

Review Article

Histopathological outcomes of transanal, robotic, open, and laparoscopic surgery for rectal cancer resection. A Bayesian network meta-analysis of randomized controlled trials

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ABSTRACT

Background: While total mesorectal excision is the gold standard for rectal cancer, the optimal surgical approach to achieve adequate oncological outcomes remains controversial. This network meta-analysis aims to compare the histopathological outcomes of robotic (R-RR), transanal (Ta-RR), laparoscopic (L-RR), and open (O-RR) resections for rectal cancer.

Materials and methods: MEDLINE, Embase, and the Cochrane Library were screened from inception to June 2024. Of the 4186 articles screened, 27 RCTs were selected. Pairwise comparisons and Bayesian network meta-analyses applying random effects models were performed.

Results: The 27 RCTs included a total of 8696 patients. Bayesian pairwise meta-analysis revealed significantly lower odds of non-complete mesorectal excision with Ta-RR (Odds Ratio, OR, 0.60; 95%CI, 0.33, 0.92; $P = .02$; $I^2:11.7\%$) and R-RR (OR, 0.68; 95%CI, 0.46, 0.94; $P = .02$; $I^2:41.7\%$) compared with laparoscopy. Moreover, lower odds of positive CRMs were observed in the Ta-RR group than in the L-RR group (OR, 0.36; 95%CI, 0.13, 0.91; $P = .02$; $I^2:43.9\%$). The R-RR was associated with more lymph nodes harvested compared with L-RR (Mean Difference, MD, 1.24; 95%CI, 0.10, 2.52; $P = .03$; $I^2:77.3\%$). Conversely, Ta-RR was associated with a significantly lower number of lymph nodes harvested compared with all other approaches. SUCRA plots revealed that Ta-RR had the highest probability of being the best approach to achieve a complete mesorectal excision and negative CRM, followed by R-RR, which ranked the best in lymph nodes retrieved.

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Conclusion: When comparing the effectiveness of the available surgical approaches for rectal cancer resection, Ta-RR and R-RR are associated with better histopathological outcomes than L-RR.

1. Introduction

Rectal cancer represents one of the main causes of cancer-related deaths worldwide, and its burden is expected to rise by 2040 [1]. In 2022, it accounted for almost one-third of all colorectal malignancies, with nearly 729,833 new diagnoses and 343,817 deaths [2]. Regarding its management, neoadjuvant chemoradiotherapy plays a major role in locally advanced disease [3–5], but total mesorectal excision (TME), as introduced by Heald in 1982 [6], remains the cornerstone treatment. Oncologically, the macroscopic completeness of the mesorectal specimen, the circumferential resection margin (CRM) clearance, and the number of harvested lymph nodes are benchmarks for surgical resection quality and predictors of survival and locoregional/distant recurrence [7–12]. Over the last two decades, the surgical treatment of rectal cancer has shifted toward minimally invasive surgery (MIS) [13–17], including laparoscopic, robotic, and transanal approaches, which have progressively replaced open surgery. Nevertheless, the debate regarding the oncological effectiveness of different MIS approaches for rectal cancer resection continues, with seven new randomized controlled trials (RCTs) [18–24] recently published. Thus, there is a compelling need to update the literature with a systematic review and network meta-analysis of RCTs that aims to analyze the current evidence and elucidate the oncological effectiveness of robotic (R-RR), transanal (Ta-RR), laparoscopic (L-RR), and open (O-RR) rectal cancer resection.

2. Materials and methods

2.1. Study design and eligibility criteria

The study protocol was established and registered in PROSPERO (registration number: CRD42024561428). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [25] checklist was followed (eTable 1 in the Supplement). The literature search was limited to RCTs that compared at least two surgical approaches for mesorectal excision for histologically confirmed rectal cancer and reported at least one of the histological outcomes of interest (listed below).

The PICOS (Population, Intervention, Comparison, Outcome, Study design) framework was applied as follows:

P: Adult patients with histologically confirmed rectal cancer requiring surgical resection;

I: Robotic, transanal, laparoscopic (including laparoscopic-assisted), and open rectal resection, irrespective of the surgical procedures employed for mesorectal excision (e.g., abdominoperineal resection and anterior resection with or without primary anastomosis). Both TME and partial mesorectal excision were eligible for inclusion.

C: Comparison of surgical approaches other than the index intervention among laparoscopic, robotic, transanal, and open surgeries.

O: Histopathological outcomes, including the following:

- Complete mesorectal excision, graded as complete, nearly complete, or incomplete according to Nagtegaal et al. [7];
- Positive CRM, defined as the presence of cancer cells within ≤ 1 mm of the surgical circumferential plane;
- Number of lymph nodes harvested;
- Positive distal margin;
- Distance (in millimeters) between the tumor and the free radial margin;
- Distance (in millimeters) between the tumor and the distal resection margin.

S: RCTs without any time limitations in terms of follow-up duration or publication date. Only English-language publications were considered. RCTs reporting surgical outcomes during the surgical team's learning curve were excluded.

2.2. Literature search strategy

MEDLINE, Embase, and the Cochrane Library were screened from inception to December 1st, 2023. The search was updated on June 29th, 2024, to verify that no additional pertinent article had been published since then. A specific research equation was developed for each database using keywords and/or MeSH terms, as reported in eTables 2, 3, and 4 in the Supplement. In addition, the reference lists of all eligible studies, plus those of clinical practice guidelines, pertinent systematic reviews, and meta-analyses were crosschecked to identify additional potentially relevant records that may have been missed.

2.3. Study selection and risk of bias assessment

Two review authors (CAS and AMP) independently screened the retrieved studies for eligibility by analyzing the titles and abstracts. To increase sensitivity, only the records excluded by both reviewers were initially removed. Thereafter, the two reviewers performed an independent full-text analysis of all records identified for potential inclusion. A third review author was consulted to resolve any disagreements on study inclusion or exclusion (Nde'A). The two reviewers independently assessed the risk of bias via the Cochrane risk-of-bias tool (ROB-II) for RCTs [26,27]. In addition, the quality of evidence was assessed via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [28].

2.4. Data extraction

Both reviewers independently extracted data in a predefined Excel database. The data were processed for qualitative and quantitative analyses, when appropriate. If needed, outcome variables were calculated from the available data in the selected studies [26,29,30]. Cohen's kappa statistic was used to assess the inter-reviewers' agreement during the study selection process [31].

2.5. Statistical analysis

A Bayesian network meta-analysis (NMA) was performed to evaluate the comparative effectiveness of treatments for rectal cancer [32]. This approach estimates the treatment effects while accounting for both within-study and between-study variability. A random effect approach was used to account for heterogeneity across studies [32], and a model configured with 4 Markov chain Monte Carlo (MCMC) methods was employed to ensure robust estimation and convergence of the model parameters. The Bayesian hierarchical model has executed over 100,000 iterations, with an initial adaptation phase of 5000 iterations to optimize the sampling process. We thinned the chains by retaining every tenth sample to reduce autocorrelation and improve computational efficiency. Uninformative priors were considered for the analyses, setting a uniform 0–5 distribution on the heterogeneity parameter. The posterior distributions obtained from the MCMC simulations were used to infer the treatment effects, integrating both direct and indirect evidence within the treatment network [32]. To quantify the relative effectiveness of each treatment, the surface under the cumulative ranking curve (SUCRA) was calculated to provide a statistical ranking of each

treatment's probability of being among the best options [33]. The convergence of the models was visually assessed via trace plots. A network plot was generated to visualize the network of treatments, and direct and indirect comparisons were generated. Publication bias was assessed via funnel plots and Egger's test [34]. Inconsistency between direct and indirect evidence was assessed via node splitting methods and the design-by-treatment interaction model. A meta-regression analysis was also conducted to assess whether the study period or neoadjuvant therapy acted as effect modifiers on the pooled meta-analytic outcomes, reporting both the Bayesian correspondence of P-Value (Probability of effect) on the posterior distribution and posterior densities of meta-regression effect with the probabilities of direction. The analyses were performed in R 3.4.2 [35] with the gemtc package [36].

3. Results

3.1. Literature search and selection

After the comprehensive literature search, a total of 4186 articles were identified. No additional studies were obtained by cross-checking the reference lists. After removing duplicates, 3218 studies were excluded by screening the titles and abstracts. The remaining 94 records underwent full-text analysis, and only 27 RCTs [18–24,37–56] fulfilled the inclusion criteria (Fig. 1). The list of the studies screened in the full-text analysis and the detailed reasons for exclusion are reported in eTable 6 in the Supplement.

The inter-reviewer percentage of agreement was 96.8 %, with a

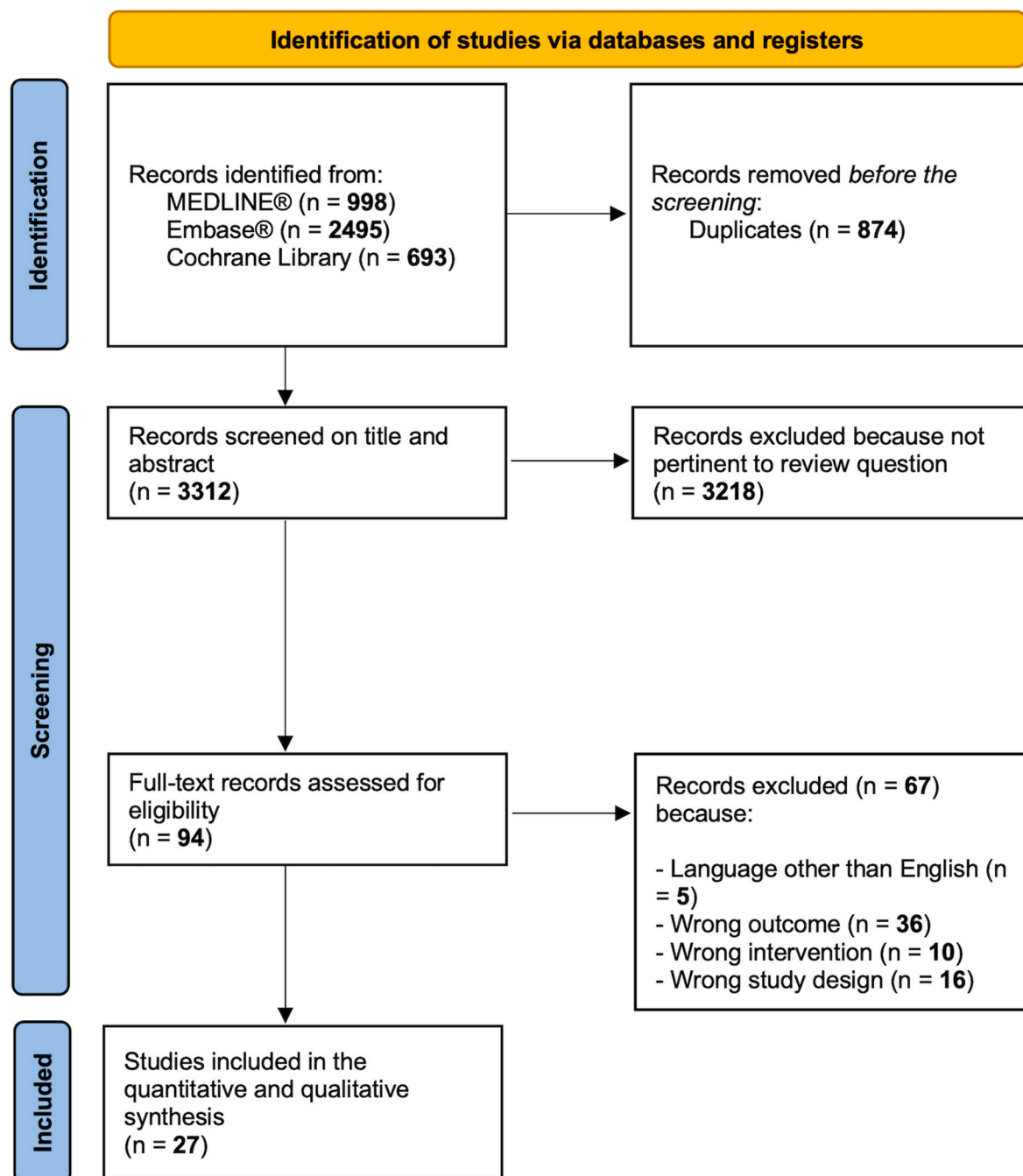


Fig. 1. PRISMA Diagram

The flowchart shows the literature search and study selection process according to the PRISMA guidelines [25].

Table 1
Main characteristics of the 27 included randomized controlled trials.

First Author (year)	Countries Study period	Inclusion criteria	Exclusion criteria	Surgical approach Number		Age Mean (SD)	Male sex %		BMI Mean (SD)		Neoadjuvant therapy %	Anatomical classification %			
Laparoscopic versus open rectal resections															
				L- RR	O- RR	L-RR	O-RR	L- RR	O- RR	L-RR	O-RR	L- RR	O- RR	L-RR	O-RR
Araujo et al. (2003)	Brazil Sep 1997–Sep 2000	Low rectal cancer with incomplete response to RCT	1, 26	13	15	59.1 (31–75) ^a	56.4 (24–78) ^a	69.2	66.6	23.5 (21.7–24.6) ^a	25.6 (17.1–38.5) ^a	100	100	Only low rectal cancers	
Zhou et al. (2004)	China Jun 2001–Sep 2002	Low rectal cancer (with anal sphincter preservation)	1, 26, 29, 43	82	89	44 (26–85) ^a	45 (30–81) ^a	56	48.3	NR	NR	NR	NR	Only low rectal cancers	
Guillou et al. (2005) <i>MRC CLASICC</i>	United Kingdom Jul 1996–Jul 2002	Colorectal cancer (excluded transverse)	11, 16, 17, 21, 32, 33	253	128	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braga et al. (2007)	Italy NR	Rectal cancer	1, 2, 10, 13, 31, 36	83	85	62.8 (12.6)	65.3 (10.3)	66.3	75.3	NR	NR	16.9	14.1	NR	NR
Pechlivanides et al. (2007)	Crete and Greece NR	Rectal cancer ≤12 cm from the AV	NR	34	39	72 (31–84) ^b	69 (41–85) ^b	58.8	58.9	NR	NR	38.2	43.6	NR	NR
Ng et al. (2008)	China Sep 1994–Feb 2005	Low rectal cancer (≤5 cm from the AV)	13, 16, 23, 24, 30, 36	51	48	63.7 (11.8)	63.5 (12.6)	60.8	62.5	NR	NR	0	0	Only low rectal cancers	
Luján et al. (2009)	Spain Jan 2002–Feb 2007	Mid or low rectal cancer	1, 13, 18, 29	101	103	67.8 (12.9)	66.0 (9.9)	61.4	62.1	NR	NR	72.3	74.8	NR	NR
Ng et al. (2009)	China Sep 1993–Oct 2002	High rectal cancer at 12–15 cm from the AV	1, 16, 23, 24, 27, 28	76	77	66.5 (11.9)	65.7 (12.0)	48.6	62.3	NR	NR	0	0	Only high rectal cancers	
Kang et al. (2010) <i>COREAN</i>	South Korea Apr 2006–Aug 2009	cT3N0-2 rectal cancer ≤9 cm from the AV	1, 5, 10, 13, 16, 21, 23, 26	170	170	57.8 (11.1)	59.1 (9.9)	64.7	64.7	24.1 (3.2)	24.1 (3.2)	100	100	NR	NR
Liu et al. (2010)	China Feb 2005–Oct 2008	Rectal cancer	16, 17, 23	98	88	59.3 (9.7)	61.5 (8.9)	57.1	56.8	25.6 (2.1)	26.1 (1.7)	NR	NR	NR	NR
Liang et al. (2011)	China May 2004–April 2008	Rectal cancer	16, 25, 26, 31, 34, 35	169	174	57.3 (14.13) ^c	57.36 (13.08) ^c	61.5	52.9	21.45 (NR) ^b	22.31 (NR) ^b	0	0	NR	NR
van der Pas et al. (2013) <i>COLOR II</i>	Belgium, Canada, Denmark, Germany, the Netherlands, Spain, South Korea, and Sweden Jan 2004–May 2010	T1-3 rectal cancer ≤15 cm from the AV	1, 2, 9, 10, 13–22	699	345	66.8 (10.5)	65.8 (10.9)	64	61	26.1 (4.5)	26.5 (4.7)	RT: 59 CT: 32	RT: 58 CT: 34	High: 32 Mid: 39 Low: 29	High: 34 Mid: 39 Low: 27
Ng et al. (2014)	China Aug 2001–Aug 2007	Mid and low rectal cancer at 5–12 cm from the AV	13, 16, 17, 23, 24, 25	40	40	60.2 (11.3)	62.1 (12.6)	60	55	23.1 (3.4)	22.4 (3.2)	0	0	NR	NR
Stevenson et al. (2015) <i>AlaCaRT</i>	Australia, New Zeland Mar 2010–Nov 2014	cT1-3 rectal cancer ≤15 cm from the AV	1, 2, 4, 7, 10, 12, 13	238	237	65 (56–74) ^d	65 (56–73) ^d	67	64	27 [24–30] ^d	26 [24–30] ^d	RT: 50	RT: 49	High: 22 Mid: 43 Low: 35	High: 21 Mid: 44 Low: 35
Jiang et al. (2022) <i>LASRE</i>	China Nov 2013–Jun 2018	cT1-4aN0-2 Low rectal cancer (<5 cm from the dentate line)	1, 2, 7, 9, 16, 21, 24, 26, 29, 33, 37, 38	685	354	58 [50–64] ^d	57 [50–63] ^d	59.7	59.6	22.9 (20.8–25) ^d	23.0 (20.9- 25.1) ^d	95.6	96.9	Only low rectal cancers	
Robotic versus laparoscopic rectal resections															

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Table 1 (continued)

First Author (year)	Countries Study period	Inclusion criteria	Exclusion criteria	Surgical approach Number		Age Mean (SD)		Male sex %		BMI Mean (SD)		Neoadjuvant therapy %		Anatomical classification %	
				R- RR	L- RR	R-RR	L-RR	R- RR	L- RR	R-RR	L-RR	R- RR	L- RR	R-RR	L-RR
Baik et al. (2008)	USA Apr 2006–Feb 2007	cT1-3 rectal cancer	26, 36, 44, 48	18	18	57.3 (6.3)	62.0 (9.0)	77.8	77.8	22.8 (1.8)	24.0 (2.5)	NR	NR	NR	NR
Jayne et al. (2017) ROLARR	United Kingdom, Italy, Denmark, United States, Finland, South Korea, Germany, France, Australia, and Singapore Jan 2011–Feb 2014	Rectal cancer ≤15 cm from the AV	1, 17, 26, 49	237	234	64.4 (10.98)	65.5 (11.93)	67.9	67.9	NR	NR	46.8	46.2	High: 30.1 Mid: 45.3 Low: 24.2	High: 30 Mid: 43 Low: 26.5
Debakey et al. (2018)	Egypt Apr 2015–Feb 2017	Rectal cancer ≤15 cm from the AV	1, 26, 29, 50	21	24	53.4 [32–67] ^b	50.3 [36–64] ^b	42.4	54.2	NR	NR	57.1	45.8	High: 42.9 Mid: 47.6 Low: 9.5	High: 54.2 Mid: 33.3 Low: 12
Kim et al. (2018)	South Korea Feb 2012–Mar 2015	Mid or low cT1-3 rectal cancer (≤9 cm from the AV)	14, 18, 21, 26, 29, 33	66	73	60.4 (9.7)	59.7 (11.7)	77.3	71.2	24.1 (3.3)	23.6 (3.0)	77.3	79.5	NR	NR
Feng et al. (2022)	China Dec 2013–Dec 2016	cT1-3N0-1 or ycT1- 3Nx rectal cancer ≤5 cm from the AV	14, 17, 18, 21, 26, 46, 51	174	173	58.2 (9.6)	59.5 (10.9)	62.1	65.3	NR	NR	21.3	20.2	Only low rectal cancer	
Feng et al. (2022) REAL	China Jul 2016–Dec 2020	Rectal cancer ≤10 cm from the AV	14, 17, 18, 21, 26, 46, 51	586	585	59.1 (11.0)	60.7 (9.8)	60.8	60.5	23.5 (3.3)	23.5 (3.1)	43.3	43.9	Mid: 51.7 Low: 48.3	Mid: 51.8 Low: 48.2
Park et al. (2023) COLRAR	South Korea Jul 2011–Feb 2016	Rectal cancer ≤10 cm from the AV	26, 33, 36	151	144	65.6 (11.4)	67.2 (10.1)	64.2	68.8	23.9 (3.3)	23.5 (2.8)	50.3	47.2	NR	NR
Laparoscopic versus transanal rectal resections															
				L- RR	Ta- RR	L-RR	Ta-RR	L- RR	Ta- RR	L-RR	Ta-RR	L- RR	Ta- RR	L-RR	Ta-RR
Denost et al. (2014)	France Jun 2008–Feb 2012	Low rectal cancer (<6 cm from the AV)	1, 43, 47	50	50	63 (31–90) ^b	64 (39–82) ^b	64	74	25.6 (18.3–38.3) ^b	25.1 (17.3–33.2) ^b	88	80	Only low rectal cancer	
Ren et al. (2021)	China Jan 2017–Dec 2019	Low rectal cancer (<7 cm from the AV) with clinical stage I–III	9, 16, 17, 26, 29, 36, 43, 45	32	32	67.16 (10.03)	65.78 (12.37)	56	59	23.05 (2.7)	22.87 (2.66)	65.6	71.9	Only low rectal cancer	
Liu et al. (2022) TaLaR	China Apr 2016–Jun 2021	Rectal cancer with clinical stage I–III below the peritoneal reflection	13, 44	545	544	60 [52–67] ^d	58 [50–67] ^d	61.1	66	22.8 (20.9–24.8) ^d	22.9 (20.7–24.9) ^d	32.8	38.8	NR	NR
Serra-Aracil et al. (2022)	Spain Apr 2015–May 2021	cT1-3N0-1 rectal cancer ≤10 cm from the AV	9, 13, 21, 26, 38, 39, 40, 41, 42, 43	50	55	68 [19] ^d	66 [19] ^d	68	76.4	26.7 (5.9) ^d	26.7 (4.9) ^d	50.3	47.2	NR	NR
Robotic versus open rectal resections															
				R- RR	O- RR	R-RR	O-RR	R- RR	O- RR	R-RR	O-RR	R- RR	O- RR	R-RR	O-RR

(continued on next page)

Table 1 (continued)

First Author (year)	Countries Study period	Inclusion criteria	Exclusion criteria	Surgical approach Number	Age Mean (SD)	Male sex %	BMI Mean (SD)	Neoadjuvant therapy %	Anatomical classification %
Somashekhar et al. (2013)	India Aug 2011–Dec 2012	Rectal cancer ≤15 cm from the AV	NR	25 25	56.36 (8.21)	59.56 (5.75)	68 60	31.19 (3.02) 28.84 (2.75)	28 36 High: 8 Mid: 40 Low: 52 High: 20 Mid: 32 Low: 48

AV = Anal verge; BMI, body mass index; O-RR, open rectal resection; L-RR, laparoscopic rectal resection; Ta-RR, Transanal rectal resection; R-RR, robotic rectal resection; RCT, radiochemotherapy; NR, not reported; RT, radiotherapy; CT, chemotherapy.

The exclusion criteria were as follows: [1] Other tumor than histologically proven adenocarcinoma [2], Age <18 years [3], Body mass index (BMI) > 34 kg/m² [4], Eastern Cooperative Oncology Group (ECOG) performance score ≥3 [5], Not receiving neoadjuvant chemoradiotherapy/radiotherapy [6], Operation not performed between 4 and 12 weeks of the final radiation treatment [7], History of invasive pelvic malignancy within 5 years [8], psychiatric or addictive disorders that affected compliance to the protocol [9], American Society of Anesthesiologists (ASA) classification IV or V [10], Severe systemic disease [11], Conditions that limit the success of laparoscopic resection [12], Life expectancy of at least 12 weeks [13], T4 tumors/involved CRM pretreatment [14], T1 tumor treated with local transanal excision [15], History of other malignancy except basocellular carcinoma of the skin or in-situ carcinoma of the cervix uteri [16], Signs of acute intestinal obstruction [17], Need for synchronous colorectal surgery [18], Familial adenomatous polyposis coli/hereditary non-polyposis [19], Colorectal cancer [20], Active Crohn's disease/ulcerative colitis [21], Pregnancy [22], T3 rectal cancer within 2 mm from the endopelvic fascia [23], Tumor perforation [24], Tumor larger than 6 cm [25], Neoadjuvant chemoradiotherapy [26], Distant metastasis [27], Distal tumor needing anastomosis within 5 cm of the dentate line [28], Previous abdominal operations near the region of the colorectal operation [29], Emergency surgery [30], recurrent disease [31], Ongoing infection/plasma neutrophil level < 2x10⁹/l [32], Associated gastrointestinal disease needing surgical intervention [33], Malignant disease in the past 5 years [34], BMI >30 kg/m² [35], previous abdominal surgery [36], Tumor infiltration to the adjacent organs [37], Age >75 years [38], Continuous systemic steroid therapy within the last month [38], Rectal cancer over 10 cm from the anal margin [39], Hepatic cirrhosis [40], undifferentiated adenocarcinoma [41], Chronic kidney failure on dialysis [42], BMI less than 18 or over 35 kg/m² [43], Indication for abdominoperineal resection (APR) [44], Tumors with ingrowth in the internal sphincter or levator ani [45], Tumor diameter larger than 5 cm [46], History of colorectal surgery, fecal incontinence, history of inflammatory bowel disease [47], Low rectal cancer treated by stapled anastomosis [48], Significant lateral pelvic nodes [49], Cancers of the anal canal [50], ASA classification ≥3 [51], Clinical complete response after preoperative chemoradiotherapy.

^a mean/range.

^b median/range.

^c median/SD.

^d median/IQR.

Table 2

Pairwise comparisons among the different surgical approaches applied for the resection of rectal cancer.

Outcome of interest	Index treatment	Reference treatment		
		Laparoscopy	Open	Robotic
Odds ratio (95 % Confidence Intervals)				
Non-complete mesorectal excision (nearly complete or incomplete)	Transanal	0.60 (0.33, 0.92) P=.02	0.79 (0.39, 1.36) P = .36	0.88 (0.46, 1.54) P = .63
	Robotic	0.68 (0.46, 0.94) P=.02	0.89 (0.52, 1.43) P = .61	–
	Open	0.76 (0.53, 1.07) P = .11	–	–
Positive circumferential resection margin	Transanal	0.36 (0.13, 0.91) P=.02	0.47 (0.16, 1.35) P = .15	0.58 (0.18, 1.65) P = .31
	Robotic	0.63 (0.37, 1.07) P = .07	0.81 (0.42, 1.75) P = .52	–
	Open	0.77 (0.47, 1.17) P = .21	-	–
Positive distal margin	Transanal	0.41 (0.09, 1.30) P = .11	2.7 (0.17, 106.52) P = .48	1.13 (0.08, 19.39) P = .92
	Robotic	0.36 (0.02, 3.06) P = .34	2.48 (0.07, 134.41) P = .61	–
	Open	0.15 (0, 1.47) P = .11	–	–
Mean differences (95 % Confidence Intervals)				
Number of lymph nodes harvested	Transanal	–1.9 (-3.77, -0.18) P=.03	–2.01 (-4.16, -0.09) P=.04	–3.15 (-5.46, -1.11) P=.005
	Robotic	1.24 (0.10, 2.52) P=.03	1.13 (–0.29, 2.63) P = .11	–
	Open	0.11 (–0.82, 1.11) P = .81	–	–
Distal resection margin distance (mm)	Transanal	–0.43 (–5.48, 4.61) P = .85	–0.6 (–6.83, 5.37) P = .82	–4.4 (–10.35, 1.74) P = .14
	Robotic	3.97 (0.45, 7.76) P=.02	3.77 (–1.13, 8.77) P = .11	–
	Open	0.19 (–3.12, 3.63) P = .89	–	–
Radial margin distance (mm)	Transanal	0.91 (–1.13, 2.58) P = .31	1.68 (–1.06, 3.82) P = .17	–1.59 (–5.22, 1.66) P = .29
	Robotic	2.49 (–0.36, 5.38) P = .07	3.27 (–0.12, 6.42) P = .05	–
	Open	–0.78 (–2.20, 0.95) P = .27	–	–

Statistically significant results are highlighted in bold ($P < .05$). The Bayesian correspondent value of p-value indicates the probability of evidencing in MCMC simulation an effect on the posterior distribution (P direction).

Odds ratios and mean differences of horizontal treatment over vertical treatment.

For the forest plot, please refer to eFig. 2 in the supplemental material.

Cohen's kappa coefficient of 0.92, demonstrating almost perfect agreement.

3.2. Study characteristics

The selected RCTs were published between May 2003 and July 2023. They included 8696 patients who underwent rectal resections between September 1993 and June 2021 [18–24,37–56].

Overall, 1278 (14.7 %), 4720 (54.3 %), 681 (7.8 %), and 2017 (23.2 %) patients were randomly assigned to R-RR, L-RR, Ta-RR, and O-RR, respectively. The main characteristics of the included studies are presented in Table 1. The results of the network meta-analyses are reported below according to the histopathological outcome considered. The network diagrams are provided in eFig. 1.

3.3. Complete mesorectal excision

Sixteen of the 27 RCTs reported data on the completeness of mesorectal excision. Pairwise meta-analysis revealed that Ta-RR and R-RR were associated with significantly lower rates of non-complete mesorectal excision compared with L-RR, whereas no difference was observed with O-RR (Table 2, eFig. 2). The SUCRA ranking for achieving complete mesorectal excision demonstrated that Ta-RR and R-RR yielded the best efficacy (Fig. 2, Panel A). O-RR displayed moderate effectiveness, whereas L-RR ranked the lowest, indicating that it is less likely to achieve complete mesorectal excision. A sensitivity analysis was conducted with the exclusion of the RCT by Denost et al. [41] because this study applied a hybrid transabdominal–perineal approach that may be considered technically different from TaTME. This analysis confirmed that Ta-RR (OR, 0.56; 95%CI, 0.25–0.94; $P = .02$; I^2 : 47.4 %) and R-RR (OR, 0.67; 95%CI, 0.43–0.94; $P = .02$; I^2 : 41.4 %) were associated with a lower probability of non-complete mesorectal excision than L-RR and still ranked first and second in the SUCRA plot, respectively (eFig. 3 and eFig. 4).

3.4. Positive circumferential resection margin

Eighteen of the 27 RCTs reported data related to CRM. The studies by Braga et al. [39] and Somashekhar et al. [53] were not included in the quantitative analysis because of the lack of a clear definition of CRM involvement. There were significantly lower odds of positive CRMs in the Ta-RR group than in the L-RR group, whereas there was no difference in the other pairwise comparisons (Table 2, eFig. 2). Based on the SUCRA plot, Ta-RR retained the highest ranking, suggesting its effectiveness in achieving negative CRM, closely followed by R-RR (Fig. 2, Panel B). However, after the data from Denost et al. [41] were excluded, the differences between Ta-RR and L-RR were no longer significant (OR, 0.52; 95%CI, 0.15–1.59; $P = .24$; I^2 : 42.8 %), and the rankograms revealed a smaller probability difference in the best approach for Ta-RR and R-RR (eFig. 3 and eFig. 4).

3.5. Positive distal margin

Fourteen RCTs were included in this analysis. No significant effects were detected regarding the likelihood of having positive distal margins, as all the credibility intervals cross the 1 OR (Table 2, eFig. 2). Based on the SUCRA plot, O-RR was the most effective at achieving a negative distal margin, followed by R-RR and Ta-RR, with L-RR once again showing the lowest effectiveness (Fig. 2, Panel C).

3.6. Number of lymph nodes harvested

The number of lymph nodes harvested was reported in 24 of the 27 RCTs. A pairwise meta-analysis revealed that the R-RR was associated with significantly more lymph nodes harvested than the L-RR and Ta-RR (Table 2, eFig. 2). Conversely, Ta-RR was associated with significantly

fewer lymph nodes harvested than all other approaches (Table 2, eFig. 2). After the exclusion of the Denost et al. [41] publication, a loss of statistical significance was observed for the comparison between Ta-RR and L-RR (MD, -1.36 ; 95%CI, -0.34 to 0.55 ; $P = .14$) and Ta-RR and O-RR (MD, -1.46 ; 95%CI, -3.69 to 0.62 ; $P = .15$), whereas it remained statistically different when comparing Ta-RR with R-RR (MD, -2.58 ; 95%CI, -4.98 to -0.43 ; $P = .02$). The SUCRA plot revealed that R-RR had the highest probability of harvesting the most lymph nodes, whereas Ta-RR was the least effective, with O-RR and L-RR positioned between the two (Fig. 2, Panel D). A further sensitivity analysis was conducted

with the exclusion of the RCT by Pechlivanides et al. [52] because the authors considered extramural tumor deposits greater than 3 mm as involved lymph nodes. The results were confirmatory of the findings from the main analyses (eFig. 5).

3.7. Distance between the tumor and the distal resection margin

The distance between the rectal cancer and the distal resection margin was reported in 16 RCTs. Compared with L-RR, R-RR was associated with significantly longer distal margins (Table 2, eFig. 2). In

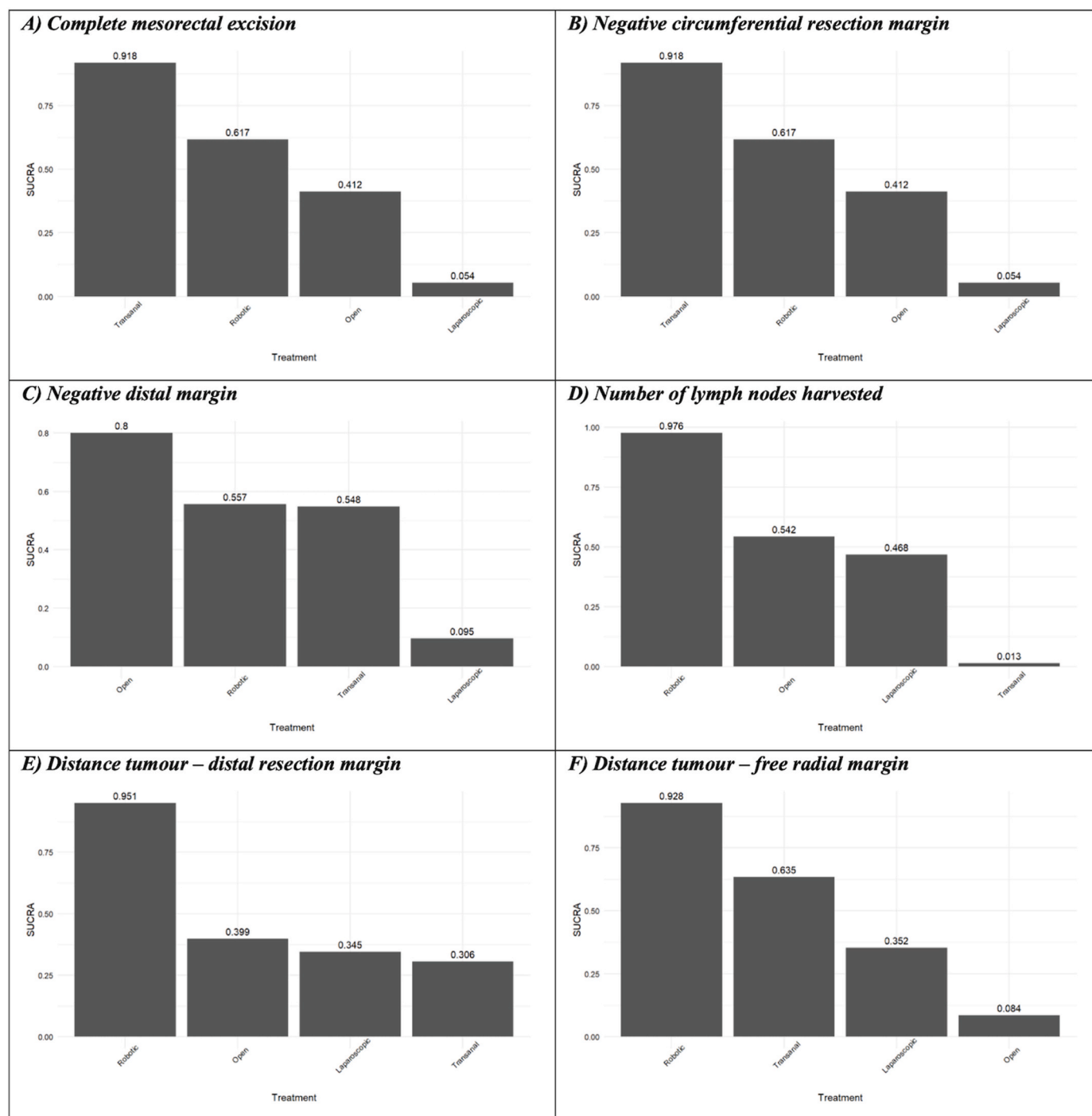


Fig. 2. SUCRA plots of outcomes of interest

SUCRA (surface under the cumulative ranking) plots, each evaluating the effectiveness of various treatments across different surgical outcome metrics in rectal cancer surgery. SUCRA values closer to 1 indicate a higher probability of a treatment being among the best options for the specified outcome.

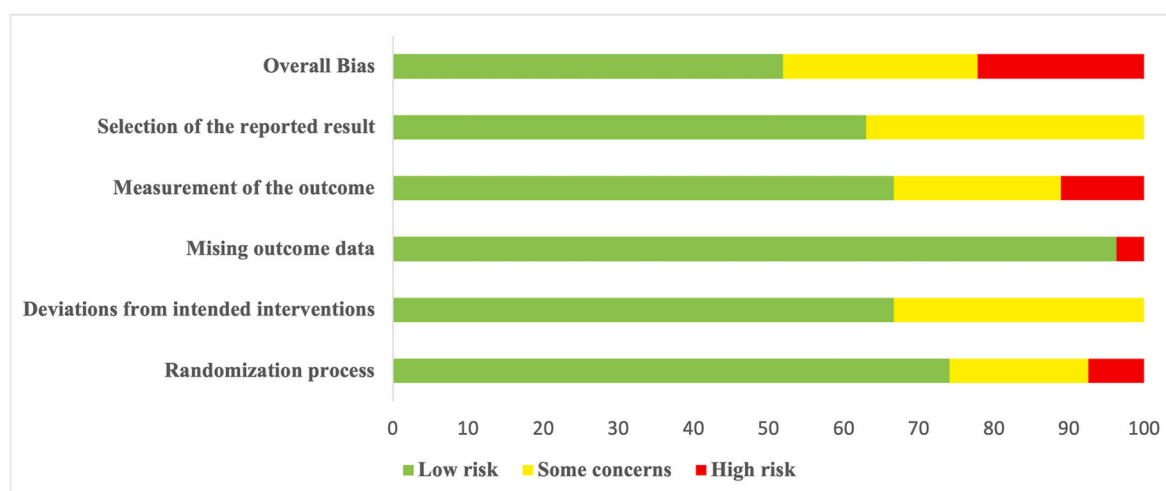


Fig. 3. Risk of bias assessment

The assessment of each risk of bias item is reported as a percentage across the included RCTs (according to the ROB-II system).

the SUCRA ranking, R-RR dominates this metric; the other treatments, including Ta-RR, O-RR, and L-RR, showed lower effectiveness in maintaining this margin (Fig. 2, Panel E).

3.8. Distance between the tumor and free radial margin

The distance to the free radial margin was reported in 7 RCTs. Pairwise meta-analysis revealed no difference in the radial margin distance between R-RR, Ta-RR, L-RR, and O-RR (Table 2, eFig. 2). Nevertheless, the SUCRA ranking revealed that R-RR was associated with the highest probability of longer distances to the radial margin. Ta-RR and L-RR offered moderate effectiveness, whereas O-RR remained the least effective treatment (Fig. 2, Panel F).

3.9. Meta-regression

The meta-regression analysis showed that both time (year of publication) and neoadjuvant therapy did not act as effect modifiers on the study outcomes (eTables 7 and 8 in the Supplement).

3.10. Risk of bias assessment

The risk-of-bias assessment is shown in Fig. 3 and eFig. 6. When addressing overall bias, 14 RCTs were classified as low risk [18–22,24, 41,43–45,49,51,54,55], 7 RCTs had some concerns [37,39,42,48,50,52, 56], and 6 RCTs were classified as having a high risk of bias [23,38,40, 46,47,53]. The funnel plot in eFig. 7 indicates a publication bias effect only for the distal resection margin together with significant Egger test asymmetry for positive distal margins and complete mesorectal excision. Trace plots revealed no discernible patterns during the iteration process, indicating suitable convergence of the model for all considered outcomes (eFig. 8). The certainty of the evidence was rated by applying the GRADE system and is reported in eTable 9 in the Supplement.

4. Discussion

The present study provides an updated systematic review of RCTs addressing the oncological safety of different surgical techniques for rectal cancer resection. Based on 27 RCTs involving 8696 patients, the present network meta-analysis shows that L-RR has the lowest effectiveness in terms of complete mesorectal excision, CRM, and distal resection margin involvement among the MIS approaches. Conversely, Ta-RR ranks the best for complete mesorectal excision, although associated with the lowest number of lymph nodes retrieved. R-RR is

associated with the highest number of lymph nodes harvested, the longest distal margins, and free-radial margin distances.

Previous network meta-analyses reported contrasting results. Simillis et al. [57] demonstrated that L-RR resulted in significantly more non-complete mesorectal excisions and more involved CRMs than O-RR and Ta-RR, respectively, whereas R-RR resulted in significantly longer distal margins than the other three techniques. Ryan et al. [58] reported similar results, whereas Seow et al. [59] did not find any difference between treatments for CRM involvement, completeness of mesorectal excision, free radial margin, or number of lymph nodes retrieved, but R-RR was superior to the open, laparoscopic, and transanal approaches in terms of distal margin length [59]. Nevertheless, these network meta-analyses were based on literature searches up to September 2018 [57], January 2020 [58], and September 2020 [59]; thus, they did not include the seven new RCTs that have been published since 2021. These significantly increased the body of evidence on rectal cancer surgery (+248 % for R-RR, +88 % for L-RR, +1262 % for Ta-RR, and +21 % for O-RR) [18–24] and allowed for new direct and indirect comparisons, justifying a new network meta-analysis.

In the last decades, the use of MIS approaches outpaced open surgery for the treatment of rectal cancer [17], with laparoscopy being progressively considered the gold standard [55]. Initially, the ACOSOG Z6051 [60] and AlaCaRT [54] trials, and the meta-analysis by Martínez-Pérez et al. [61] raised concerns about the quality of oncological resection of laparoscopy over open surgery, whereas the subsequent meta-analysis by Acuna et al. [62] demonstrated the non-inferiority of L-RR and supported its widespread use. In real-world practice, robotic mesorectal excision has drastically expanded [15,63,64], and transanal mesorectal excision has been progressively implemented, particularly for mid-low rectal cancer resection [65,66]. Thus, investigating the comparative oncological effectiveness of R-RR, Ta-RR, L-RR, and O-RR remains pertinent and clinically relevant.

Concerning the completeness of mesorectal excision, the present results revealed significantly higher rates with the Ta-RR and R-RR approaches than with laparoscopy, with the transanal approach ranking the best for achieving complete mesorectal excision. A sensitivity analysis was performed by excluding the RCT by Denost et al. [41] to assess the robustness of the aforementioned results. Indeed, Denost et al. [41] performed hybrid transabdominal–perineal procedures between 2008 and 2012, which may be considered technically different from the Ta-TME technique described by Lacy et al., in 2015 [67]. The authors performed the perineal dissection with traditional instruments under direct vision and without a transanal surgical platform, only dissecting the distal rectum up to 10 cm from the anal verge. Then, proximal

mesorectal dissection was performed via laparoscopy and extended posteriorly up to the levator ani muscles [41]. Still, in this sensitivity analysis, Ta-RR remained the most effective treatment for achieving a complete mesorectal excision. This is considered a marker of the oncological resection quality, being highly correlated with locoregional recurrence rates and 3-year disease-free survival [7–9,68]. However, a phase 2 multicenter prospective trial by Silla et al. [69], which evaluated the efficacy of Ta-TME, revealed 32 % minor and 14 % major discordances in TME grading between site and central pathologist reviewers, suggesting a potential overestimation bias of TME completeness and raising the attention about the need for rigorous quality control measures in clinical trials. For this reason, the grading of the mesorectum may not represent the best and only surrogate for surgical quality in rectal cancer patients.

CRM involvement is another benchmark in rectal resection quality assessment related to locoregional recurrence, distant metastases, and overall and disease-free survival [9–12]. The present pooled data revealed lower odds of positive CRM after Ta-RR than after L-RR. This result is in accordance with those reported by two previous network meta-analyses [57,58], but, after excluding the study of Denost et al. [41], the difference in positive CRM rate was no longer significant between Ta-RR and L-RR.

In contrast with the previous network meta-analyses [57–59], the present results show that Ta-RR yielded the smallest number of lymph nodes harvested compared with R-RR, L-RR, and O-RR, whereas R-RR ranked the best for this outcome. This finding aligns with those of a recent European multicenter propensity score-matched study analyzing 468 mid- and low-rectal cancers, which showed comparable CRM involvement and a significantly lower number of retrieved lymph nodes for transanal TME than robotic and laparoscopic TMEs [64]. Nevertheless, the included RCTs did not report sufficient data to analyze the proportion of patients with 12 or more lymph nodes retrieved across the four surgical approaches. Several studies demonstrated a decrease in the number of lymph nodes harvested in the surgical specimen after neoadjuvant chemoradiotherapy or radiotherapy alone [70–72]. A meta-analysis by Mechera et al. [70] published in 2017 reported a mean reduction of 3.9 and 2.1 lymph nodes after neoadjuvant chemoradiotherapy and radiotherapy, respectively. Nevertheless, the random-effects meta-regression analysis found no modifier effect of neoadjuvant therapy on histopathological outcomes across the four surgical approaches (eTable 7 in the Supplement).

4.1. Limitations

This network meta-analysis has several limitations. First, the literature search was limited to RCTs published in English. Sensitivity analyses based on different tumor locations, stages, and neoadjuvant chemoradiotherapy regimens were not possible because data were not available in all the included RCTs. The overall period of patient inclusion in the selected studies exceeded 25 years, leading to potential differences related to treatment protocols or available surgical technologies over time. While the inclusion of diverse populations strengthens the generalizability of the findings, it also introduces greater heterogeneity. However, the meta-regression analysis did not reveal a significant impact of the time frame on the study outcomes (eTable 8 in the Supplement). Moreover, several RCTs were based on primary endpoints different from histopathological outcomes [18–21,23,24,37–40,43,44,46,47,49–51,55,56], whereas others were interrupted before reaching the targeted sample size [22,42]. Consequently, some studies may lack sufficient power to detect variations in histopathological outcomes between treatments. This may result in an underestimation of pooled data analyses. Moreover, the absence of closed loops in the network precludes a formal consistency assessment. While this limitation does not invalidate the consistency of the present findings, as the direct comparisons remain robust, it suggests that future studies should better investigate the indirect estimates reported in this network.

5. Conclusion

The present network meta-analysis sheds light on the effectiveness of MIS for rectal cancer histopathological outcomes. Based on direct and indirect evidence from 27 RCTs, Ta-RR and R-RR have the highest probability of achieving optimal histopathological outcomes, whereas L-RR has the lowest. Thus, while MIS represents the gold standard for rectal cancer surgery, L-RR may not consistently achieve the same level of histopathological outcomes as R-RR and Ta-RR. Further research is needed to optimize a comprehensive treatment strategy and fully identify the optimal surgical approach for TME, considering patient's factors, tumor characteristics, available resources, surgeon's expertise, and institutional experience.

CRedit authorship contribution statement

Nicola de'Angelis: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Carlo Alberto Schena:** Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Danila Azzolina:** Conceptualization, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. **Maria Clotilde Carra:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. **Jim Khan:** Validation, Visualization, Writing – review & editing. **Caroline Gronnier:** Validation, Visualization, Writing – review & editing. **Sébastien Gaujoux:** Validation, Visualization, Writing – review & editing. **Paolo Pietro Bianchi:** Validation, Visualization, Writing – review & editing. **Antonino Spinelli:** Validation, Visualization, Writing – review & editing. **Philippe Rouanet:** Validation, Visualization, Writing – review & editing. **Aleix Martínez-Pérez:** Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – review & editing. **Patrick Pessaux:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

Data availability statement

Datasets analyzed during the current study are available upon reasonable request to the authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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