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Does Postoperative Rehabilitation for Radical Cystectomy Call for Enhanced Recovery after Surgery? A Systematic Review and Meta-analysis*

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Summary: The aim of this review was to systematically compare the outcomes of enhanced recovery after surgery (ERAS) with standard care (SC) after radical cystectomy. We performed a systematic search of PubMed, Ovid, Web of Science, and the Cochrane Library to identify studies published until September 2017 which involved a comparison of ERAS and SC. A meta-analysis was performed to assess the outcomes of ERAS versus SC. Sixteen studies including 8 prospective and 8 retrospective trials met the eligibility criteria. A total of 2100 participants were assigned to ERAS (1258 cases) or SC (842 cases). The time to first flatus passage [WMD=–0.95 days, 95% CI (–1.50, –0.41), *P*=0.0006], time until return to a regular diet [WMD=–2.15 days, 95% CI (–2.86, –1.45), *P*<0.00001] and the length of hospital stay [WMD=–3.75 days, 95% CI (–5.13, –2.36), *P*<0.00001] were significantly shorter, and the incidence of postoperative complications [OR=0.60, 95% CI (0.44, 0.83), *P*=0.002], especially postoperative paralytic ileus [OR=0.43, 95% CI (0.30, 0.62), *P*<0.00001] and cardiovascular complications [OR=0.28, 95% CI (0.09, 0.90), *P*=0.03] was significantly lower in the ERAS group than those in the SC group. This meta-analysis demonstrated that ERAS was associated with a shorter time to first flatus passage, return of bowel function, and the length of hospital stay than SC in patients undergoing radical cystectomy, as well as a lower rate of postoperative complications, especially paralytic ileus and cardiovascular complications.
Key words: enhanced recovery after surgery; postoperative rehabilitation; bladder cancer; radical cystectomy; meta-analysis

In China, bladder cancer represents the second most common tumour of the genitourinary tract in adults[1], and it is the fourth most commonly diagnosed malignancy in men in the United States[2]. Radical cystectomy (RC) with urinary diversion represents the gold standard treatment for muscle-invasive bladder cancer[3]. Despite improvements in perioperative care protocols and standardisation of surgical techniques, such as laparoscopic and robot-assisted protocols, RC is still associated with a greater risk of complications, affecting 30%–64% of patients[4].

Enhanced recovery after surgery (ERAS) protocols, also known as enhanced recovery protocol and fast-track surgery, were introduced by Kehlet in 2001 to reduce postoperative complications associated with colorectal surgery[5]. ERAS has been used in clinical practice for more than a decade in patients undergoing colorectal surgery, resulting in a significantly reduced complication rate and a shorter length of hospital stay (LOS)[6].

In 2013, Yannick *et al* published a set of ERAS guidelines for operative care after RC for bladder cancer. According to these guidelines, ERAS protocols include preoperative counselling and education, preoperative medical optimisation, omission of mechanical bowel preparation (MBP), carbohydrate loading, limited preoperative fasting,

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venous thromboembolism prophylaxis, epidural analgesia, minimally invasive approaches, standard anaesthetic protocol, goal-directed perioperative fluid management, antimicrobial prophylaxis, early removal of nasogastric tubes, prevention of nausea and vomiting, early return to diet, prevention of paralytic ileus, early mobilisation, and auditing of compliance with the protocol[7], as depicted in fig. 1. Preoperative counselling and education include surgical details, hospital stay and discharge criteria. Preoperative medical optimization, such as smoking cessation, muscle training, reduction of alcohol intake and nutritional screening, can protect against postoperative complications and improve recovery rate. Cystectomy patients benefit from antibiotic prophylaxis, although the best antibiotic regimen is unclear and likely depends on local antibiotic-resistance profiles. Low-molecular-weight heparin drugs are the most tolerable, efficacious, and cost-effective in thromboprophylaxis. Other protective measures include the use of intermittent pneumatic compression devices and compression stockings during hospitalization. Intraoperative ERAS elements include avoidance of long-acting anesthetic agents, mid-thoracic epidural anesthesia, no drains and maintenance of normothermia.

No nasogastric tubes, early removal of catheter, early oral nutrition, non-opioid oral analgesia/non-steroidal antiinflammatory drugs (NSAIDs), early mobilization, stimulation of gut motility and audit of compliance and outcomes are the postoperative elements. The benefits of early oral nutrition after major abdominal surgery include decreased paralytic ileus, fewer infectious complications, and a faster recovery. Early postoperative mobilization may have benefits, including counteracting insulin resistance and reducing chest complications. It can reduce pain and the likelihood of developing ileus, therefore hastening functional recovery. Prokinetic agents, such as metoclopramide, were traditionally advocated for use within ERAS programs to stimulate gut motility. Gum chewing appears to be beneficial for abdominal and gastrointestinal surgery patients. All patients should be audited for protocol compliance and outcomes. Auditing ERAS programs can help assess compliance with recommended pathways, which is necessary to ensure successful implementation and evaluate the effect on clinical and financial outcomes[7].

Several clinical trials of ERAS for RC have been published over the years. These studies have demonstrated a significant reduction in postoperative complications and LOS, and an improvement in health-related quality of life[8–10]. However, according to a survey of urologic oncologists, ERAS isn't widely applied after RC[11]. Thus, we conducted a systematic review and meta-analysis of the literature to compare the outcomes of ERAS with standard care (SC) in patients after RC.

1 MATERIALS AND METHODS

1.1 Search Protocol and Data Sources

We conducted a systematic search of the PubMed, Ovid, Web of Science, and Cochrane Central Register of Controlled Trials (Cochrane Library) electronic databases to identify potentially relevant studies published until September 2017. The following Medical Subject Headings (MESH) terms were used: ["fast-track surgery" OR "fast-track rehabilitation" OR "enhanced recovery protocol" OR "enhanced recovery after surgery"] AND ["bladder cancer" OR "bladder tumor" OR "cystectomy" OR "radical cystectomy"]. We also checked the reference lists of all related articles to identify any studies which might have been missed.

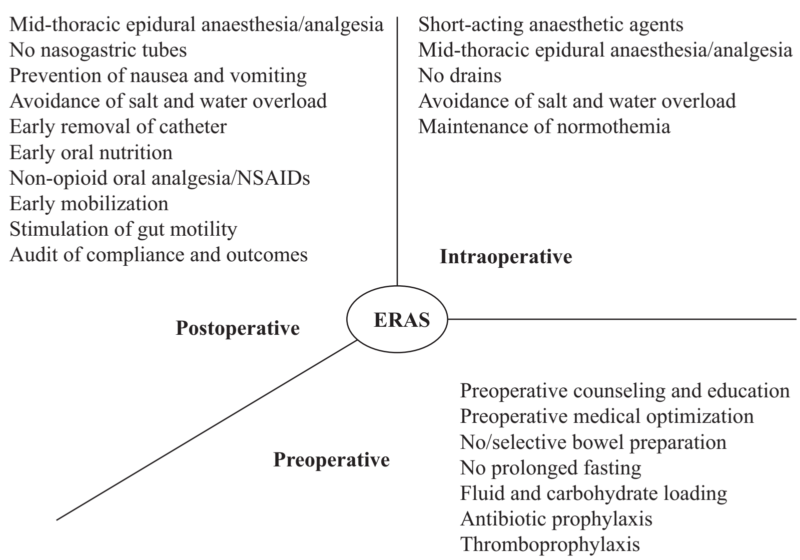


Fig. 1 ERAS guideline for preoperative, intraoperative and postoperative care

1.2 Inclusion Criteria and Exclusion Criteria

To be eligible for inclusion, studies had to report one or more of the following: (1) participants, patients who were diagnosed as having bladder cancer and underwent RC; (2) intervention, an ERAS protocol was applied for patients who underwent RC; (3) controls, SC was applied for patients who underwent RC; (4) outcomes, the primary outcomes included the time to first flatus, the LOS, complication rate within the first 30 or 90 days (Clavien-Dindo classification), and postoperative paralytic ileus (POI) rate; (5) studies, only controlled trials were considered, including randomised controlled trials (RCTs) and non-randomised clinical studies; and (6) the enhanced recovery protocol should be described in detail, and must involve at least two or more elements (fig. 1). The guidelines varied by specialty, but always included at least 20 elements categorised into preoperative, intraoperative, and postoperative elements[12].

The studies which met one of the following criteria were excluded: (1) the inclusion criteria were not met; (2) trial or study did not report the postoperative outcomes of interest, or it was not possible to calculate or extrapolate the necessary data from the published results; (3) trial or study compared ERAS and improved ERAS; (4) article was a review, case report, or letter, or was not a comparative study; and (5) non-English publications.

1.3 Outcomes of Interest

The primary outcomes of interest of this systematic review included the following: (1) time to first flatus; (2) LOS; (3) postoperative complication rate within the first 30 or 90 days (Clavien-Dindo classification), and (4) POI rate. The secondary outcomes included the 30- or 90-day hospital readmission rate, number of patients returning to theatre, short-term mortality, long-term mortality, and specific complications.

1.4 Study Selection and Data Extraction

Two authors (Meng WANG and Jun XIAO) independently screened all studies identified during the search by extracting the titles and abstracts. The full-text version and reference lists of all relevant articles were retrieved and reviewed to confirm the eligibility of the studies. Data including the first author, country, publication year, study design, operation type, number of patients, elements of ERAS, outcomes of interest, complications, patient demographics, clinical data, perioperative variables, and pathologic and oncological variables were extracted by our authors using a standardised data collection form. Any disagreements regarding data selection or analysis were resolved by a third reviewer (Zhi-hua WANG) through discussion and consultation until a consensus was reached. If the median, range, or interquartile range were reported, we imputed the mean and standard deviation according to the Cochrane Handbook for Systematic Review of Interventions.

1.5 Statistical Analysis

The present meta-analysis was conducted according to the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analysis (QUOROM) guidelines[13]. The results of the meta-analysis were assessed using weighted mean differences (WMD) and odds ratios (OR) for continuous and dichotomous variables, all with 95% confidence intervals (CI). When continuous data were measured in different units, we used the standardised mean difference (SMD). An OR significantly <1.0 favours the ERAS group, whereas an OR significantly >1.0 favours the SC group. Forest plots were constructed, and the results were considered statistically significant when $P<0.05$. For continuous data, we calculated the difference in mean values and the 95% CI between the ERAS and SC if the study reported the standard errors of the mean, standard deviations, or CIs. However, some studies reported continuous data as the median and range, in which case we imputed the mean and standard deviation using the method described by Hozo[14]. If the median and interquartile range were presented, we made an approximate transformation according to section 7.7.3.5 of the Cochrane Handbook for Systematic Review of Interventions[15].

When two comparisons (e.g., enhanced recovery protocol A versus SC and enhanced recovery protocol B versus SC) were included in the meta-analysis, we planned to combine the results of enhanced recovery A and enhanced recovery protocol B into a single intervention and then compare them with SC according to section 7.7.3.8 of the Cochrane Handbook for Systematic Review of Interventions[15].

Mantel-Haenszel fixed-effects meta-analysis was performed, and the amount of heterogeneity was formally tested using the chi-square test ($P<0.10$) and the I^2 statistic. A random-effects meta-analysis was adopted when significant heterogeneity was found between studies. Publication bias was assessed using funnel plots and the Egger's test of funnel plot symmetry.

Sensitivity analyses were performed on prospective studies only. Subgroup analyses were performed according to the type of intervention. Variables were pooled only when study numbers we selected were more than three in the overall meta-analysis.

The meta-analysis was performed and forest plots generated using Review Manager (Revman) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the metabias procedure of STATA version 12.0 (StataCrop, USA).

2 RESULTS

2.1 Characteristics of Eligible Studies

Sixteen studies met the eligibility criteria, including

8 retrospective[2, 7, 16–21] and 8 prospective[3–5, 22–26] trials. A total of 2100 participants among the 16 studies were assigned to enhanced recovery protocol (1258 participants) or SC (842 participants) groups (table 1). By scanning the full-text articles and their reference lists, we identified an additional 5 studies that reported the results of patients with ERAS in RC. We also found three closely related studies published by a cooperative organisation: the first study[2] published in 2008 reported a comparison between groups submitted to ERAS1 and SC, the second study[27] published in 2010 reported a comparison between the ERAS1 and ERAS2 groups, and the third study[20] published in 2015 reported a comparison among the three groups. We extracted data from the study[2] published in 2008 as it reported the most primitive data about postoperative complications for the 7 trials. Excluding one study which was a three-armed trial[21], the rest studies were all two-armed trials. Propensity score matching was only used in one study to match patients in order to reduce bias[3]. Six trials included 838 patients who underwent robot-assisted RC[3, 16, 25, 28–30], 3 trials included 331 patients who underwent laparoscopic RC[17, 24, 28], 6 trials included 608 patients who underwent open RC[21, 23, 24, 28, 30, 31], and 6 trials included 285 patients for whom the type of surgery was not reported[2, 7, 9, 18, 19, 32]. Three types of urinary diversion were reported, including neobladder (968 participants), ileal conduit (1194 participants), and continent reservoir (364 participants).

The patient demographics and characteristics of each study are presented in table 1. The elements of enhanced recovery that differed between the intervention and control groups in each of the studies are summarised in table 2.

2.2 Patient Demographics and Clinical Characteristics

There were no significant differences in demographic parameters including age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, history of previous surgeries, and previous therapy (including neoadjuvant chemotherapy and radiotherapy) between the groups. There was a significant difference in patients with tumour staging ≤T2 [OR=0.74, 95% CI (0.58, 0.95), P=0.02] in the SC group, with higher preoperative tumour staging [OR=1.42, 95% CI (1.11, 1.82), P=0.005] observed in the ERAS group (table 3).

2.3 Perioperative Variables

We extracted the theatre duration from 6 studies[3, 7, 19, 23–25], estimated blood loss (EBL) from 6 studies[3, 7, 17, 24, 25, 31], and the number of lymph nodes removed from 4 studies[3, 7, 21, 25]. There were no statistically significant differences between the ERAS and SC groups in theatre time [WMD=10.33 min, 95% CI (–10.03, 30.70), P=0.32], EBL [WMD=–136.02 mL, 95% CI (–293.43, 21.38), P=0.09), and number of lymph nodes removed [WMD=1.29, 95% CI (–1.52, 4.11), P=0.37), as shown in table 3.

2.4 Postoperative Recovery Outcomes

ERAS was associated with a significant reduction in the mean time until the first flatus [WMD=–0.95 days, 95% CI (–1.50, –0.41), P=0.0006), with significant heterogeneity (I^2=92%, P<0.00001), as shown in fig. 3A. Five papers included the time to first flatus as a primary outcome[2, 7, 23, 28, 31]. Six studies presented data on the time until the patient returned to a

Table 1 Characteristics of included studies

First author, year	Country	Study interval	Design	ERAS/SC (n)	Operation type (ERAS/SC)			Type of urinary diversion (ERAS/SC)			Age, year	Matching/ comparable[a]
					ORC	LRC	RARC	NEO	CR	IC		
Arumainayagam, 2008	UK	2005.10	Retrospective	56/56				9/11		47/45	mean 65.9/65.9	1,2,4,5,6,9
Cerruto, 2013	Italy	2010.2–2011.6	Retrospective	9/13				9/13			61.22±10.63/67.08±5.47[b]	1,2,3,4,7,9,10,11,12
Collins, 2016	Sweden	2003.12–2014.5	Retrospective	135/86			135/86	38/48		97/38	70 (63-74)/66(59-71) [d]	1,2,3,4,6,7,8,9
Guan, 2014	China	2011.3–2013.2	Retrospective	60/55		60/55				60/55	60.32±8.59/59.95±8.86[b]	1,2,3,8,9,11
Koo, 2013	UK	2006–2010	Retrospective	20/20				4/4		16/16	mean 65.8/65.9	1,2,4,6,7,9
Kukreja, 2016	USA	2011.6–2015.4	Prospective	79/75	35/36		44/39	5/3	3/1	71/71	70.6 (65.2-77.7)/73.9 (64.1-79.2)[d]	1,2,3,4,6,8,9,10,11,12
Maffezzini, 2007	Italy	2002.12–2005.12	Retrospective	71/40				50/0	0/40	21/28	mean 74/70	1,2,4,7,9,10
Mukhtar, 2013	UK	2007.10–2012.4	Prospective	51/26	51/26			3/2		48/24	67.7±7.8/69.8±8.3[b]	1,2,3,4,5,7,8,9,10
Ortega, 2015	Spain	2010.2–2012.10	Prospective	48/51	98[$]	1[$]		16/15	2/2	30/34	67.2±10.6/64.9±9[b]	1,2,4,5,8,9,10,11
Persson, 2015	Sweden	2010–2011.12	Retrospective	31/39	31/39			5/13		26/26	67 (42-80)/66 (53-80)[c]	1,2,3,4,5,6,7,8,9,10,11
Saar, 2012	Germany	2007.2–2010.3	Prospective	31/31			31/31	8/12		23/19	67.2±10.2/61.6±12.6[b]	1,2,3,4,5,7,8,9,10,11,12
Smith, 2014[#]	UK	2008.10–2013.4	Retrospective	37/27/69	37/27/69					37/27/69	70.2±9.6/71.0±9.8/68.3±12.4[b]	1,2,3,4,6,7,8,9,12
Frees, 2017	Canada	Not mentioned	Prospective	10/13							65.75 (49-86)/70.4 (51-84)[c]	1,2,3,4,9,10,11
Pang, 2017	UK	2007.2–2016.10	Prospective	393/60			425/28	25/25		368/35	71 (65-76)/66 (60.8-70.3)[d]	1,2,3,6,7,8,9,12
Semerjian, 2017	USA	2015.10–2016.5	Prospective	56/54	48/52		8/2			89/56	median 68.6/69.5	1,2,3,6,7,8,9,12
Lin, 2017	China	2014.10–2016.7	Prospective	144/154	25/34	112/103	7/8	53/56		89/56	62.9±10.1/63.3±10.3[b]	1,2,3,7,8,9,10

ORC: open radical cystectomy; LRC: laparoscopic radical cystectomy; RARC: robot-assisted radical cystectomy; NEO: neobladder; CR: continent reservoir; IC: ileal conduit. [a]Matching/comparable variables: 1=age, 2=gender, 3=body mass index (BMI), 4=American Society of Anesthesiologists (ASA) score, 5=previous surgery history, 6=previous therapy, 7=clinical stage, 8=operation type, 9=diversion type, 10=operation time, 11=estimated blood loss (EBL), 12=number of lymph nodes removed; [b]Mean±SD; [c]Median (range); [d]Median (Interquartile range); [#]data from SC patients and phase 1 ERAS and phase 2 ERAS patients. Data are represented as ERAS 1/ERAS 2/SC; [$]All interventions were open except in a case where access was laparoscopic.

Table 2 Element of each ERAS protocol

Study name	Arumainayagam, 2008	Cerruto, 2013	Collins, 2016	Guan, 2014	Koo, 2013	Kureja, 2016	Maffezzini, 2007	Mukhtar, 2013	Ortega, 2015	Persson, 2015	Sarr, 2012	Smith, 2104	Frees, 2017	Pang, 2017	Lin, 2017	Semerjian, 2017
Preoperative education	YES	YES	YES	YES	YES	YES	NG	YES	NG	YES	NG	YES	YES	YES	YES	YES
Preoperative medical optimization	NG	NG	YES	NG	NG	YES	NG	NG	YES	NG	NG	NG	NG	YES	NG	NG
MBP omission	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NG	YES	NG	YES
Preoperative carbohydrate loading	NG	YES	YES	NG	YES	YES	NG	YES	NG	YES	YES	YES	NG	NG	NG	YES
Limited preoperative fast	YES	YES	YES	NO	YES	YES	NO	YES	YES	NG	YES	YES	YES	YES	YES	YES
Antimicrobial prophylaxis	NG	YES	YES	NG	NG	YES	YES	NG	YES	YES	YES	NG	NG	YES	YES	YES
Preoperative nutrition	YES	YES	YES	YES	YES	YES	NG	YES	YES	NG	YES	YES	YES	NG	NG	NG
Venous thromboembolism prophylaxis	NG	NG	YES	YES	NG	YES	NG	NG	NG	YES	NG	NG	NG	YES	NG	NG
EDA	YES	YES	YES	NG	YES	YES	YES	YES	YES	YES	NG	YES	YES	YES	NG	NG
Prevention of intraoperative hypothermia	NG	NG	YES	YES	NG	YES	YES	YES	YES	YES	NG	NG	NG	NG	NG	NG
GDFT	NG	NG	YES	YES	YES	YES	NG	YES	NG	YES	NG	YES	YES	YES	NG	NG
Avoidance of NGT	NG	NG	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
PONV	YES	YES	YES	NG	YES	YES	NG	YES	YES	YES	NG	NG	NG	YES	NG	NG
Prevention of POI	YES	YES	YES	YES	YES	YES	NG	NG	NG	YES	YES	NG	NG	NG	NG	NG
Pain control	YES	YES	YES	YES	YES	YES	YES	YES	NG	YES	YES	YES	NG	NG	YES	YES
Early mobilization	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NG	YES	YES	YES
Early oral diet	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NG	YES	YES	YES
Early removal of UC	YES	YES	YES	NG	YES	NG	NG	YES	YES	YES	NG	NG	NG	NG	NG	NG
Non-opiate oral analgesia	NG	YES	NG	NG	YES	YES	NG	YES	NG	YES	YES	NG	NG	YES	YES	YES
Total elements	11	14	18	11	15	18	8	15	12	17	11	11	6	13	13	8

MBP: mechanical bowel preparation; EDA: epidural analgesia; GDFT: goal-directed fluid therapy; NGT: nasogastric intubation; PONV: prevention of nausea and vomiting; POI: postoperative paralytic ileus; UC: urine catheter; NG: not given

Table 3 Demographic and clinical characteristics

Outcome of interest	Studies (*n*)	ERAS/SC (*n*)	OR/WMD (95% CI)	*P* value	Study heterogeneity				Egger's test (*P*-value)
					Chi²	df	I^2	*P*-value	
Age, years	15	1102/714	0.93 [–0.86, 2.72]	0.31	37.09	11	70%	0.0001	0.231
Proportion of males	12	1249/820	0.80 [0.63, 1.02]	0.07	5.99	14	0%	0.97	0.465
BMI (kg/m²)	9	610/577	0.18 [–0.21, 0.58]	0.36	2.04	8	0%	0.98	0.412
ASA score									
≤2	12	605/519	0.86 [0.53, 1.39]	0.54	25.78	11	57%	0.007	0.447
≥3	12	605/519	1.17 [0.72, 1.92]	0.52	26.84	11	59%	0.005	0.588
Previous surgery	5	217/203	0.97 [0.56, 1.68]	0.91	2.44	4	0%	0.66	0.027
Previous radiochemotherapy	6	385/345	1.18 [0.85, 1.63]	0.33	4.16	5	0%	0.53	0.300
Clinical stage									
Organ confined ≤cT2	11	692/598	0.74 [0.58, 0.95]	**0.02**	14.32	10	30%	0.16	0.322
Non-organ confined ≥cT3	11	692/598	1.42 [1.11, 2.13]	**0.005**	11.46	10	13%	0.32	0.206
Diversion type									
NEO	13	1124/696	0.75 [0.37, 1.50]	0.41	67.21	11	84%	<0.00001	0.179
CR	4	254/166	0.42 [0.02, 8.34]	0.57	9.69	2	79%	0.008	0.394
IC	15	1249/820	1.20 [0.60, 2.40]	0.60	77.85	12	85%	<0.00001	0.306
Theatre time (min)	6	289/236	10.33 [–10.33, 30.70]	0.32	29.51	5	83%	<0.00001	0.523
EBL (mL)	5	227/263	–136.02 [–293.43, 21.38]	0.09	35.35	4	89%	<0.00001	0.197
No. of lymph nodes removed	4	183/188	1.29 [–1.52, 4.11]	0.37	8.09	3	63%	0.04	0.950

ERAS: enhanced recovery after surgery; SC: standard surgery; OR: odds ratio; WMD: weighted mean difference; CI: confidence interval; BMI: body mass index; ASA: American Society of Anesthesiologists; ORC: open radical cystectomy; LRC: laparoscopic radical cystectomy; NEO: neobladder; CR: continent reservoir; IC: ileal conduit; EBL: estimate blood loss. Statistically signifcant results are shown in bold.

regular diet, with the pooled data showing a significant difference favouring the ERAS group [WMD=–2.15 days, 95% CI (–2.86, –1.45), P<0.00001][3, 17, 19, 23, 25, 28]. Fourteen studies reported the LOS, with ERAS associated with a statistically significant reduction in LOS [WMD=–3.75 days, 95% CI (–5.13, –2.36), P<0.00001], with significant heterogeneity (I^2=92%, P<0.00001). Fig. 3B and 3C show the forest plots for time until implementation of a regular diet and LOS, respectively. Eight studies reported short-term mortality (in-hospital mortality or mortality within 3months)[2, 3, 7, 17, 18, 21, 28, 29], and 4 studies reported 90-day mortality[3, 16, 29, 31]. There was no statistically significant difference in short-term mortality [OR=1.08, 95% CI

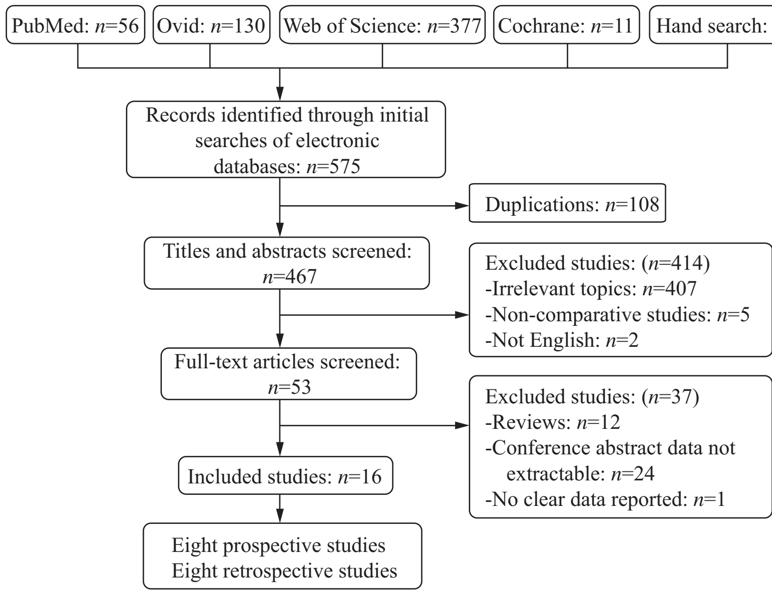


Fig. 2 Flowchart of literature selection

(0.36, 3.25), *P*=0.89] or 90-day mortality [OR=0.79, 95% CI (0.33, 1.86), *P*=0.58] between the ERAS group and the SC group. The results are shown in fig. 4.

2.5 Readmissions and Return to Theatre

In total, 456 patients in the ERAS group and 395 patients in the SC group had to be readmitted [30-day readmission OR=0.78, 95% CI (0.34, 1.82), *P*=0.57; 90-day readmission OR=1.35, 95% CI (0.82, 2.23), *P*=0.24; fig. 5A]. There was no significant difference between the ERAS group and the SC group in the rate of patients returned to theatre [OR=0.72, 95% CI (0.40, 1.32), *P*=0.29; table 4), with low heterogeneity observed (I2=0%, P=0.86; fig. 5B).

2.6 Outcomes of Complications

All studies reported data on total postoperative complications, and one of the 12 studies reported the 90-day complications[21]. There was a significant reduction in the overall postoperative complication rate in the ERAS group than in the SC group [OR=0.60, 95% CI, (0.44, 0.83), *P*=0.002], and there was no significant heterogeneity between studies (I^2=43%, *P*=0.05; fig. 6A). Eight studies used the Clavien classification system as a surrogate measure to comprehensively and meticulously review all complications. There were no significant differences in low-grade Clavien complications (Claviengrades ≤Ⅱ) [OR=0.64, 95% CI (0.34, 1.21), *P*=0.17] and high-grade Clavien complications (Claviengrades ≥Ⅲ) [OR=0.92, 95% CI (0.64, 1.31), *P*=0.64] between the ERAS and SC groups (table 5).

A comprehensive and meticulous classification of all complications showed that the ERAS group had a lower incidence of POI [OR=0.43, 95% CI (0.30, 0.62), *P*<0.0001], with low heterogeneity (I^2=0%, *P*=0.77), as shown in fig. 6B. There was also a reduction in the rate of cardiovascular complications [OR=0.28, 95% CI (0.09, 0.90), *P*=0.03; table 5). There were no significant differences between the ERAS and SC

Table 4 Outcomes of postoperative recovery

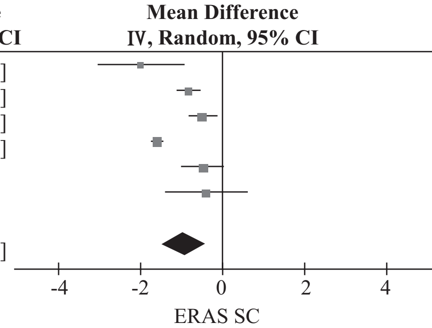
Outcome of interest	Studies (*n*)	ERAS/SC (*n*)	OR/WMD (95% CI)	*P* value	Study heterogeneity				Egger's test (*P*-value)
					Chi²	df	I^2	*P*-value	
First flatus (days)	6	359/352	–0.95 [–1.50, –0.41]	**0.0006**	59.98	5	92%	<0.00001	0.184
Time to regular diet (days)	6	436/372	–2.15 [–2.86, –1.45]	**<0.00001**	100.01	5	95%	<0.00001	0.139
LOS (days)	14	1192/766	–3.75 [–5.13, –2.36]	**<0.00001**	153.09	13	92%	<0.00001	0.164
Mortality*									
30-day	8	825/493	1.08 [0.36, 3.25]	0.89	2.48	4	0%	0.65	0.790
90-day	4	638/260	0.79 [0.33, 1.86]	0.58	1.41	2	0%	0.49	–
Readmission*									
30-day	7	322/309	0.78 [0.34, 1.82]	0.57	10.04	5	50%	0.07	0.425
90-day	3	208/168	1.35 [0.82, 2.23]	0.24	0.76	1	0%	0.38	–
Return to theatre	6	383/396	0.72 [0.40, 1.32]	0.29	1.30	4	0%	0.86	0.640

ERAS: enhanced recovery after surgery; SC: standard care; OR: odds ratio; WMD: weighted mean difference; LOS: length of hospital stay. *overlap data; Statistically significant results are shown in bold.

A. Mean time to the first flatus

Study or Subgroup	ERAS Mean	ERAS SD	ERAS Total	SC Mean	SC SD	SC Total	Weight	Mean Difference IV, Random, 95% CI
Cerruto, 2013	2	1.48	9	4	0.74	13	11.7%	-2.00 [-3.05, -0.95]
Guan, 2014	2.92	0.38	60	3.75	0.78	55	19.5%	-0.83 [-1.12, -0.54]
Lin, 2017	2.42	1.27	144	2.92	1.83	145	19.0%	-0.50 [-0.86, -0.14]
Mukhtar, 2013	4.6	0.2	51	6.2	0.4	39	20.4%	-1.60 [-1.74, -1.46]
Saar, 2012	1.9	0.8	31	2.4	1.3	31	17.2%	-0.50 [-1.04, 0.04]
Smith, 2014	4.58	2.88	64	5	3	69	12.2%	-0.42 [-1.42, 0.58]
Total (95% CI)			359			352	100.0%	-0.95 [-1.50, -0.41]

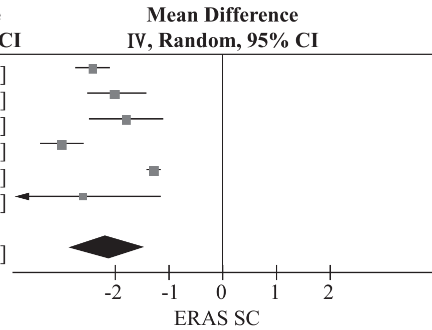
Heterogeneity: Tau^2=0.37; Chi^2=59.98, df=5 (P<0.00001); I^2=92%
Test for overall effect: Z=3.45 (P=0.0006)



B. Time to regular diet

Study or Subgroup	ERAS Mean	ERAS SD	ERAS Total	SC Mean	SC SD	SC Total	Weight	Mean Difference IV, Random, 95% CI
Guan, 2014	4.43	0.83	60	6.84	0.92	55	18.5%	-2.41 [-2.73, -2.09]
Kukreja, 2016	3	0.74	79	5	2.22	75	17.4%	-2.00 [-2.53, -1.47]
Lin, 2017	5.21	2.96	144	7	3.12	145	16.2%	-1.79 [-2.49, -1.09]
Maffezzini, 2017	4	1	71	7	1	40	18.2%	-3.00 [-3.39, -2.61]
Mukhtar, 2013	4.6	0.2	51	5.9	0.3	26	19.1%	-1.30 [-1.43, -1.17]
Saar, 2012	4	2.2	31	6.6	3.5	31	10.6%	-2.60 [-4.06, -1.14]
Total (95% CI)			436			372	100.0%	-2.15 [-2.86, -1.45]

Heterogeneity: Tau^2=0.67; Chi^2=100.01, df=5 (P<0.00001); I^2=95%
Test for overall effect: Z=6.00 (P=0.00001)



C. Length of hospital stay (LOS)

Study or Subgroup	ERAS Mean	ERAS SD	ERAS Total	SC Mean	SC SD	SC Total	Weight	Mean Difference IV, Random, 95% CI
Arumainayagam, 2008	13	4.44	56	17	5.93	56	8.2%	-4.00 [-5.94, -2.06]
Cerruto, 2013	15	0.74	9	15	0.74	13	9.6%	0.00 [-0.63, 0.63]
Collins, 2016	8	2.96	135	9	3.7	86	9.4%	-1.00 [-1.93, -0.07]
Guan, 2014	6.9	1.1	60	10	1.5	55	9.7%	-3.10 [-3.58, -2.62]
Koo, 2013	13.6	4.5	20	20.1	8.25	20	5.3%	-6.50 [-10.62, -2.38]
Kukreja, 2016	5	2.22	79	8	5.93	75	8.9%	-3.00 [-4.43, -1.57]
Lin, 2017	15	6.67	144	17	7.41	145	8.6%	-2.00 [-3.63, -0.37]
Maffezzini, 2007	15	6.67	71	22	8.25	40	6.7%	-7.00 [-9.99, -4.01]
Mukhtar, 2013	10.4	14	51	11.5	4.25	26	5.2%	-1.10 [-5.28, 3.08]
Ortega-Lucea, 2015	17	9	48	29	14	51	4.7%	-12.00 [-16.61, -7.39]
Pang, 2017	8	5.19	393	18	8.89	60	7.7%	-10.00 [-12.31, -7.69]
Persson, 2015	11	24.5	31	12	13.5	39	1.7%	-1.00 [-10.61, 8.61]
Saar, 2012	18	5.1	31	18.1	6.3	34	6.9%	-0.10 [-2.95, 2.75]
Smith, 2014	11.15	6.9	64	15.98	7.97	69	7.4%	-4.83 [-7.36, -2.30]
Total (95% CI)			1192			766	100.0%	-3.75 [-5.13, -2.36]

Heterogeneity: Tau^2=5.10; Chi^2=153.09, df=13 (P<0.00001); I^2=92%
Test for overall effect: Z=5.30 (P=0.00001)

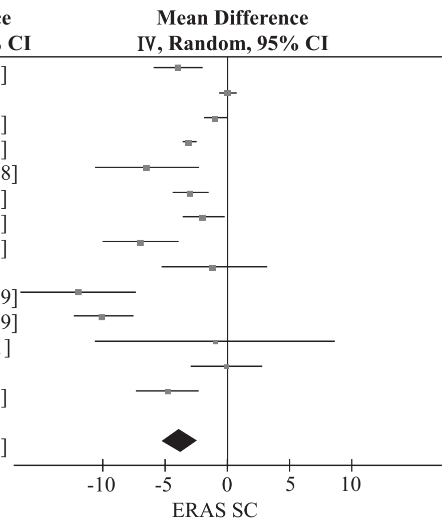


Fig. 3 Forest plots of random-effects meta-analysis of the effect of ERAS on mean time to the first flatus (A), time to regular diet (B) and length of hospital stay (C)

groups with respect to the other complications, shown in table 5.

2.7 Sensitivity Analysis and Publications Bias

A sensitivity analysis was carried out for the prospective studies alone. This sensitivity analysis found no significant changes in the above outcomes, except for the POI rate. The funnel plots and Egger's tests (tables 3–5) revealed that significant publication bias existed for previous surgeries, number of neobladders, and the incidence of POI among the 38 comparisons performed in the present analysis.

3 DISCUSSION

In this systematic meta-analysis, we analyzed 16 studies to evaluate the benefits and harms of ERAS protocols, including 8 prospective trials and 8 retrospective trials. Our meta-analysis demonstrated that ERAS protocols were associated with quicker return of bowel function, a lower incidence of POI,

Table 5 Overall analysis of complications

Outcome of interest	Studies (*n*)	ERAS/SC (*n*)	OR (95% CI)	*P* value	Study heterogeneity Chi^2	df	I^2	*P*-value	Egger's test (*P*-value)
Overall postoperative complications	13	799/706	0.60 [0.44, 0.83]	0.002	20.97	12	43%	0.05	0.059
Clavien classification system									
Clavien ≤ Ⅱ	8	448/390	0.64 [0.34, 1.21]	0.17	20.96	7	67%	0.004	0.932
Clavien ≥ Ⅲ	8	448/390	0.92 [0.64, 1.31]	0.64	1.82	7	0%	0.97	0.400
POI	9	491/442	0.43 [0.30, 0.62]	<0.00001	4.93	8	0%	0.77	0.003
Cardiovascular complications	3	161/140	0.28 [0.09, 0.90]	0.03	3.72	2	46%	0.16	0.838
Bowel anastomosis	5	170/178	0.53 [0.18, 1.60]	0.26	1.05	4	0%	0.9	0.298
Clostridium difficile infection	4	181/160	1.33 [0.50, 3.57]	0.57	1.79	3	0%	0.62	0.541
Wound infection	7	415/430	1.16 [0.65, 2.08]	0.62	7.50	6	20%	0.28	0.687
Wound dehiscence	3	138/121	0.34 [0.10, 1.14]	0.08	1.15	2	0%	0.56	0.364
Lower respiratory tract infection	3	155/133	0.48 [0.17, 1.38]	0.17	0.76	2	0%	0.68	0.325
Acute kidney injury	3	158/165	1.60 [0.53, 4.78]	0.40	1.19	2	0%	0.55	0.926
Sepsis	5	353/336	0.75 [0.44, 1.27]	0.28	4.62	4	13%	0.33	0.915
UTI	4	221/205	0.56 [0.31, 1.03]	0.06	0.89	3	0%	0.83	0.799
Urine leak	6	389/397	1.23 [0.62, 2.45]	0.56	2.20	5	0%	0.82	0.118
DVT	3	195/196	0.61 [0.23, 1.58]	0.31	0.23	2	0%	0.89	0.989

ERAS: enhanced recovery after surgery; SC: standard care; OR: odds ratio; CI: confidence interval; POI: postoperative paralytic ileus; UTI: urinary tract infection; DVT: deep vein thrombosis

Study or Subgroup	ERAS Events	ERAS Total	SC Events	SC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 30-d mortality						
Smith, 2014	1	64	0	69	7.7%	3.28 [0.13, 82.07]
Pang, 2017	1	393	1	60	28.3%	0.15 [0.01, 2.44]
Lin, 2017	0	144	0	145		Not estimable
Kukreja, 2016	3	79	2	75	32.3%	1.44 [0.23, 8.87]
Koo, 2013	1	20	1	20	15.6%	1.00 [0.06, 17.18]
Guan, 2014	0	60	0	55		Not estimable
Cerruto, 2013	0	9	0	13		Not estimable
Arumainayagam, 2008	1	56	1	56	16.1%	1.00 [0.06, 16.39]
Subtotal (95% CI)		**825**		**493**	**100.0%**	**1.08 [0.36, 3.25]**
Total events	7		5			
Heterogeneity: Chi^2=2.48; df=4 (*P*=0.65); I^2=0%						
Test for overall effect: Z=0.13 (*P*=0.89)						
2.4.2 90-d mortality						
Persson, 2015	0	31	0	39		Not estimable
Pang, 2017	8	393	3	60	45.0%	0.39 [0.10, 1.53]
Kukreja, 2016	5	79	4	75	33.9%	1.20 [0.31, 4.65]
Collins, 2016	3	135	2	86	21.1%	0.95 [0.16, 5.83]
Subtotal (95% CI)		**638**		**260**	**100.0%**	**0.79 [0.33, 1.86]**
Total events	16		9			
Heterogeneity: Chi^2=1.41; df=2 (*P*=0.49); I^2=0%						
Test for overall effect: Z=0.55 (*P*=0.58)						

Test for subarouo differences: Chi^2=0.20; df=1 (*P*=0.66); I^2=0%

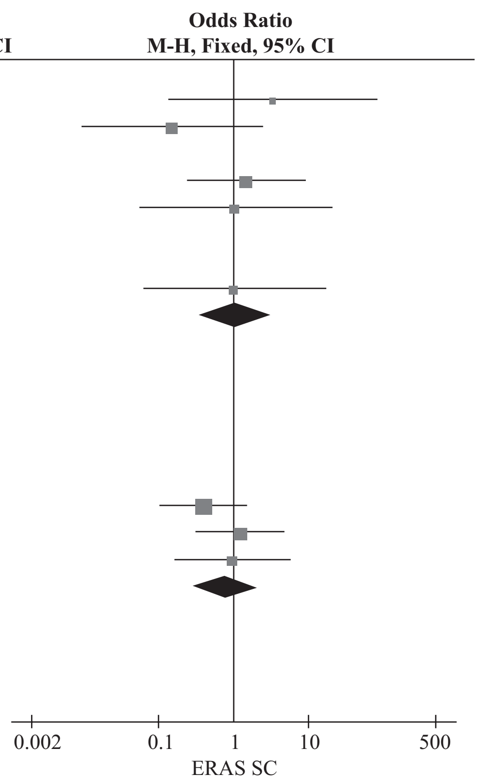
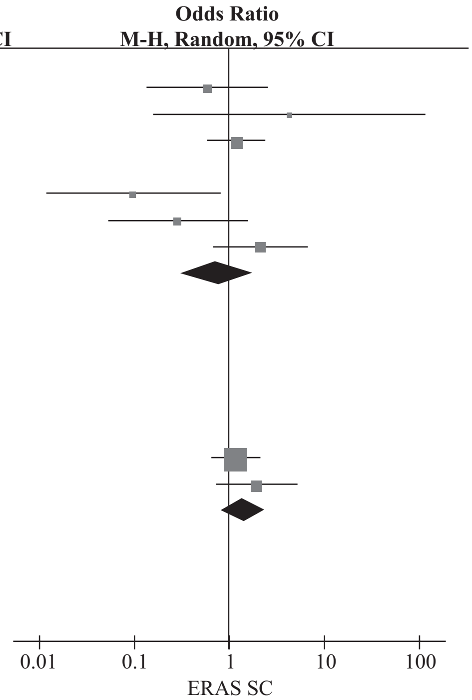


Fig. 4 Forest plots of fixed-effects meta-analysis of ERAS on 30- and 90-day mortality after cystectomy

and shorter LOS than SC in patients undergoing RC. Because no exactty same ERAS elements were applied for the selected studies, we can not define the most significantly specific measures. However, many of the elements of ERAS have a physiologic basis, such as, preoperative carbohydrate loading enhances perioperative insulin sensitivity and maintains lean body mass and muscle strength[6]; the incidence of ileus by maintaining splanchnic perfusion is reduced by goal-directed fluid management[33]; body temperature monitoring, the maintenance of normothermia, early mobilization, and early oral feeding reduce

A. 30-d readmission and 90-d readmission

Study or Subgroup	ERAS Events	ERAS Total	SC Events	SC Total	Weight	Odds Ratio M-H, Random, 95% CI
2.2.1 30-d readmission						
Arumainayagam, 2008	3	56	5	56	17.2%	0.58 [0.13, 5.54]
Frees, 2017	1	10	0	13	5.5%	4.26 [0.16, 116.34]
Kukreja, 2016	24	79	20	75	29.4%	1.20 [0.60, 2.42]
Mukhtar, 2013	0	51	0	26		Not estimable
Persson, 2015	1	31	10	39	11.1%	1.00 [0.01, 0.80]
Saar, 2012	2	31	6	31	14.9%	0.29 [0.05, 1.55]
Smith, 2014	9	64	5	69	21.9%	2.09 [0.66, 6.62]
Subtotal (95% CI)		**322**		**309**	**100.0%**	**0.78 [0.34, 1.82]**
Total events	40		46			
Heterogeneity: Tau^2=0.50; Chi^2=10.04; df=5 (P=0.07); I^2=50%						
Test for overall effect: Z=0.57 (P=0.57)						
2.2.2 90-d readmission						
Cerruto, 2013	0	0	0	13		Not estimable
Collins, 2016	44	135	25	86	72.5%	1.18 [0.66, 2.12]
Smith, 2014	13	65	8	69	27.5%	1.94 [0.75, 5.06]
Subtotal (95% CI)		**208**		**168**		**1.35 [0.82, 2.23]**
Total events	57		33		**100.0%**	
Heterogeneity: Tau^2=0.00; Chi^2=0.76; df=1 (P=0.38); I^2=0%						
Test for overall effect: Z=1.18 (P=0.24)						



Test for subarouo differences: Chi^2=1.19; df=1 (P=0.27); I^2=16.1%

B. Patients return to theatre

Study or Subgroup	ERAS Events	ERAS Total	SC Events	SC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Arumainayagam, 2008	4	56	3	56	10.9%	1.36 [0.29, 6.37]
Cerruto, 2013	0	9	0	13		Not estimable
Kukreja, 2016	5	79	8	75	30.0%	0.57 [0.18, 1.81]
Lin, 2017	4	144	4	144	15.2%	1.00 [0.25, 4.08]
Persson, 2015	2	31	5	39	16.2%	0.47[0.08, 2.60]
Smith, 2014	5	64	8	69	27.7%	0.65 [0.20, 2.09]
Subtotal (95% CI)		**383**		**396**	**100.0%**	**0.72 [0.40, 1.32]**
Total events	20		28			
Heterogeneity: Chi^2=1.30; df=4 (P=0.86); I^2=0%						
Test for overall effect: Z=1.06 (P=0.29)						

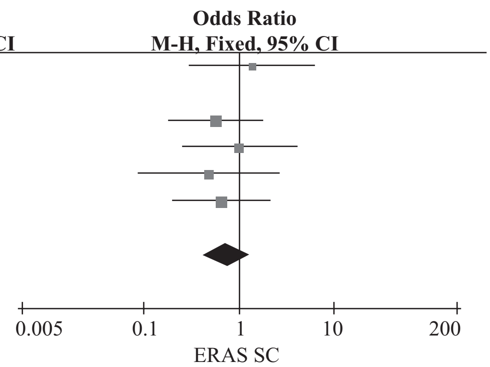


Fig. 5 Forest plots of random-effects and fixed-effects meta-analysis of ERAS on 30- and 90-day readmission rates (A) and patients returning to theatre (B) after cystectomy

complications by maintaining body homeostasis[12, 34]. Every factor of ERAS protocol should be systematically applied to the perioperative period of patients undergoing RC to reduce postoperative complications and enhance recovery.

RC with urinary diversion represents the gold standard treatment for muscle-invasive bladder cancer[22]. Despite improvements in perioperative care protocols and standardisation of the surgical technique, such as laparoscopic and robot-assisted protocols, RC is still associated with a high complication rate[4]. ERAS protocols have been successfully applied in colorectal surgery, and successful application of ERAS protocols is more recently being reported for RC. In 2008, Arumainayagam *et al* reported the use of ERAS protocols in RC. When compared to SC, patients submitted to ERAS had a reduced LOS (decrease in average LOS from 17 to 13 days) and quicker recovery after RC, with no increases in morbidity or mortality rates[2]. Since then, many researchers have also reported a reduction in LOS after RC associated with the implementation of ERAS protocols[10, 21, 24, 35, 36].

ERAS protocols are multimodal pathways, each of which is evidence-based. For example, several RCTs and a meta-analysis have demonstrated that omitting MBP with urinary diversion has no influence on the incidence of postoperative wound infection, anastomotic leakage, and POI when compared to protocols that include MBP[37–40]. All studies in this meta-analysis included no MBP as one of their ERAS protocols. Other evidence-based elements of ERAS protocols include omission of a nasogastric tube[1, 41],

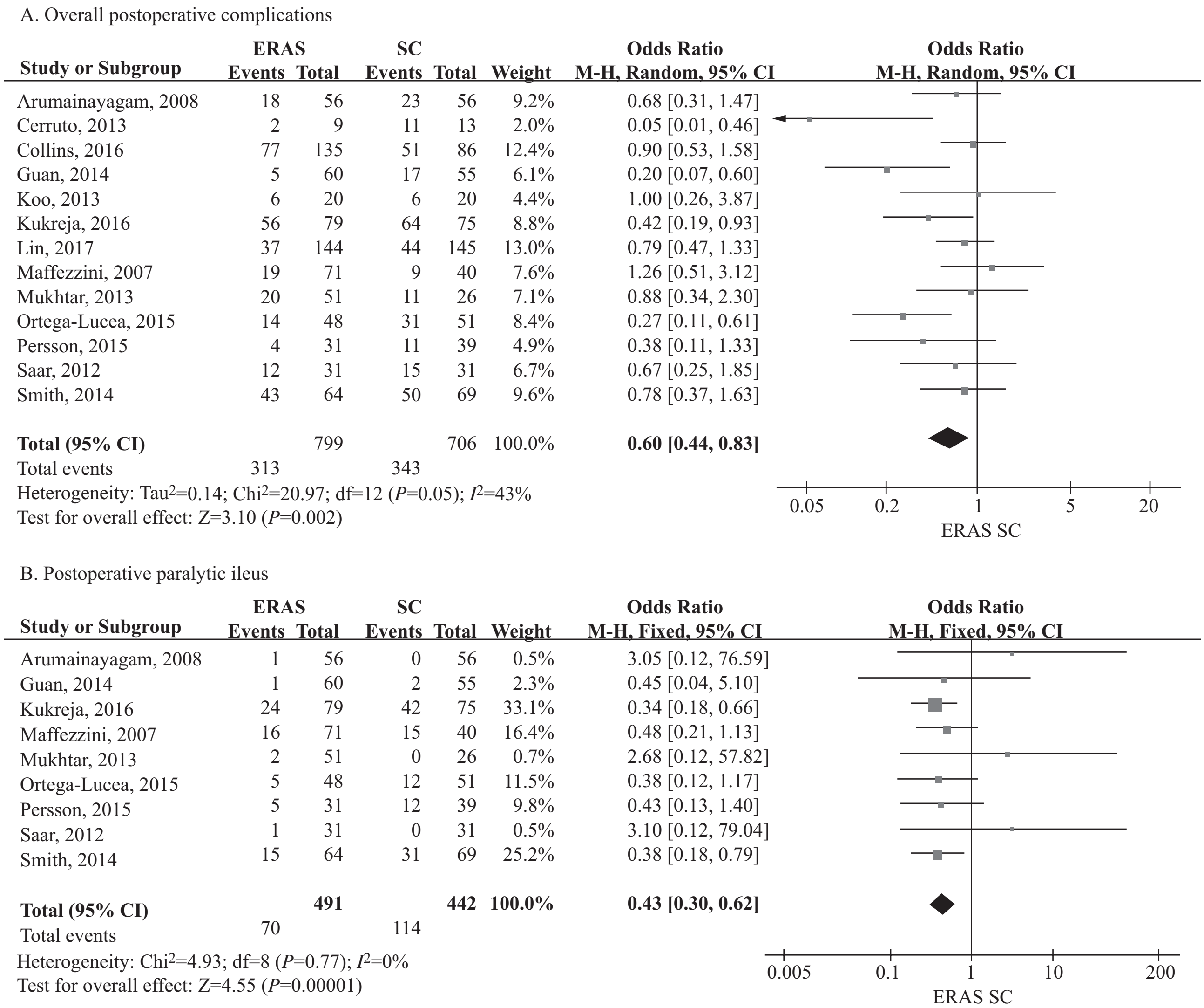


Fig. 6 Forest plots of a random-effects and fixed-effects meta-analysis of overall postoperative complications (A) and postoperative paralytic ileus (B) after cystectomy

no prolonged fasting[42], fluid and carbohydrate loading before surgery[43], perioperative fluid management[33, 44, 45], early oral feeding[46], and early mobilisation, among others.

Although more patients in the ERAS group had advanced preoperative tumour staging (T3 or T4; OR=1.42, P=0.005), implementation of the ERAS protocol was found to be associated with a significant decrease in LOS[16]. The current meta-analysis revealed no significant differences in baseline characteristics, including BMI, ASA score, previous surgeries, previous neoadjuvant radiochemotherapy, EBL, and the number of lymph nodes removed. Thus, the groups appeared to be well matched among the included studies; however, there were significant differences in the variables of theatre time and advanced tumour staging between ERAS and SC groups.

This meta-analysis demonstrated that ERAS is beneficial for patients, as it was associated with a lower rate of overall complications, shorter time to first flatus, reduced time to return to a regular diet, and decreased LOS when compared to SC after RC. However, previous results regarding bowel recovery have been conflicting, as some studies found a significant difference in the time to first flatus[7, 17, 23], while others reported no difference[21, 25]. In our meta-analysis, pooled results revealed that patients who underwent RC with ERAS had a significantly reduced time to first flatus compared to patients who underwent RC with SC (WMD=–0.95, P=0.0006). The outcome of each study focused on different elements of ERAS, for instance, some studies assessed whether chewing gum was associated with an earlier return of bowel function as one of their ERAS elements[47]. One of the most common complications after RC is POI, which has been shown to prolong the LOS from days to weeks, and is also associated with increased morbidity and cost of treatment. Therefore, it is important to prevent POI in clinical practice after RC. It remains controversial whether ERAS protocols can reduce the incidence of POI based on previous studies, as some trials found a difference[3, 21], while others showed no effect[2, 17, 23, 25, 31, 45]. Although we observed a bias (*P*=0.003) which may contribute to the varied definition of POI between different reports, our meta-analysis demonstrated that implementation of the ERAS protocol was associated with a significantly decreased rate of POI (OR=0.43, *P*<0.0001). There were no statistically significant differences with regard to the rates of readmission, short-term morality, 90-day morality, patients return to theatre, low-grade Clavien complications, and high-grade Clavien complications.

Despite our strict systematic approach, there are limitations which cannot be ignored when interpreting our results. The major limitation of this review is the limited number of well-designed RCT studies. In this meta-analysis only 8 prospective studies met the inclusion criteria. We identified one RCT with 101 patients, but this study could not be included due to the absence of discrete data in the results section and patient demographic data[9].

We applied stringent inclusion criteria to identify studies that compared the two procedures, including the Egger's test to assess the publication bias, and a sensitivity analysis to minimise the effects of heterogeneity between studies. However, despite our rigorous systematic approach, all studies had an unclear bias in one or more domains. No studies in this meta-analysis reported whether the study was blinded, meaning that all the remaining outcomes are likely to be biased toward the ERAS protocols due to a lack of blinding. In order to confirm our findings, large, long-term, prospective, multi-centre follow-up studies and RCTs should be undertaken.

To sum up, despite the limited number of studies and the prevalence of low-quality studies, this meta-analysis demonstrated that ERAS protocols are associated with a faster return of bowel function, reduced incidence of POI, and shorter LOS when compared to SC in patients undergoing RC. However, the validity of the results is uncertain due to the inherent limitations of the included trials. Further large, long-term, prospective, multi-centre follow-up studies and RCTs should be undertaken to confirm our findings.

Conflict of Interest Statement

The authors declare no competing financial interests.

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