

Surgical Options in the Treatment of Rectal Cancer: A Systematic Review and Meta-Analysis

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Rezumat

Opțiuni chirurgicale în tratamentul cancerului rectal: un review sistematic de literatură și o metaanaliză

Introducere: Chirurgia rectală a evoluat prin eforturile conjugate ale anatomicștilor și chirurgilor. Chirurgia minim invazivă a câștigat recunoaștere în raport cu chirurgia deschisă datorită complicațiilor perioperatorii mai puține și a recuperării postoperatorii mai rapide.

Metode: A fost efectuată o căutare sistematică în bazele de date PubMed, Scopus și Web of Science pentru a identifica studiile publicate între 2014 și decembrie 2024 care comparau chirurgia laparoscopică (CL) cu chirurgia deschisă (CD) în cancerul rectal. Principalii parametri evaluați au fost complicațiile postoperatorii, numărul de ganglioni limfatici excizați, supraviețuirea globală și supraviețuirea fără semne de boală.

Rezultate: Au fost analizate opt studii clinice randomizate și un studiu nerandomizat, totalizând 3.935 de pacienți. CL a prezentat o incidență mai redusă a complicațiilor postoperatorii [OR: 0.64; 95% CI, 0.53, 0.77; p=0.008] și un ușor avantaj în ceea ce privește numărul de ganglioni limfatici excizați (MDP: 0.66; IC 95%: -0.63–1.95). Nu s-au constatat diferențe semnificative în ceea ce privește supraviețuirea globală sau supraviețuirea fără semne de boală.

Concluzii: CL reprezintă o opțiune sigură și eficace în tratamentul cancerului rectal, oferind o recuperare postoperatorie mai bună și o excizie ganglionară eficientă, menținând totodată rezultate oncologice pe termen lung comparabile cu cele ale CD.

Cuvinte cheie: chirurgie laparoscopică, cancer rectal, chirurgie minim invazivă, chirurgie deschisă

Abstract

Background: Rectal surgery has evolved through the combined efforts of anatomists and surgeons. Minimally invasive surgery has gained recognition over open surgery due to fewer perioperative complications, and faster postoperative recovery.

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Methods: A systematic search was conducted in PubMed, Scopus, and Web of Science to identify studies published between 2014 and December 2024 comparing laparoscopic surgery (LS) and open surgery (OS) for rectal cancer. Primary outcomes included postoperative complications, number of lymph nodes harvested, overall survival, and disease-free survival.

Results: Eight randomized controlled trials and one non-randomized study, including a total of 3,935 patients, were analyzed. LS showed a lower incidence of postoperative complications [OR: 0.64; 95% CI, 0.53, 0.77; $p=0.008$] and a slight advantage in lymph node harvest (WMD: 0.66; 95% CI: -0.63–1.95). No significant differences were found in overall or disease-free survival.

Conclusions: LS is a safe and effective option for rectal cancer treatment, offering better postoperative recovery and efficient lymph node retrieval, while maintaining long-term oncological outcomes comparable to OS.

Keywords: laparoscopic surgery, rectal cancer, minimally invasive surgery, open surgery

Introduction

Cancer remains one of the primary causes of mortality globally, posing a major challenge to improving life expectancy across nations. In 2020, colorectal cancer accounted for more than 1.9 million new cases and 935,000 deaths worldwide. In Eastern Europe, rectal cancer incidence rates are among the highest globally, reaching 16.9 per 100,000 men and 8.9 per 100,000 women (1). The pathophysiology of rectal cancer differs due to the limited pelvic anatomy and the presence of the rectal sphincter. This has led to continuous advancements in surgical techniques for treating the disease.

The evolution of rectal surgery represents and combines an exhaustive effort of anatomists and surgeons to be able to approach an intrapelvic organ and, therefore, deep, and not easy to dissect. Milles abdominoperineal amputation was, until the middle of the last century, considered the surgical option with the best long-term survival outcomes for patients affected by rectal cancer or rectosigmoid junction cancer (2,3).

Currently, Total Mesorectal Excision (TME) and neoadjuvant therapy are highly recommended by NCCN Guidelines® in the treatment of advanced rectal cancer (4). Over the last few years, the preference for minimally invasive surgical techniques over traditional open surgery has significantly increased, primarily attributed to decreased perioperative complications and earlier postoperative recovery. Although important advances have been made in this surgery, significant challenges persist for surgeons, especially in obese patients or those with low rectal cancer (5,6).

Short-term outcomes have been studied, where laparoscopic surgery shows similar results to open surgery (7), however, long-term oncologic outcomes,

such as overall survival and local recurrence rates, remain critical factors that require further thorough investigation to fully assess the role of minimally invasive techniques in the treatment of rectal cancer (8,9). Both surgical options have been evaluated through RCTs to assess their safety regarding long-term survival, with similar although inconclusive results due to sample size, but who are inclined towards the advantages of laparoscopic surgery over conventional surgery (10,11).

These conflicting or not fully elucidated results on the effect of surgical variations in improving overall survival and disease-free survival in rectal cancer patients leave the superiority of one approach over the other uncertain.

Some of the meta-analyses available in the literature compare conventional surgery with laparoscopic surgery; however, these comparisons are mainly based on short-term outcomes and usually include a limited number of randomised clinical trials, which increases the risk of bias and limits the robustness of the conclusions drawn (7,12,13).

Therefore, the objective of this meta-analysis is to systematically evaluate and compare laparoscopic surgery with conventional surgery in terms of short-term and long-term outcomes in patients with rectal cancer.

Material and Methods

Study Selection

This review followed the methodological guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic search was conducted in the PubMed, Scopus, and Web of Science databases for Randomized Controlled Trials (RCTs) and Non-randomized Controlled Trials (NRCTs) published

between 2014 and December 2024, without language restrictions, that compared laparoscopic surgery and open surgery in the treatment of rectal cancer. The search terms included the following: (rectal cancer OR rectal tumour OR rectal neoplasms OR rectum carcinoma) AND (laparoscopic OR laparoscopy OR rectum resection OR minimally invasive OR open surgery). Two reviewers reviewed all titles and abstracts. Following this initial screening, articles meeting the inclusion criteria were subjected to full-text evaluation by both reviewers.

Data Extraction

Two reviewers independently extracted relevant data from all studies. Any discrepancies were resolved by consulting a third reviewer. The data extracted from the selected studies included: a) first author and publication year, b) study design, c) patient characteristics (e.g., gender, age, body mass index (BMI)), d) inclusion and exclusion criteria, e) number of patients undergoing each surgical technique, and f) intra-operative details, postoperative recovery, and long-term results.

Inclusion Criteria

The inclusion criteria for this systematic review were as follows: (1) patients with rectal cancer were included; (2) studies comparing minimally invasive surgery and open surgery for rectal cancer; (3) studies documenting surgical procedures, and documenting surgical techniques; (4) studies with total sample size more than 50; (5) short-term and/or long-term postoperative outcomes and/or survival outcome were reported; (6) inclusion of RCTs with low to moderate risk of bias, as well as high-quality NRCTs, determined by a Newcastle-Ottawa Scale (NOS) score above 5 (14,15).

Exclusion Criteria

The criteria for excluding studies were as follows: (1) studies including benign diseases such as polyps or inflammatory bowel disease; (2) conference proceedings, abstracts, case reports, review articles, case-control studies, and commentaries (3) animal studies; (4) the reporting of patient outcomes and parameters lacked clarity; (5) it was not feasible to extract the relevant data from the published results.

Outcome Interest

The outcomes of interest were divided into three

groups. A first group dedicated to operative outcomes including estimated blood loss, operative time, length of hospital stays, time to first flatus, time to initiation of normal diet, postoperative complications, anastomotic leakage, urinary and sexual complications. A second group dedicated to pathologic outcomes were evaluated in terms of number of lymph nodes resected, distance to distal resection margin, and positive resection margins. Finally, a third group of outcomes to determine overall survival and disease-free survival.

Quality Assessment

Evaluations were performed independently by three reviewers and disagreements were resolved by discussion. The quality of the randomized controlled trials (RCTs) was assessed by using the Cochrane reviewer's handbook (15). The domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluators, incomplete outcome data, and selective reporting of outcomes were systematically evaluated. The risk of bias was categorized as low (all criteria met) or high (no criteria met).

The quality of non-randomized controlled trials (NRCTs) was estimated by Newcastle – Ottawa Scale (NOS), a validated instrument that evaluates three domains: selection of study groups, comparability of groups, and assessment of outcomes (14). A total score of 9 was possible. Studies scoring 6 or above were regarded as high quality, while those with a score below 6 were classified as low quality.

Statistical Analysis

The data was analysed using the Revision Manager (RevMan) software, version web, developed by Cochrane Collaboration (<https://training.cochrane.org/online-learning/core-software/revman>) in accordance with the Cochrane Handbook (15). A 95% confidence interval (CI) was applied, with statistical significance defined as a p-value < 0.005. Odds Ratios (OR) were utilized as summary measures for dichotomous variables and were pooled using the Mantel-Haenszel method. For continuous variables, the Weighted Mean Difference (WMD) served as the summary measure, combined using the inverse variance method. Hazard Ratios (HRs) were used to assess the effect size for survival outcomes. When continuous variables were provided as medians with ranges, the Hozo method was employed to estimate the corresponding mean and standard deviation (16). The Chi-squared test and Higgins I² test were used for heterogeneity. Heterogeneity was indicated by a p-values < 0.05 and

I^2 - value > 50%. If these conditions were met, a random effects model was used; otherwise, if the I^2 - value < 50% and p-value > 0.05, data were analysed using a fixed effects model.

Results

Selected Studies

An initial literature search utilizing electronic databases resulted in the identification of 899 studies. Following the removal of duplicate records, 640 unique studies were available for screening. After reviewing the titles and abstracts, 601 studies were removed, remaining 39 articles for a detailed full-text evaluation. Thirty studies were omitted due to the following reasons: 14 studies because they were not randomized

clinical trials, 7 studies because they reported poor results comparing minimally invasive surgery to open techniques, and 9 studies because the data could not be distinguished between surgeries performed for colon cancer and those for rectal cancer. No additional studies were identified through hand searching, reference list crosswalks, Gray literature, or on ClinicalTrials.gov. For this systematic review and meta-analysis, a total of 9 studies were considered (9,10, 17–23). The flowchart outlining the literature search and article selection process is presented in Fig. 1.

This meta-analysis incorporated eight randomized controlled trials, and one non-randomized controlled trial published between 2014 and December 2024. The studies originated from institutions in China,

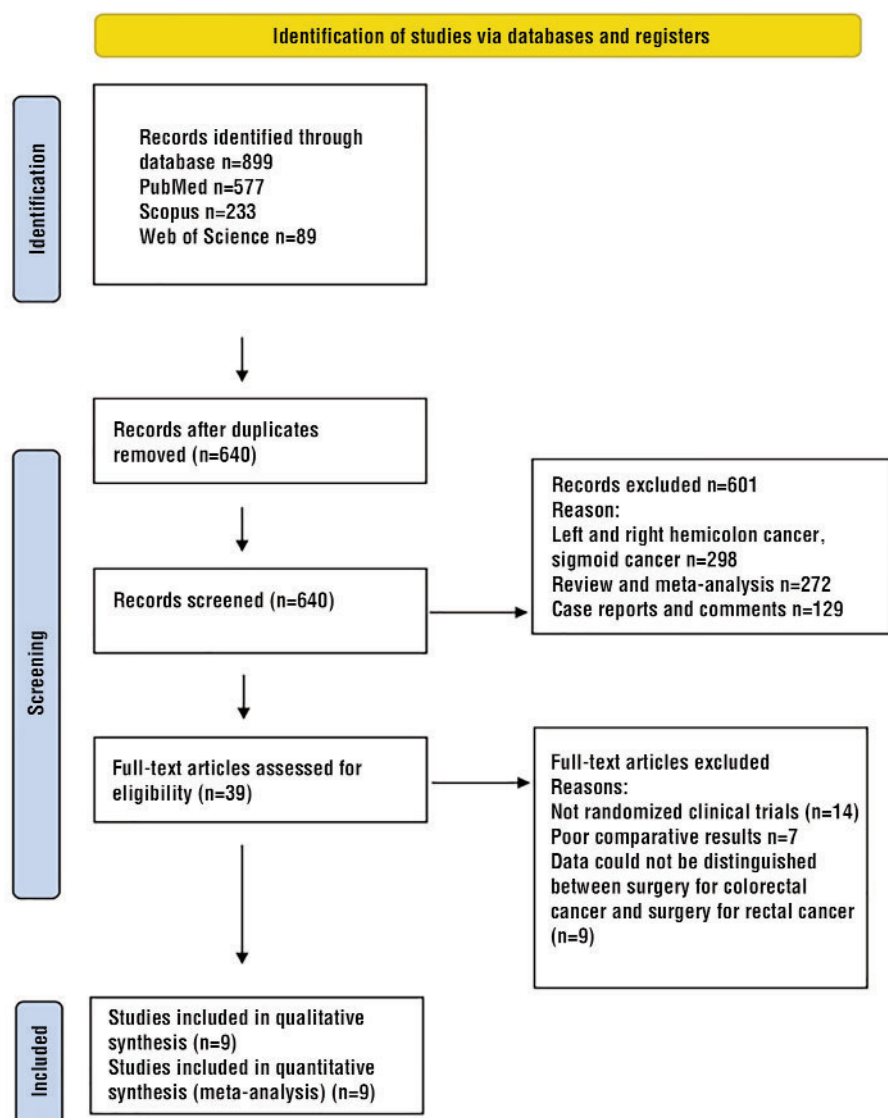


Figure 1. Flowchart of study identification and selection following PRISMA statement.

Table 1. Study Characteristic

Study (Author)	Year	Design	Country	Patients (n)		Age (mean)		BMI (mean) (kg/m ²)	
				LS/M	OS/M	LS	OS	LS	OS
Bonjer HJ	2015	RCT	Netherlands, Spain, Sweden, Denmark, Germany	699/448	345/211	66.8	65.8	26.1	26.5
Chang	2023	RCT	China	86/56	85/59	65.5	64.4	23.7	23.9
Fleshman	2019	RCT	USA	243/156	243/258	57.7	57.2	26.4	26.8
Fujii	2021	RCT	Japan	92/55	98/49	79	75	21.7	22.3
Hu	2014	Non – RCT	China	51/34	86/56	55	55	23.4	24.2
Ji	2021	RCT	South Korea	170/110	168/109	59.1	57.8	<25	<25
Jiang	2022	RCT	China	685/409	354/211	58.0	57.0	22.9	22.9
Ng	2014	RCT	Japan	40/24	40/22	60.2	62.1	23.1	22.4
Stevenson	2019	RCT	Australia/New Zealand	225/150	225/145	65	65	27	26

RCT: randomized controlled trial, non – RCT: non-randomized controlled trial, LS: laparoscopic surgery, OP: open surgery, M: male, BMI: body mass index

Australia, the United States, Japan, the United Kingdom, and South Korea. This meta-analysis included 3935 patients (open = 1644, laparoscopic = 2291), the characteristics of the studies included are summarized in *Table 1*. Blinding of participants and personnel was found to be the highest risk of bias in the included studies, with no risk of bias for data outcomes and reporting selection, the summary of the risk of bias of the studies is shown in *Fig. 2*. The NOS risk of bias analysis for the NRCT resulted in a 7-star rating.

Operative Outcome

Blood loss was observed in seven studies involving a total of 2420 patients (10, 17, 18, 20–23), and Laparoscopic surgery was associated with significantly lower blood loss compared to open surgery (WMD: -70.44 ml; 95% CI, -92.19, -48.70; $p < 0.0001$) (*Table 2*). Operative time was assessed in seven studies involving a total of 2,420 patients (10, 17, 18, 20–23), although laparoscopic surgery showed a trend towards longer duration compared to open surgery, this difference was not statistically significant (WMD 0.67; 95% CI, 0.23, 1.12;

Figure 2. (A) Risk of bias graph: judgments about each risk of bias item presented in all included RCTs; (B) risk of bias summary: judgments about each risk of bias item for each included RCT.

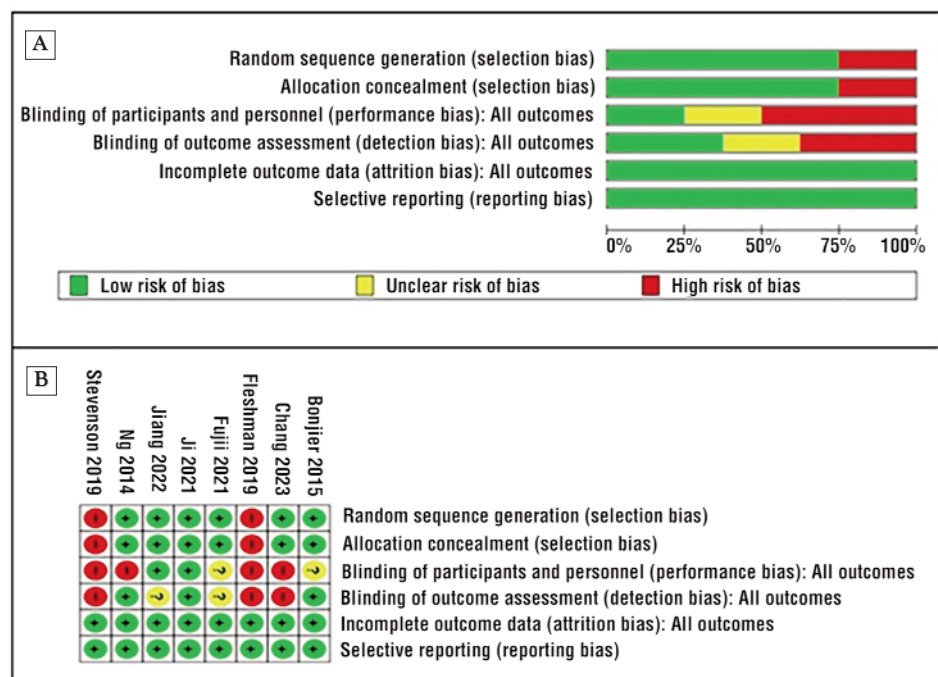


Table 2. Results of meta-analyses of operative outcome and postoperative complications

Outcome Measures	Number of studies	Patients (LS/OS)	I ² (%)	HG p value	Analysis model	Statistics method	OR/WMD	95% CI	p value
Blood Loss (ml)	7	1369/1051	94%	<0.0001	Random	IV	-70.44	-92.19, -48.70	<0.00001
Operative Time (min)	7	1369/1051	96%	<0.00001	Random	IV	0.67	0.23, 1.12	0.003
Postoperative Hospital Stay (day)	7	1369/1051	99%	<0.00001	Random	IV	-1.74	-3.64, 0.16	0.07
Time to pass first flatus (hours)	6	1340/1022	99%	<0.00001	Random	IV	-8.92	-18.82, 0.98	0.08
Time to resume normal diet (hours)	5	1100/800	97%	<0.00001	Random	IV	-14.94	-24.73, -5.15	0.003
Postoperative Complications	7	1369/1051	49%	0.07	Fixed	M-H	0.64	0.53, 0.77	<0.00001
Anastomotic Leakage	7	1369/1051	0%	0.80	Fixed	M-H	0.71	0.44, 1.14	0.15
Genito – Urinary Complications	7	1369/1051	21%	0.44	Fixed	M-H	0.89	0.49, 1.60	0.69

LS: laparoscopic surgery, OP: open surgery, HG: heterogeneity, OR: odds ratio, WMD: Weighted mean difference, CI: confidence interval, IV: inverse variance, M-H: Mantel – Haenszel.

p=0.003) (Table 2). In seven studies, no significant difference was observed in postoperative hospital stay between the two groups (10, 17, 18, 20–23), (WMD: -1.74; 95% CI, -3.64, 0.16; p=0.07) (Table 2). When analysing time to first flatus, six studies (17, 18, 20–23) reported data showing that laparoscopic surgery patients had their first flatus earlier than open surgery patients (WMD -8.92; CI 95%, -18.82, 0.98; p=0.08) (Table 2). Similarly, five studies (17, 18, 21–23) reported earlier initiation of diet in patients under-going laparoscopic surgery (WMD: -14.94; 95% CI, -24.73, -5.15; p=0.003) (Table 2).

Postoperative Complications

Overall complications were reported in seven studies (10, 17, 18, 20–23), all of which showed fewer complications in patients who underwent laparoscopic surgery (OR 0.64; 95% CI, 0.53, 0.77; p=0.008) (Fig. 3). The analysis of the above-mentioned studies showed a low rate of anastomotic leakage as a postoperative complication in those patients who were treated with laparoscopic surgery (OR 0.71; 95%CI, 0.44, 1.14; p = 0.15). However, these studies found no significant

difference in urogenital complication rates comparing the two groups (OR 0.89; 95% CI, 0.49, 1.60; p=0.69) (Table 2).

Pathological Outcomes

Seven studies reported on comparisons in terms of the number of nodules that were removed (10,17–22), although there is a general similarity in the number of nodules removed with both procedures, most of these trials have shown that laparoscopic surgery offers a better benefit in this aspect (WMD: 0.66; 95% CI, -0.63, 1.95;p=0.32; I²=98%) (Fig. 4 A)

The meta-analysis corresponding to the length of the distal margins is shown in Fig. 4 B, where only five studies were analysed (17,18,20,22,23), no significant differences were observed between the laparoscopic and open groups. (WMD: -0.29; 95% CI, -0.69, 0.10; p=0.15, I²=94%). However, this is contradicted by the outcome of positive margins, which were assessed in all 9 trials (9,10, 17–23), and analysis of these showed that laparoscopic surgery had a higher number of cases with positive margins, favouring the conventional approach (Fig. 4 C).

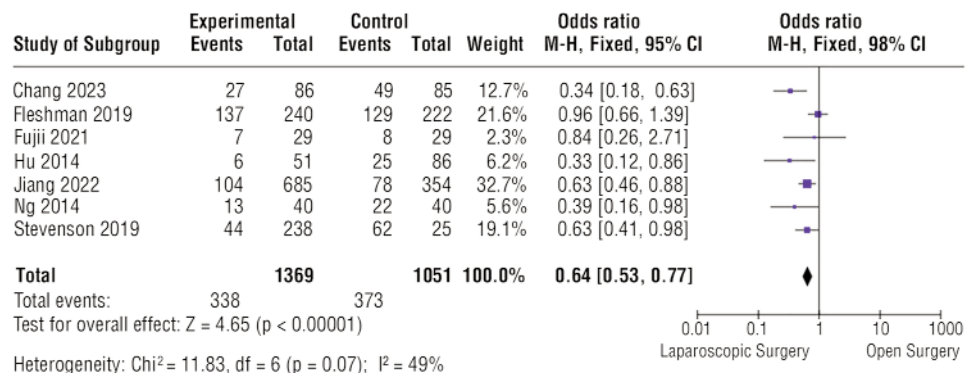
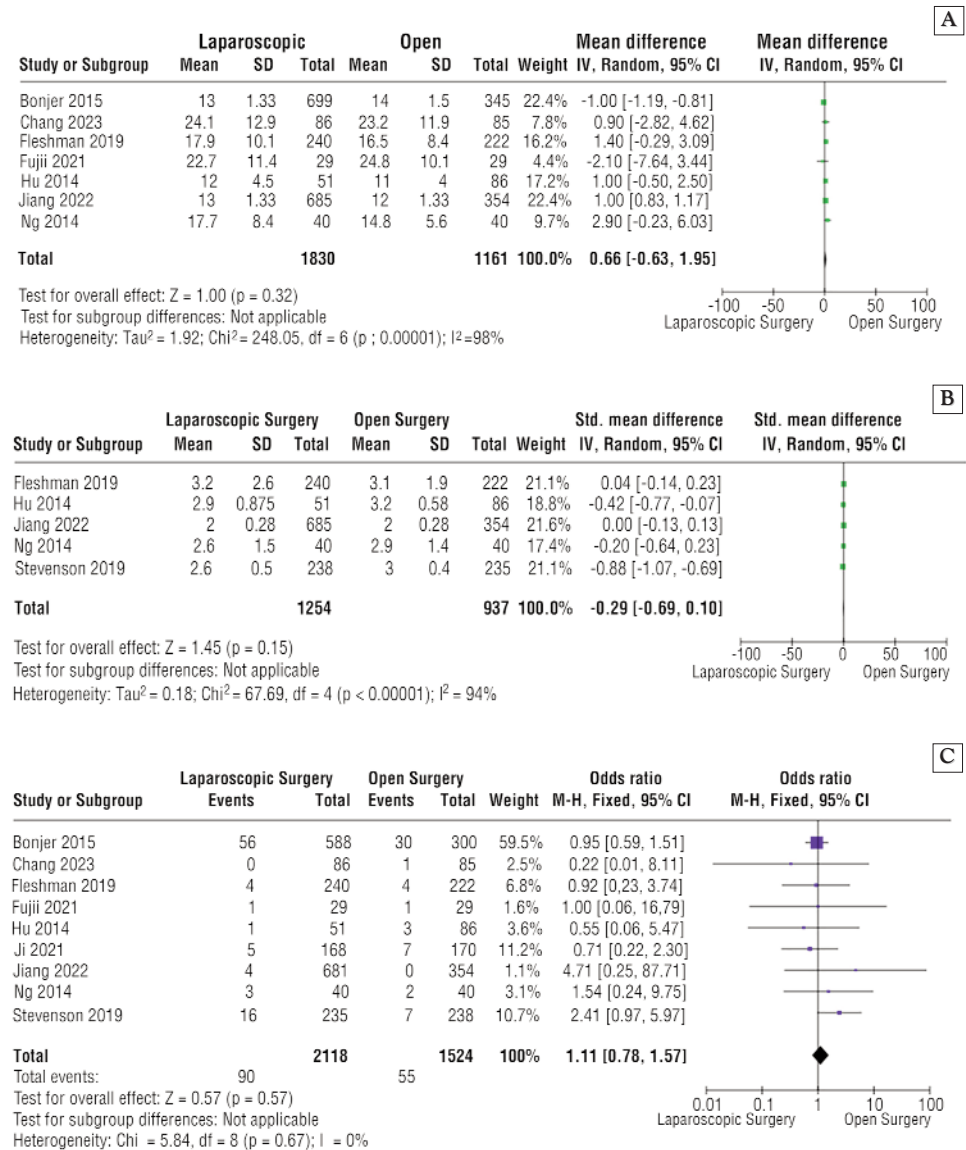


Figure 3. Meta-analysis of postoperative complications.

Figure 4. Meta-analysis of pathological outcomes: **(A)** number of lymph nodes harvest; **(B)** length of the distal margins; **(C)** positive margins



Overall survival was assessed in 6 trials (9,10,18, 19,21,23). There was a discreet difference in favour of laparoscopic surgery (HR: 0.94; 95% CI, 0.78, 1.14; p=0.55; I²= 0%). As for disease-free survival, which was evaluated in 7 trials (9,10,18-21,23), it was shown that patients in the conventional surgery group were favoured. Both variables, although with slight deviations to one side or the other, are not separated from the epicentre of the graph, as shown in *Fig. 5 A, B*.

Publication Bias Analysis and Sensitivity Analysis

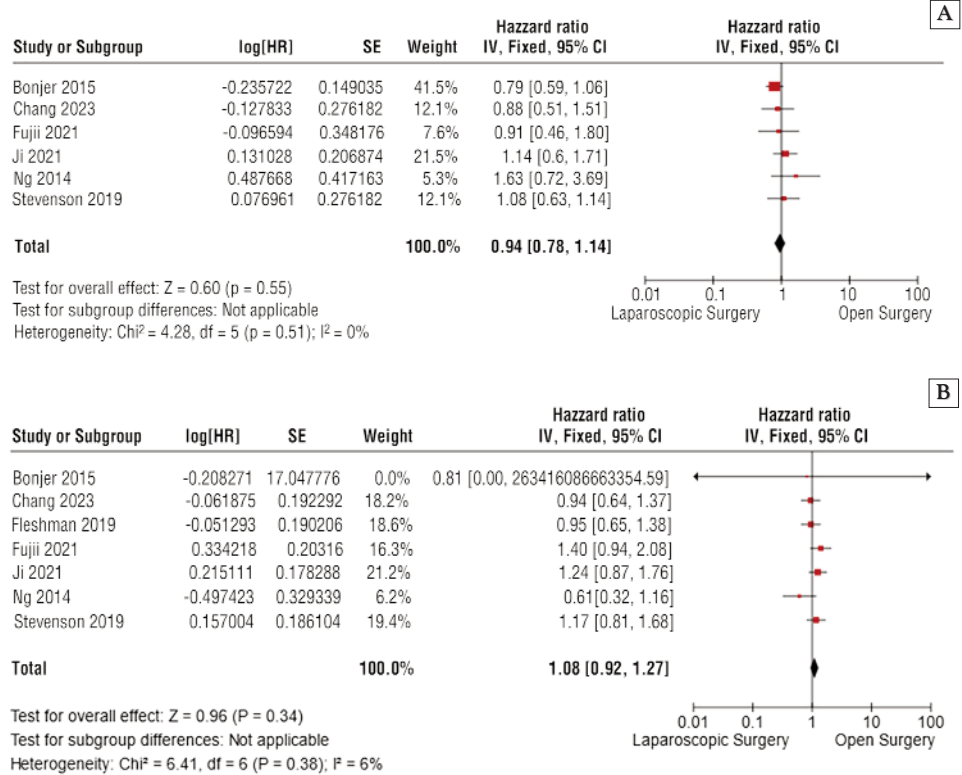
To assess potential publication bias in studies reporting overall survival, a funnel plot was created. The analysis showed no indication of publication bias, as both large

and small sample studies were evenly distributed within the triangular plot area. The dotted lines on either side reflect the meta-analysis results (*Fig. 6*).

Discussion

This meta-analysis aimed to compare laparoscopic and conventional surgery for rectal cancer by analysing short- and long-term outcomes, including surgical safety, postoperative complications, anatomopathological quality, and postoperative disease survival. The main discoveries of this research were that laparoscopic surgery offers a better outcome with respect to safety and postoperative recovery, although laparoscopic surgery requires more operating time than open

Figure 5. Meta – analysis of Survivals outcomes: **(A)** overall survival; **(B)** disease – free survival



surgery, no significant differences were identified between the two groups regarding anatomopathological quality or survival outcomes in colorectal cancer.

Laparoscopic surgery leads to longer operative time during the treatment of rectal cancer compared to open surgery, even so this meta-analysis showed that it offers greater advantages. Patients who underwent

laparoscopic surgery experienced less blood loss, rapid recovery of gastrointestinal function, and were able to resume a normal diet and be discharged from the hospital sooner. Additionally, it was found that patients who underwent open surgery generally faced more postoperative complications, including higher rates of suture dehiscence and damage to the genitourinary system. Martínez – Pérez et al. (7) performed a meta-analysis comparing short-term outcomes between laparoscopic and open surgery, which was consistent with our studies and indicated that patients who underwent laparoscopic surgery experienced a longer surgical duration but still had a lower rate of bleeding, shorter bowel recovery time and diet normalisation, and a shorter hospital stay (7). Laparoscopic surgery offers greater precision in tissue dissection, which reduces bleeding, and there is minimal interaction with the bowel loops during laparoscopic surgery, which favours rapid recovery from postoperative paralytic ileus and earlier reintroduction of food from the normal diet.

Sasi et al. performed a propensity-matched cohort analysis to compare the short-term oncological outcomes of laparoscopic versus open surgery in patients with rectal cancer. In the mentioned study, a higher incidence of complications was observed in the open

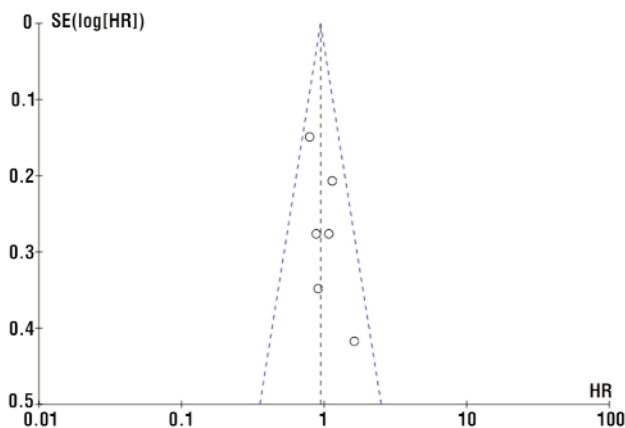


Figure 6. Funnel of overall survival
 SE: standard error, HR: Hazard Ratio

surgery group, with a difference of approximately 15%, despite the fact that both groups had comparable tumour characteristics, thus eliminating possible biases related to tumour stage or location. In addition, higher blood loss and an increased need for intraoperative transfusions were reported in patients undergoing open surgery, which could negatively impact postoperative recovery and increase the risk of morbidity and mortality (24).

According to the available evidence, laparoscopic surgery offers greater precision in tissue dissection, which reduces bleeding, and there is minimal interaction with the bowel loops during laparoscopic surgery, which favours rapid recovery from postoperative paralytic ileus and earlier reintroduction of food from the normal diet (25,26).

When analysing the number of lymph nodes harvested, no differences were observed compared to the two groups, even though there was a slight shift towards laparoscopic surgery without losing contact with the centre of the graph. This difference is minimal and clinically insignificant, as both groups exceeded the recommended threshold of 12 lymph nodes harvested. This result contradicts the meta-analysis conducted by Chen et al. (27), which found that a greater number of lymph nodes were removed in open surgery. However, they indicated that laparoscopic surgery resulted in the removal of an average of 12 lymph nodes. A possible reason for this discrepancy is the difference of more than 10 years between the two meta-analyses, a period during which skills in minimally invasive surgery have improved. In addition, our review included trials that included data from both conventional laparoscopic surgery and robotic surgery, where the latter has been shown to be superior in terms of lymph node dissection (28). A recent study demonstrated that the extraction of 11 or more lymph nodes is sufficient to assess the pathological stage of nodular metastasis in rectal cancer. Additionally, the study suggests that this number of lymph nodes is adequate to determine adjuvant treatment strategies (29).

Laparoscopic surgery has been shown not to be an obstacle to obtaining oncologically adequate resections. In the meta-analysis by Chen et al. (27) laparoscopic surgery showed slightly higher resection rates than those observed in open surgery, although in both groups a distance of distal resection margin of more than 2 cm was achieved, in line with current scientific evidence recommendations (30-32). In addition, studies identified in databases suggest that minimally invasive surgery, and even more so its robotic variant, offers greater access to the intrapelvic structures: surgery for rectal cancer is favoured by this aspect, thus achieving

better results with regard to greater distance of resection of the distal margin of the tumour. Moreover, recent studies have shown that minimally invasive surgery achieves negative circumferential margins in more than 90% of cases, comparable or even superior to open surgery (33,34).

The results for distal resection margin distance were consistent with the patients who had positive margins. While patients in the open surgery group showed a slight advantage, the difference compared to the laparoscopic surgery group was not statistically significant, Chen et al. (27) conducted a meta-analysis suggesting that laparoscopic surgery offers greater safety than open surgery in terms of tumour-free margins, with their findings showing a difference of less than 5% favouring laparoscopic surgery in the rate of positive margins detected. Similarly, Ma et al. (35), in a meta-analysis including over 20,000 patients, found that laparoscopic surgery was associated with a significantly lower rate of positive distal margins (relative risk (RR) 0.75; 95% CI 0.66-0.85) and positive CRM (RR 0.79; 95% CI 0.72-0.85), supporting its non-inferiority and potential advantages over open surgery. Furthermore, Khan et al. (36) reinforced these findings in their analysis of 15 randomized controlled trials (RCTs), demonstrating that laparoscopic and robotic approaches achieved higher rates of clear resection margins and lower conversion rates, without compromising oncologic radicality.

One of the gaps identified in the literature review that motivated this review was that few meta-analyses included survival outcomes of at least 3 years, also due to the lack of available clinical trials that assessed longer survival. These meta-analyses demonstrated that overall survival was not different in one group compared to the other, although it should be noted that the favoured group was the laparoscopic surgery group, which affirms the safety of this procedure in the treatment of rectal cancer. Similar results were found in the meta-analysis by Chen et al. (27), they reported that no differences were found between the two groups, and also showed that patients included in the laparoscopic surgery group were favoured. Major studies have shown disease decline after neoadjuvant therapy. In this study, no difference in disease-free survival was found, with both groups showing equivalent results. Chen et al. align with the findings of our study, demonstrating no notable difference in disease-free survival, thereby reinforcing the assertion that laparoscopic surgery is a viable and safe treatment option for rectal cancer.

Drawing from the results of both RCTs and nRCTs, this meta-analysis concludes that laparoscopic surgery (LS) is a risk-free and achievable treatment option for

rectal cancer, offering advantages in intraoperative outcomes, postoperative recovery, and lymphadenectomy. Additionally, long-term survival outcomes are comparable to those of open surgery. However, further prospective and multicentre RCTs are required to confirm survival benefits beyond five years.

This meta-analysis has limitations that must be taken into consideration in its interpretation, although recent and high-quality studies were included, variations in outcome definitions and the limited number of randomised clinical trials reduce the overall strength of the evidence. The predominance of short-term outcomes and the lack of long-term oncological data, such as overall survival and disease-free survival, represent another important limitation. In addition, the possibility of publication bias cannot be ruled out, as studies with positive results are more likely to be published. It is worth noting the heterogeneity present in the included studies, both in relation to surgical experience, patient selection criteria, tumour stage, and perioperative management protocols, which may affect the generalisability of the results.

Conflicts of Interest

Drs. Alain David Medina Lago, Marius Alexandru Moga, Oscar Díaz Pi, Anda Hoge, Catalin Misarca, Mircea Hoge have no conflicts of interest or financial ties to disclose.

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<https://www.crd.york.ac.uk/PROSPERO/view/CRD42024623700>

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