported as odds ratios (OR) or mean difference (MD) with 95% confidence intervals (CI). For measured outcomes with zero event in either arms, we adhered to the guidance of the Cochrane Handbook (16.9.3) by using OR-based method as it excludes those reporting bias whether or not they are published [29]. We also performed subgroup analyses based on study design (RCTs vs OS), quality of studies and location of colorectal cancer for all the measured outcomes.

Using the trial sequential analysis viewer version 0.9.5.5 Beta (Copenhagen Trial Unit, 2016), trial sequential analysis was performed on all the measured outcomes based on all the included RCTs to prevent the risk of random error and multiplicity phenomenon due to repeated significant testing in meta-analyses [30]. The required information size and adjusted significance thresholds were calculated based on a two-sided adjusted fixed-effects/random-effects model with 5% risk of type 1 error, low risk bias model and power of 80%.

Results

The results of the literature search and study selection process are outlined in the PRISMA flowchart (Fig. 1). The titles and abstracts of 1,350 non-duplicate articles were screened, in which 138 articles were retrieved. After applying inclusion and exclusion criteria, 73 studies with a total of 169,236 subjects were included in this review. Details of the excluded studies are outlined in eTable 3. The robotic-assisted laparoscopic surgery included both total and hybrid approach (mobilization of the left colon and the splenic flexure laparoscopically). It also included the da Vinci® surgical system (Intuitive Surgical, Inc., Menlo Park, CA, USA), regardless of the generation Si or Xi.

The clinical characteristics of all included studies are illustrated in Table 1. The majority of them [3, 6, 12, 14, 16, 17, 31–85] were single-center, and 12 (1 RCT [13] and 11 observational studies [2, 4, 5, 7, 86–92]) were multicenter. Among all the included studies, 53 studies (4 RCTs [12–14, 32], 49 non-RCTs [4, 5, 7, 16, 17, 31, 33–37, 40, 42, 44, 47–49, 51, 52, 56, 60, 62–72, 78, 80–91]) compared the benefits of RAS versus CLS in rectal cancer, 11 (1 RCT [79], 10 non-RCTs [3, 6, 38, 43, 45, 50, 58, 59, 74, 92]) in colon cancer and 9 (1 RCT [39], 8 non-RCTs [2, 41, 53–55, 57, 61, 77]) in colorectal cancer. In the overall risk of bias assessment, the quality of majority studies was high/unclear risk (eTable 4 for RCTs

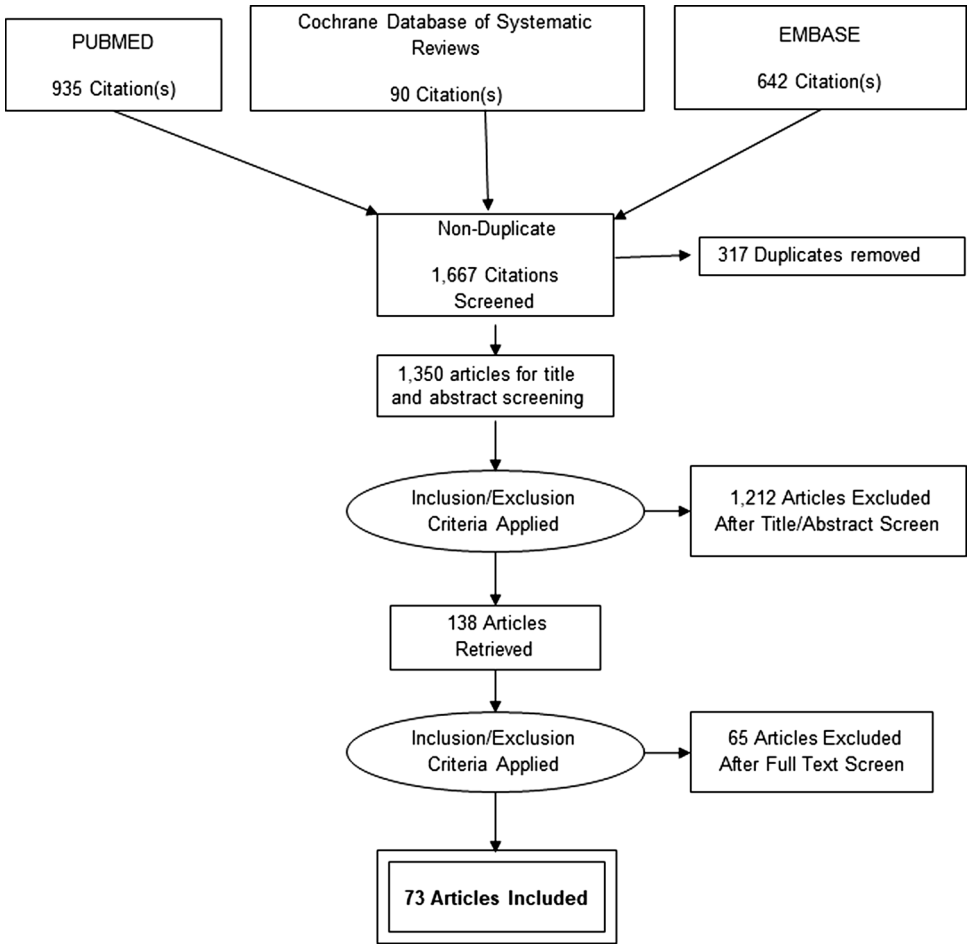

Fig. 1 Prisma diagram

and eTable 5 for OS). Table 2 summarizes all the subgroup analyses of primary and secondary outcomes for RCTs and OS, and trial sequential analysis of RCTs for all measured outcomes. The GRADE summary of findings for RCTs and OS is shown in eTable 6 and eTable 7, respectively. The PRISMA checklist is provided in eTable 8.

Sixty-three [2, 6, 7, 13, 14, 16, 17, 31–40, 42–53, 55–59, 61–64, 66–81, 83–90, 92] out of 73 studies (146,143 patients) examined the incidence of open conversion between RAS and CLS. The statistical heterogeneity was high across all studies. It showed that the RAS group had significantly lower incidence of open conversion rate compared with the CLS arm ($\rho < 0.001$; $I^2 = 65\%$; OR 0.40; 95% CI 0.30, 0.53) (Fig. 2). In the subgroup of non-RCTs (58 OS [2, 6, 7, 16, 17, 31, 33–38, 40, 42–53, 55–59, 61–64, 66–78, 80, 81, 83–90, 92], 145,378 participants), the open conversion rate was more likely to occur in CLS group as compared to RAS ($\rho < 0.001$; OR 0.38; 95% CI 0.28, 0.51), although the heterogeneity in this subgroup was substantial ($I^2 = 66\%$, $\rho < 0.001$). However, no significant difference was observed in the subgroup of RCTs (5 RCTs [13, 14, 32, 39, 79], 765 patients; $\rho = 0.15$, $I^2 = 0\%$; OR 0.66; 95% CI 0.37, 1.16). Based on all the included RCTs, the trial sequential analysis of a diversity-adjusted required information size for incidence of conversion rate was 2140 patients, based on 5% risk of type 1 error (two-sided), power 80%, low bias-based relative risk reduction of 36.47% and incidence in control arm of 8.38% with a model variance-based heterogeneity correction. The cumulative *z*-curve (blue line) did not cross the estimated information size boundary (Fig. 3). Thus, the current meta-analytic data ($n = 695$) based on 4 RCTs [13, 14, 32, 39] were inconclusive that RAS reduces the incidence of open conversion rate for colorectal cancer.

Forty-eight studies [4–7, 12, 13, 16, 17, 34, 37–40, 42–46, 48, 51, 52, 55, 56, 59, 61–64, 66–68, 70–72, 74–76, 78–80, 83, 85–87, 89–91] (40,814 patients) reported all-cause mortality rate in patients with colorectal cancer, who received either RAS or CLS. Statistical heterogeneity was assessed as low in the pooled effect. This review demonstrated that RAS cohort was associated with significant reduction in the mortality rate (overall) as compared to the CLS group ($\rho < 0.001$, $I^2 = 7\%$; FEM: OR 0.48; 95% CI 0.36, 0.64) (Fig. 4). Similarly, in the subgroup of non-

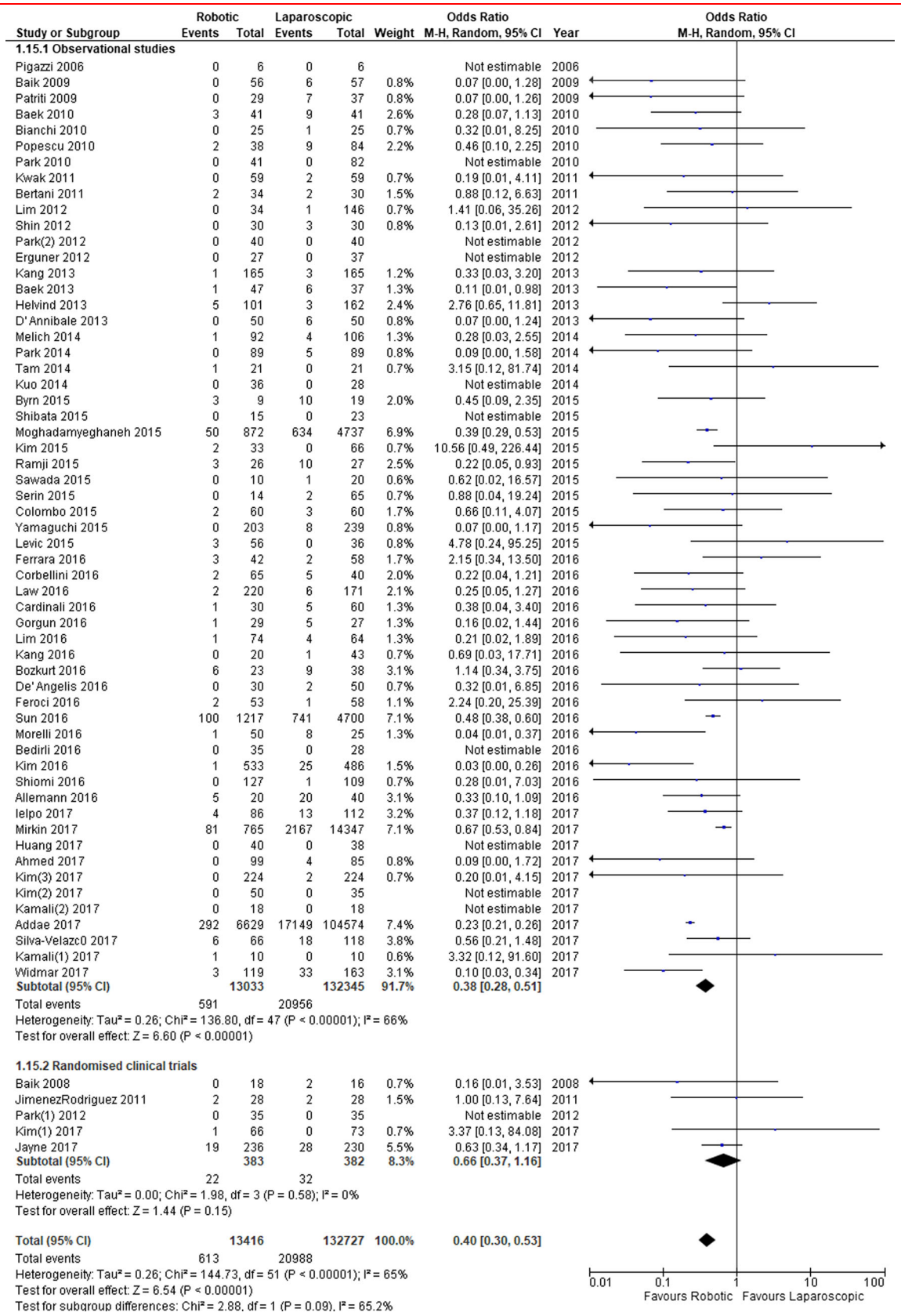

Fig. 2 Forest plot of the incidence of open conversion rate

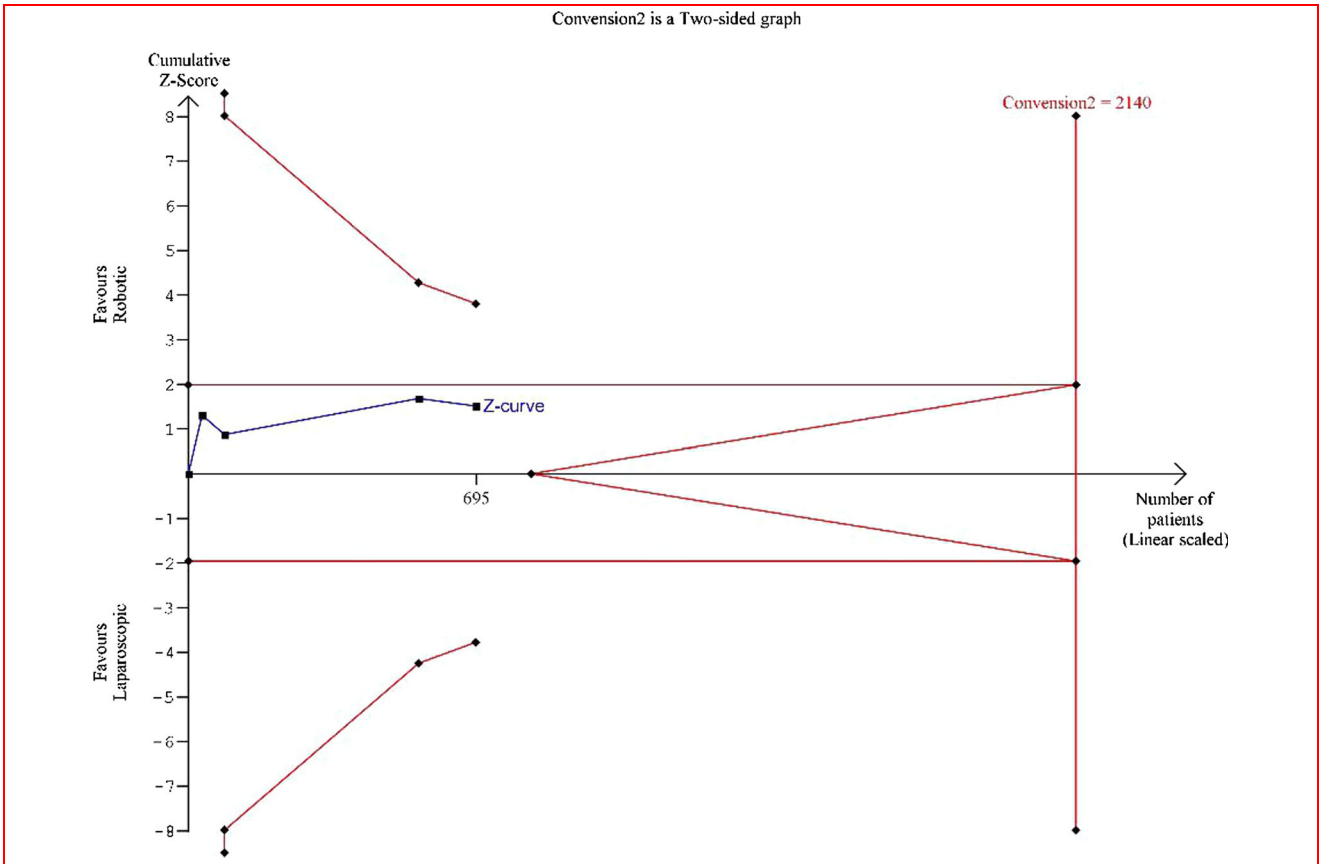

Fig. 3 Trial sequential analysis of the incidence of open conversion rate

RCTs (44 OS [4–7, 16, 17, 34, 37, 38, 40, 42–46, 48, 51, 52, 55, 56, 59, 61–64, 66–68, 70–72, 74–78, 80, 83, 85–87, 89–91], 40,085 patients), the all-cause mortality rate was significantly lower in RAS group ($\rho < 0.001$, $I^2 = 10\%$; OR 0.47; 95% CI 0.35, 0.63). However, in the subgroup of RCTs (4 RCTs [12, 13, 39, 79], 729 patients), all-cause mortality rate in RAS was similar to CLS group ($\rho = 0.98$; OR 0.97; 95% CI 0.14, 6.98). There was only one RCT [13] with 2 perioperative deaths in each group and none in the other RCTs. Thus, the trial sequential analysis for all-cause mortality was not performed due to too little information available for the statistical analysis.

There was a significant difference in the incidence of SSI, the risk being lower in the RAS than CLS (42 studies [2, 3, 6, 12, 13, 16, 17, 34–36, 38–40, 42- 46, 49, 50, 53, 56–58, 62, 64, 66–68, 71–75, 79, 84–90,]; 123,211 patients; $\rho < 0.001$, $I^2 = 0\%$; FEM: OR 1.24; 95% CI 1.11, 1.39) (eFigure 1). In the subgroup of non-RCTs (38 OS [2, 3, 6, 16, 17, 34–36, 38, 40, 42–46, 49, 50, 53, 56–58, 62, 64, 66–68, 71–75, 84–90,], 122,482 patients), SSI was more likely to occur in CLS compared to RAS ($\rho < 0.001$, $I^2 = 0\%$; OR 1.27; 95% CI 1.13, 1.43). However, in the subgroup of RCTs (4 RCTs [12, 13, 39, 79], 729 patients), no significant difference in SSI was observed ($\rho = 0.44$, $I^2 = 0\%$; OR 0.81; 95% CI 0.48, 1.37).

The estimated intraoperative blood loss was reported in 37 studies [6, 14, 16, 31, 34, 36–38, 42, 43, 46–49, 51–53, 55, 56, 59, 62, 63, 66–69, 72, 73, 77, 79–81, 83, 85, 86, 89, 90] (4508 patients). This meta-analysis demonstrated that RAS group was associated with significant lower intraoperative blood loss as compared to the CLS arm ($\rho = 0.01$, $I^2 = 88\%$; REM: MD − 18.05; 95% CI − 32.24, − 3.85; ml) (eFigure 2). In the subgroup of non-RCTs (35 OS [6, 16, 31, 34, 36–38, 42, 43, 46–49, 51–53, 55, 56, 59, 62, 63, 66–69, 72, 73, 77, 80, 81, 83, 85, 86, 89, 90], 4299 patients), the intraoperative blood loss was significantly lower in RAS than CLS ($\rho < 0.001$, $I^2 = 85\%$; MD − 25.23; 95% CI − 38.88, − 11.57). In the subgroup of RCTs (2 RCTs [14, 79], 209 patients), both CLS and RAS had no significant difference in the estimated intraoperative blood loss ($\rho = 0.43$, $I^2 = 98\%$; MD 87.93; 95% CI − 128.62, 304.49).

In comparison to the CLS arm, the duration of hospital stay was significantly shorter in RAS (59 studies [2–4, 6, 7, 13, 14, 16, 17, 31–39, 42–52, 55, 56, 58, 59, 61–64, 66, 68–73, 75, 77–81, 83–91], 150,083 patients; $\rho < 0.001$,

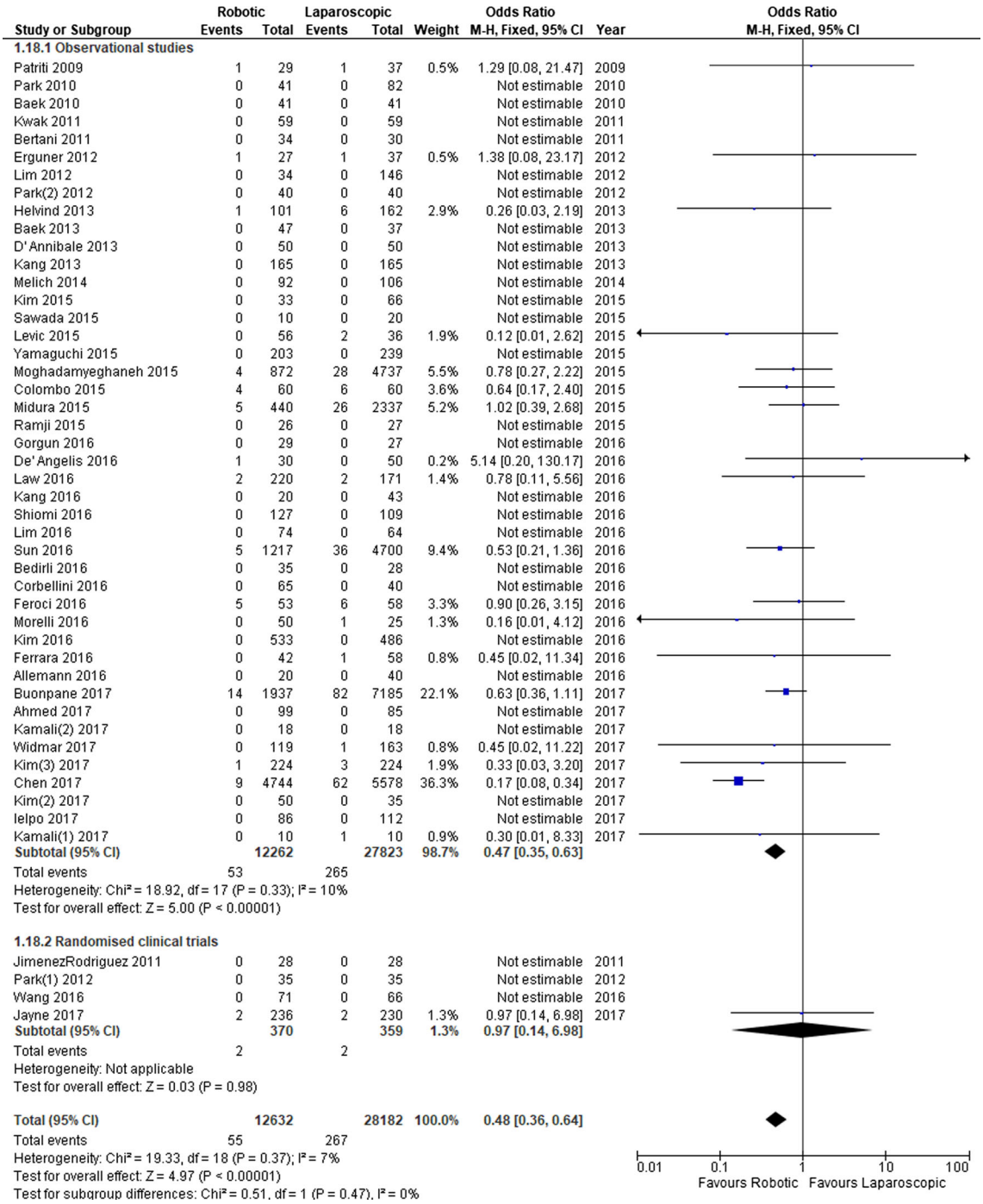

Fig. 4 Forest plot of the mortality rate

I^2 = 94%; REM: MD − 0.77; 95% CI, − 1.12, − 0.41; days), with substantial degree of heterogeneity (eFigure 3). In the subgroup of non-RCTs (54 OS [2–4, 6, 7, 16, 17, 31, 33–38, 42–52, 55, 56, 58, 59, 61–64, 66, 68–73, 75, 77, 78, 80, 81, 83–91], 149,340 patients), CLS cohort had significant longer length of hospitalization than RAS ($\rho < 0.001$, I^2 = 95%; MD − 0.77; 95% CI − 1.14, − 0.39). However, in the subgroup of RCTs (5 RCTs [13, 14, 32, 39, 79], 743 patients), no significant difference in the length of hospital stay was demonstrated in between both groups (ρ = 0.05, I^2 = 35%; MD − 0.85; 95% CI − 1.69, 0.00).

Twenty-two studies [6, 14, 16, 33, 36, 38, 39, 43, 44, 46, 47, 56, 58, 59, 69, 72, 78–81, 85, 88] (19 non-RCTs [6, 16, 33, 36, 38, 43, 44, 46, 47, 56, 58, 59, 69, 72, 78, 80, 81, 85,

Table 1 Characteristics of included studies

Author	Year	Country	Setting	N	Location of cancer	Preoperative tumor stage (AJCC 7th edition)	Overall risk of bias
Randomized controlled trials							
Baik	2008	Korea	Single-center	36	Rectum	0, I, IIA, IIIA-C	High
Jimenez Rodriguez	2011	Spain	Single-center	56	Colon and rectum	0, I, IIA, IIIA-C	Unclear
Park(1)	2012	Korea	Single-center	70	Colon	0-III	Unclear
Wang	2016	China	Single-center	137	Rectum	NA	Unclear
Jayne	2017	UK, Italy, Denmark, USA, Finland, Korea, Germany, France, Australia, Singapore	Multi-center	466	Rectum	0-III	Low
Kim(1)	2017	Korea	Single-center	139	Rectum	0-III	High
Observational studies							
Pigazzi	2006	USA	Single-center	12	Rectum	NA	High
Baik	2009	Korea	Single-center	113	Rectum	0, I, IIA, IIIA, IV	High
Patriti	2009	Italy	Single-center	66	Rectum	0-IV	High
Baek	2010	USA	Single-center	82	Rectum	NA	Low
Bianchi	2010	Italy	Single-center	50	Rectum	0, I, IIA, IIIA-C, IV	High
Park	2010	Korea	Single-center	123	Rectum	0-III	Low
Popescu	2010	Romania	Single-center	122	Rectum	0, I, IIA, IIIA-C, IV	High
Bertani	2011	Italy	Single-center	64	Colon	0, I, IIA, IIIA-C	High
Kwak	2011	Korea	Single-center	118	Rectum	0-IV	Low
Patel	2011	USA	Single-center	16	Colon and rectum	NA	High
Erguner	2012	Turkey	Single-center	64	Rectum	NA	High
Lim	2012	Korea	Single-center	180	Colon	I-III	High
Park(2)	2012	Korea	Single-center	80	Rectum	0-IV	High
Shin	2012	Korea	Single-center	60	Colon and rectum	I-IV	High
Baek	2013	Korea	Single-center	84	Rectum	0, I, IIA, IIIA-C, IV	High
D'Annibale	2013	Italy	Single-center	100	Rectum	NA	High
Helvind	2013	Denmark	Single-center	263	Colon	0-IV	High
Kang	2013	Korea	Single-center	330	Rectum	NA	Low
Kuo	2014	Taiwan	Single-center	64	Rectum	0-IV	High
Melich	2014	Korea	Single-center	198	Rectum	I-IV	High
Park	2014	Korea	Single-center	178	Rectum	I-IV	Low
Tam	2014	USA	Single-center	42	Rectum	NA	High
Byrn	2015	USA	Single-center	28	Colon	NA	High
Cho	2015	Korea	Single-center	211	Rectum	0-III	High
Colombo	2015	France	Single-center	120	Rectum	0, I, II, III	High
Gorgun	2015	USA	Single-center	66	Colon and rectum	0-III	Low
Kim	2015	Korea	Single-center	99	Rectum	0-III	Low
Levic	2015	Denmark	Multi-center	92	Rectum	0-IV	High
Midura	2015	USA	Multi-center	2777	Rectum	I-III	High
Moghadamyeghaneh	2015	USA	Multi-center	5609	Rectum	0-III	Low
Ramji	2015	Canada	Single-center	53	Rectum	NA	High
Sawada	2015	Japan	Single-center	30	Colon and rectum	I, II, IIIA-B	Low
Serin	2015	Turkey	Multi-center	79	Rectum	IIA-C, IIIB-C	High
Shibata	2015	Japan	Single-center	38	Colon and rectum	0-IV	High
Yamaguchi	2015	Japan	Single-center	442	Rectum	0-IV	High
Allemann	2016	Switzerland	Single-center	60	Rectum	NA	Low
Bedirli	2016	Turkey	Single-center	63	Rectum	II, IIIB-C	High
Bozkurt	2016	Turkey	Single-center	61	Colon and rectum	0-III	High
Cardinali	2016	Italy	Single-center	90	Colon	I, IIA-C, IIIA-C, IVA	High
Corbellini	2016	Italy	Multi-center	105	Rectum	0, I, II, III	High
De'Angelis	2016	France	Single-center	80	Colon	0, I, IIA, IIIA-B	High
deJesus	2016	Brazil	Single-center	100	Rectum	IIA-C, IIIB-C	High

Table 1 continued

Author	Year	Country	Setting	N	Location of cancer	Preoperative tumor stage (AJCC 7th edition)	Overall risk of bias
Feroci	2016	Italy	Multi-center	111	Rectum	0, I, IIA, IIIA-C	Low
Ferrara	2016	Italy	Single-center	100	Colon and rectum	0-III	High
Gorgun	2016	USA	Single-center	56	Rectum	NA	High
Jung	2016	Korea	Single-center	212	Colon	II, III	Low
Kang	2016	Korea	Single-center	63	Colon	0-III	Low
Kim	2016	Korea	Single-center	1019	Rectum	0-III	High
Law	2016	Hong Kong	Single-center	391	Rectum	NA	High
Lim	2016	Korea	Single-center	138	Rectum	0-III	High
Morelli	2016	Italy	Single-center	75	Rectum	0, I, IIA, IIIA-C, IV	High
Panteleimonitis	2016	UK	Single-center	126	Rectum	NA	High
Shiomi	2016	Japan	Single-center	236	Rectum	0-IV	High
Sun	2016	USA	Multi-center	5917	Rectum	0-III	High
Addae	2017	USA	Multi-center	111,203	Colon and rectum	NA	Low
Ahmed	2017	UK	Single-center	184	Rectum	0-IV	High
Buonpane	2017	USA	Multi-center	9122	Rectum	0-IV	High
Chen	2017	USA	Multi-center	10,322	Rectum	NA	Low
Huang	2017	Taiwan	Single-center	78	Rectum	0-III	High
Ielpo	2017	Spain	Single-center	198	Rectum	0, I, IIA, IIIA-C, IV	High
Kamali(1)	2017	UK	Single-center	22	Rectum	I–III	High
Kamali(2)	2017	UK	Single-center	36	Rectum	I–III	Low
Kim(2)	2017	Korea	Single-center	85	Rectum	III–IV	Low
Kim(3)	2017	Korea	Single-center	732	Rectum	0-IV	High
Mirkin	2017	USA	Multi-center	15,112	Colon	I–III	Low
Silva-Velazco	2017	USA	Single-center	184	Rectum	I–III	High
Widmar	2017	USA	Single-center	282	Colon	I–IV	Low

88], 3 RCTs [14, 39, 79]) measured the time to oral diet in postoperative days, and this meta-analysis demonstrated that RAS cohort was associated with shorter time to oral diet than CLS cohort (2373 patients; $\rho < 0.001$, $I^2 = 60\%$; MD − 0.43; 95% CI − 0.64, − 0.21; days) (eFigure 4). The statistical heterogeneity was high across all studies ($I^2 = 60\%$, $\rho < 0.001$). Time to oral diet was recorded to be significantly shorter in RAS cohort in the non-RCT subgroup (2108 patients; $\rho < 0.001$, $I^2 = 65\%$; MD − 0.43; 95% CI − 0.68, − 0.19) but not in the RCTs subgroup (265 patients; $\rho = 0.15$, $I^2 = 0\%$; MD − 0.30; 95% CI − 0.70, 0.11).

The rate of local recurrence was not significant in both RAS (2.3%) and CLS (4.1%) groups (10 OS [16, 34, 36, 40, 67, 72, 81, 85, 86, 90], 1045 patients; $\rho = 0.13$; $I^2 = 0\%$; OR 0.58; 95% CI 0.29, 1.18) (eFigure 5). No substantial heterogeneity was found across studies.

Ten OS [16, 33, 34, 36, 40, 67, 72, 85, 86, 90] ($n = 979$) reported the incidence of distant recurrence in colorectal cancer patients who underwent either RAS or CLS. No significant difference was noted in both groups ($\rho = 0.26$; $I^2 = 0\%$, FEM: OR 1.28; 95% CI 0.83, 1.97) (eFigure 6).

The incidence of anastomotic leak was reported in 48 studies [3, 12–14, 16, 17, 33–40, 42–44, 46, 51, 52, 56, 57, 59, 61–63, 65–73, 75, 78–86, 88–90] (43 non-RCTs [3, 16, 17, 33–38, 40, 42–44, 46, 51, 52, 56, 57, 59, 61–63, 65–73, 75, 78, 80–86, 88–90], 5 RCTs [12–14, 39, 79], a total of 7480 patients). There was no significant difference in between both RAS and CLS cohort ($\rho = 0.19$, $I^2 = 0\%$; FEM: OR 0.88; 95% CI 0.72, 1.07) (eFigure 7). In the subgroups of both RCTs ($n = 763$) and non-RCTs ($n = 6717$), the rate of anastomotic leak was not significant ($\rho > 0.05$), with low heterogeneity ($I^2 = 0\%$).

The duration of surgery was significantly longer in RAS cohort (59 studies [3, 6, 12–14, 16, 17, 31–52, 55, 56, 58, 59, 61–64, 66, 68–81, 83–86, 88–90]; 8293 patients, $\rho < 0.001$, $I^2 = 93\%$; REM: MD 38.19; 95% CI 28.78–47.60; minutes), with a pooled mean difference of 38 min to CLS group (eFigure 8). In the subgroup of non-RCTs (53 OS [3, 6, 16, 17, 31, 33–38, 40–52, 55, 56, 58, 59, 61–64, 66, 68–78, 80, 81, 83–86, 88–90], 7391 patients; $\rho < 0.001$, $I^2 = 93\%$; MD 36.63; 95% CI 26.41, 46.86) and RCTs (6 RCTs [12–14, 32, 39, 79], 902 patients; $\rho < 0.001$, $I^2 = 88\%$; MD 51.75; 95% CI 31.95, 71.55), the

Table 2 Subgroup analyses table based on study design (non-RCTs vs RCTs), quality of studies (high/unclear risk vs low risk studies) and location of cancer (rectum vs colon vs colon and rectum) and trial sequential analysis based on RCTs only

Outcomes	Studies	*n*	I^2	MD/OR (95% CI)	ρ value	TSA (based on RCTs only)—required information size
Conversion rate	63	146,143	65%	OR 0.40 (0.30, 0.53)	<0.001	
Non-RCTs	58	145,378	66%	OR 0.38 (0.28, 0.51)	<0.001	
RCTs	5	765	0%	OR 0.66 (0.37, 1.16)	0.15	Inconclusive—2140
High/unclear risk of bias studies	46	12,156	20%	OR 0.41 (0.30, 0.57)	<0.001	
Low risk of bias studies	17	133,987	84%	OR 0.39 (0.25, 0.63)	<0.001	
Rectum	46	18,363	14%	OR 0.39 (0.30, 0.49)	<0.001	
Colon	10	16,232	43%	OR 0.56 (0.28, 1.10)	0.09	
Colon and rectum	7	111,548	66%	OR 0.59 (0.21, 1.67)	0.32	
All-cause mortality rate	48	40,814	7%	OR 0.48 (0.36, 0.64)	<0.001	
Non-RCTs	44	40,085	10%	OR 0.47 (0.35, 0.63)	<0.001	
RCTs	4	729	NA	OR 0.97 (0.14, 6.98)	0.98	Not performed—too little events
High/unclear risk of bias studies	33	22,998	0%	OR 0.62 (0.43, 0.89)	0.01	
Low risk of bias studies	15	17,816	59%	OR 0.32 (0.20, 0.52)	<0.001	
Rectum	38	39,626	18%	OR 0.47 (0.35, 0.64)	<0.001	
Colon	7	1002	14%	OR 0.58 (0.15, 2.21)	0.43	
Colon and rectum	3	186	NA	OR 0.45 (0.02, 11.34)	0.63	
Wound infection/Surgical site infection	42	123,211	0%	OR 1.24 (1.11, 1.39)	<0.001	
Non-RCTs	38	122,482	0%	OR 1.27 (1.13, 1.43)	<0.001	
RCTs	4	729	0%	OR 0.81 (0.48, 1.37)	0.44	Inconclusive—3806
High/unclear risk of bias studies	30	4636	0%	OR 0.78 (0.56, 1.10)	0.16	
Low risk of bias studies	12	118,575	0%	OR 1.33 (1.18, 1.50)	<0.001	
Rectum	29	10,601	0%	OR 1.00 (0.79, 1.26)	0.99	
Colon	9	1252	0%	OR 0.77 (0.42, 1.41)	0.40	
Colon and rectum	4	111,358	0%	OR 1.39 (1.21, 1.59)	<0.001	
Intraoperative estimated blood loss	37	4508	88%	MD − 18.05 (− 32.24, − 3.85)	0.01	
Non-RCTs	35	4299	85%	MD − 25.23 (− 38.88, − 11.57)	<0.001	
RCTs	2	209	98%	MD 87.93 (− 128.62, 304.49)	0.43	Not performed—too little events
High/unclear risk of bias studies	29	3569	90%	MD − 20.52 (− 36.25, − 4.78)	0.01	
Low risk of bias studies	8	939	71%	MD − 6.59 (− 42.97, 29.78)	0.72	
Rectum	30	3961	88%	MD − 24.09 (− 41.76, − 6.41)	0.008	
Colon	5	457	90%	MD 8.34 (− 18.53, 35.22)	0.54	
Colon and rectum	2	90	0%	MD − 27.87 (− 72.61, 16.88)	0.22	
Length of hospitalization	59	150,083	94%	MD − 0.77 (− 1.12, − 0.41)	<0.001	
Non-RCTs	54	149,340	95%	MD − 0.77 (− 1.14, − 0.39)	<0.001	
RCTs	5	743	35%	MD − 0.85 (− 1.69, 0.00)	0.05	Not performed—too little events
High/unclear risk of bias studies	44	21,156	86%	MD − 0.95 (− 1.39, − 0.51)	<0.001	
Low risk of bias studies	15	128,927	98%	MD − 0.33 (− 1.12, 0.47)	0.42	
Rectum	45	37,584	94%	MD − 0.81 (− 1.29, − 0.33)	0.001	
Colon	9	1050	92%	MD − 1.09 (− 2.85, 0.68)	0.23	
Colon and rectum	5	111,449	68%	MD − 0.39 (− 1.75, 0.98)	0.58	
Time to first oral diet	22	2373	60%	MD − 0.43 (− 0.64, − 0.21)	<0.001	
Non-RCTs	19	2108	65%	MD − 0.43 (− 0.68, − 0.19)	<0.001	
RCTs	3	265	0%	MD − 0.30 (− 0.70, 0.11)	0.15	Inconclusive—988
High/unclear risk of bias studies	17	1594	63%	MD − 0.47 (− 0.74, − 0.20)	<0.001	

Table 2 continued

Outcomes	Studies	*n*	I^2	MD/OR (95% CI)	ρ value	TSA (based on RCTs only)—required information size
Low risk of bias studies	5	779	55%	MD − 0.30 (− 0.70, 0.10)	0.14	
Rectum	15	1770	67%	MD − 0.47 (− 0.78, − 0.15)	0.004	
Colon	6	547	45%	MD − 0.36 (− 0.69, − 0.03)	0.03	
Colon and rectum	1	56	NA	MD − 0.20 (− 0.68, 0.28)	0.41	
Local recurrence rate	10	1045	0%	OR 0.58 (0.29, 1.18)	0.13	
Non-RCTs	10	1045	0%	OR 0.58 (0.29, 1.18)	0.13	
RCTs	0	0	NA	Not estimable	NA	–
High/unclear risk of bias studies	5	502	0%	OR 0.59 (0.22, 1.62)	0.31	
Low risk of bias studies	5	543	0%	OR 0.57 (0.21, 1.54)	0.27	
Rectum	10	1045	0%	OR 0.58 (0.29, 1.18)	0.13	
Colon	0	0	NA	Not estimable	NA	
Colon and rectum	0	0	NA	Not estimable	NA	
Distant recurrence rate	10	979	0%	OR 1.28 (0.83, 1.97)	0.26	
Non-RCTs	10	979	0%	OR 1.28 (0.83, 1.97)	0.26	
RCTs	0	0	NA	Not estimable	NA	–
High/unclear risk of bias studies	6	614	0%	OR 1.28 (0.71, 2.31)	0.41	
Low risk of bias studies	4	365	0%	OR 1.28 (0.69, 2.39)	0.44	
Rectum	10	979	0%	OR 1.28 (0.83, 1.97)	0.26	
Colon	0	0	NA	Not estimable	NA	
Colon and rectum	0	0	NA	Not estimable	NA	
Anastomotic leak	48	7480	0%	OR 0.88 (0.72, 1.07)	0.19	
Non-RCTs	43	6717	0%	OR 0.81 (0.65, 1.01)	0.06	
RCTs	5	763	0%	OR 1.36 (0.80, 2.30)	0.25	Inconclusive—5654
High/unclear risk of bias studies	36	5705	0%	OR 0.86 (0.68, 1.10)	0.24	
Low risk of bias studies	12	1775	0%	OR 0.90 (0.63, 1.28)	0.56	
Rectum	40	6657	0%	OR 0.87 (0.71, 1.07)	0.19	
Colon	5	606	0%	OR 1.10 (0.32, 3.77)	0.88	
Colon and rectum	3	217	0%	OR 0.80 (0.18, 3.52)	0.77	
Operative time	59	8293	93%	MD 38.19 (28.78, 47.60)	<0.001	
Non-RCTs	53	7391	93%	MD 36.63 (26.41, 46.86)	<0.001	
RCTs	6	902	88%	MD 51.75 (31.95, 71.55)	<0.001	Inconclusive—4482
High/unclear risk of bias studies	45	6078	94%	MD 36.64 (25.78, 47.50)	<0.001	
Low risk of bias studies	14	2215	89%	MD 43.82 (23.46, 64.17)	<0.001	
Rectum	44	6699	94%	MD 40.71 (29.34, 52.08)	<0.001	
Colon	10	1332	86%	MD 14.07 (− 1.89, 30.03)	0.08	
Colon and rectum	5	262	80%	MD 72.44 (36.62, 108.27)	<0.001	

Randomized control trials (RCTs), trial sequential analysis (TSA)

finding remained the same where RAS required longer duration of operation as compared to the CLS cohort.

Discussions

To the best of our knowledge, this is the largest review comparing the benefits of robotic-assisted and conventional laparoscopic surgery for colorectal cancer. An exhaustive literature search was conducted with all included studies that underwent a rigorous assessment of methodological and evidence quality. This meta-analysis demonstrated that RAS reduces the incidence of open conversion as compared to the CLS cohort, although the trial sequential analysis was inconclusive due to limited number of RCTs available. RAS was superior to CLS in term of all-cause mortality, incidence of SSI, intraoperative blood loss, length of hospital stay and time to oral diet, at the expense

of longer duration of operative time. No significant effects on local or distant recurrence rate and incidence of anastomotic leak were detected in this review. Among all the measured outcomes, the subgroup analyses of RCT showed no significant group difference, except in the operative time.

Several meta-analyses [18–21] were available in the literature with some methodological issues and limitations. A meta-analysis conducted by Liao and his team in 2014 included a RCT [34], which was not randomized after the enrollment of first few patients. Our review updated the previous meta-analysis by removing that RCT and adding a three new RCTs [12–14]. Detailed subgroup analyses were performed for each end-point to demonstrate the effects of study design, level of risk of bias and location of cancer on the statistical significance of all our measured outcomes. In a meta-analysis by Wilder and team [18], keywords were searched in the databases instead of medical subject headings without a pre-planned review protocol. Another two meta-analyses [20, 21] updated the search until August 2017 and it missed out three RCTs, which were included in this current review. We adhered to the guideline of PRISMA and Cochrane Review to conduct this systematic search with a pre-planned review protocol and synthesize comprehensive findings regarding the efficacy and safety of RAS and CLS in colorectal cancer.

A recent review (n = 53,329) reported that an average open conversion rate in laparoscopic colorectal cancer resection was 14.3%, resulting in longer operative time, greater intraoperative blood loss and poorer survival rate in the converted cohort as compared to the laparoscopically completed cohort [93, 94]. The main reasons for conversion to open colorectal surgery were mainly due to the complex anatomy, technical challenges or major intraoperative complications [95–97]. In this review, the incidence of open conversion was 2.9% in RAS and 15.8% in CLS, which was statistically significant. In comparison to the four-degrees-of-freedom instruments in CLS, the seven-degrees-of-freedom robotic arms allow surgeons to perform more meticulous and precise procedure. In addition, RAS provides high-quality 3-dimensional imaging with magnification, free moving multi-joint forceps, better ergonomic and stable platform of camera controlled by surgeons [98–100]. In the subgroup analysis on the location of tumor, the benefits of RAS were more prominent in the rectal cancer population because laparoscopic tumor resection was technically more challenging in the confined space of distal pelvis, which was consistent with previous meta-analyses [101–110]. However, the recently published ROLARR trial [13] (n = 466) reported no statistical significance in the overall incidence of conversion for rectal cancer between RAS and CLS cohorts, although it showed promising result in the subgroup of challenging cohorts (men, obese patients, and abdominoperineal resection). Our trial sequential analysis based on 4 RCTs [13, 14, 32, 39] was inconclusive as it has yet to achieve the required information size (n = 2140). The quality of evidence was low due to potential publication bias and small study size. Future adequately powered RCTs are warranted in order to draw firm conclusion on the incidence of open conversion.

The delicate handling of robotic-assisted approach in laparoscopic surgery is believed to provide safer surgical procedure and more efficient tumor resection than CLS. Apart from providing clear microscopic view of blood vessels and nerves with the 3D imaging and magnification, RAS has multi-articulated instrument, which allows the surgeon to carefully manipulate the blood vessels, rapidly control and minimize bleeding [72, 111]. Complete tremor elimination and enhanced dexterity of RAS also help to minimize the risk of visceral organs perforation and contaminated wound, which are the major risk factors for SSI [112]. Our review demonstrated that RAS cohort was associated with a significant reduction in all-cause mortality, intraoperative blood loss and postoperative SSI as compared to the CLS cohort. The high heterogeneity for intraoperative blood loss might be contributed by different types of procedure for colorectal cancer [105, 107]. The combination of different types of colorectal procedure (abdominoperineal resection, low and high anterior resection, colectomy, Hartmann's procedure/proctosigmoidectomy) was used across all the included RCTs, which may introduce variability to our findings. Thus, it is very difficult to perform a subgroup analysis based on the type of procedure.

In recent years, there has been an increase focus in studies examining the enhanced recovery program for patients after laparoscopic colorectal surgery [113]. Minimal manipulation on colon during colorectal surgery promotes faster bowel function recovery and shorter length of hospitalization. Our study showed that RAS cohort was associated with shorter time to oral diet and duration of hospital stay than CLS. It is believed that the robotic arms improved ergonomics and precise movement in removing the colorectal tumors [114]. Several studies supported that early oral feeding after colorectal surgery can expedite postoperative recovery, reduce complications, and shorten length of hospitalization [115–118]. However, our review does not provide evidence of a causal relationship between the time to oral diet and length of hospitalization. Length of hospital stay can be very subjective, and it could potentially be affected by many confounding factors, namely age, comorbidities, different discharge criteria and different stages of colorectal cancer. Hence, our results have to be interpreted with caution as both time to oral diet and length of hospitalization were noted to have high degree of heterogeneity.

Our review demonstrated no significant difference in the incidence of anastomotic leak between RAS and CLS cohorts, which was in line to other meta-analyses [103, 104, 107, 108, 110, 114, 119, 120]. Homogeneity was present across all subgroups in this outcome ($I^2 = 0\%$). The types of suture used (hand-sewn or stapled) in each cohort were not fully explored in this systematic review, which may potentially introduce variances to this finding. No statistical significances were noted in both local and distant recurrence rates during the follow-up of 3–5 years from 10 observational studies. This finding needs to be validated by future RCTs with longer duration of follow-up.

In this review, RAS cohort required an average of 38 minutes longer operative time in comparison to CLS cohort, which was statistically significant. The high degree of heterogeneity in operative time was consistent with all the previous meta-analyses [18, 19, 101–107, 109, 114, 119]. The high heterogeneity could be influenced by different surgeon's experience level, robotic approach (complete robotic versus hybrid) and specimen-retrieval technique [19, 106, 107]. Many authors [107, 108, 120] believed that the total operative time could be improved when there are sufficient robotic cases performed to overcome the new learning curve for RAS [48, 55, 83].

Our review had several limitations. First, non-randomized studies were included in this meta-analysis and there was an inherent selection bias. However, authors performed subgroup analyses to overcome this limitation. No industry support bias was found in any of the included studies. Also, we were not able to control the confounding factors (the level of expertise of surgeons involved, total versus hybrid robotic surgery and the type of colorectal procedures) in all included studies at this review level. The information of some measured outcomes was mainly obtained from studies with high risk of bias. The exclusion of trials published as abstract or presented at conferences may potentially introduce publication bias to our findings.

In conclusion, this meta-analysis suggests that RAS may reduce the incidence of open conversion and all-cause mortality, at the expense of longer duration of operative time. The inconclusive trial sequential analysis and low quality of evidence warranted future adequately powered RCTs to fill the knowledge gap.

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Compliance with ethical standards

Conflict of interest All authors have declared that they do not have any conflicts of interest in this review.

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