

SURGICAL ASPECTS OF COLORECTAL CANCER TREATMENT

Ph.D. Thesis

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“It is not the strongest of the species that survives, nor the most intelligent, but the one most adaptable to change.”

Leon Megginson

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2. LIST OF ABBREVIATIONS

TME	Total Mesorectal Excision
EEA	End-to-end anastomosis
CJP	Colonic J-Pouch
SEA	Side-to-end anastomosis
QoL	Quality of Life
ELAPE	Extralevator Abdominoperineal Excision
APE	Standard Abdominoperineal Excision
OS	Overall Survival
DFS	Disease-free survival
LRFS	Local Recurrence-free survival
IOP	Intraoperative perforation
CRM	Circumferential resection margin positivity
TCP	Transverse coloplasty
RCT	Randomized Controlled Trials
AL	Anastomotic Leakage

3. STUDENT PROFILE

3.1. Vision and mission statement, specific goals

As a specialist in General Surgery, my vision is to facilitate the translation of high-quality scientific evidence into everyday surgical practice, thereby contributing to evidence-based patient care and improved clinical outcomes. My mission is to optimize both the short-term postoperative results and the long-term quality of life of patients undergoing surgery for rectal cancer.

This PhD project is comprised of two complementary studies. The first aimed to evaluate the surgical, functional, and quality-of-life outcomes of different reconstructive techniques following total mesorectal excision. The second aimed to investigate the oncological outcomes of different abdominoperineal excision techniques in patients for whom sphincter-preserving surgery was not feasible.



Scientometrics

Number of all publications:	4
Cumulative IF:	14,9
Av IF/publication:	3,725
Ranking (SCImago):	D1:3, Q1:1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	6,2
Av IF/publication:	3,1
Ranking (Sci Mago):	D1:2
Number of citations on Google Scholar:	12
Number of citations on MTMT (independent):	7
H-index:	2

The detailed bibliography of the student can be found on pages 63-64.

3.2. Future plans

My future professional goal is to further specialize in colorectal surgery, with a particular focus on minimally invasive techniques, including laparoscopic and robotic surgery. In parallel, I intend to obtain a second specialization in Gastroenterology,

enabling me to provide comprehensive care for patients with colorectal diseases from diagnosis through surgical treatment and long-term follow-up.

From an academic perspective, I aim to remain actively involved in clinical research and international scientific collaborations. I aspire to contribute to the development of evidence-based guidelines and recommendations that improve patient outcomes and quality of life. Furthermore, I seek to work within multidisciplinary teams committed to advancing surgical knowledge through high-quality research and innovation.

4. SUMMARY OF THE THESIS

Rectal cancer surgery presents a unique challenge in balancing oncological radicality with the preservation of postoperative function and quality of life. The scientific work included in this PhD thesis focused on these two major aspects of rectal cancer treatment through two systematic reviews and meta-analyses addressing restorative and radical surgical strategies.

The first study evaluated different reconstructive techniques following total mesorectal excision (TME), with particular focus on end-to-end anastomosis (EEA), colonic J-pouch (CJP), and side-to-end anastomosis (SEA). The study investigated surgical outcomes, bowel function, and quality of life (QoL) following rectal cancer surgery. A total of 29 studies were included. The analysis demonstrated that EEA achieved comparable rates of anastomotic leakage and postoperative mortality to both CJP and SEA. Furthermore, despite differences in bowel function parameters, QoL outcomes at six and twelve months were similar between the reconstructive techniques. These findings suggest that EEA provides surgical and functional outcomes comparable to more complex reconstructive procedures and may represent a valid alternative following TME.

The second study focused on patients with advanced low rectal cancer in whom sphincter-preserving surgery was not feasible. It compared extralevator abdominoperineal excision (ELAPE) with standard abdominoperineal excision (APE), with particular emphasis on long-term oncological outcomes. Thirty-eight studies involving more than 5000 patients were included. Individual patient data reconstructed from Kaplan–Meier curves were used to evaluate overall survival (OS), disease-free survival (DFS), and local recurrence-free survival (LRFS). The results demonstrated a significant survival advantage for ELAPE, with improved OS and DFS, alongside reduced rates of intraoperative perforation (IOP) and circumferential resection margin (CRM) positivity. These findings support the oncological benefits of ELAPE in appropriately selected patients with advanced low rectal cancer.

Together, these studies address both ends of the surgical spectrum in rectal cancer treatment: optimization of reconstruction when bowel continuity can be restored and improvement of oncological outcomes when radical extirpative surgery is required.

5. GRAPHICAL ABSTRACT

5.1. Study I



End-to-end Anastomosis Provides Similar Quality-of-life, Compared with Other Reconstructive Techniques Six Months Following Total Mesorectal Excision: Systematic Review and Meta-analysis



- Colorectal malignancy ranks third in global cancer incidence
- Total mesorectal excision is the gold-standard treatment for rectal cancer
- We compared end-to-end anastomosis (EEA) to side-to-side anastomosis (SEA) and colonic J pouch (CJP)



We hypothesized that EEA is as good as SEA or CJP

RESULTS:

Outcomes	EEA vs SEA	EEA vs CJP
Surgical	No difference in anastomotic leakage and mortality	No difference in anastomotic leakage
Functional	At 12 months no statistical difference	NA
Quality of life	Similar at 6 and 12 months	Similar at 6 months

CONCLUSION:

EEA is equally effective as other reconstructive techniques. At six months postoperatively, QoL following EEA seems unaffected by the number of stools per day, since it resulted in similar well-being compared with CJP or SEA.

@EJSOtweets @OncologyAdvance

Kávási et al, @drkavasi

5.2. Study II

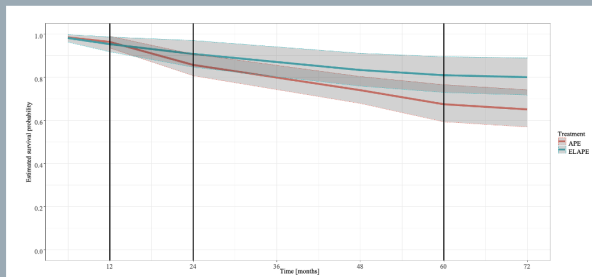
Extralevator Abdominoperineal Excision Improves Overall Survival Compared to Standard Abdominoperineal Excision: A Systematic Review and Meta-Analysis

Background:

- Low rectal cancer → APE has high CRM positivity & IOP
- ELAPE designed for better oncological radicality
- Survival benefit uncertain

Study population:

- 38 studies | >5,000 patients
- Meta-analysis with IPD-based survival analysis
- Follow-up up to 5 years



Results:

Overall survival: ↑ HR 0.54, 5-year OS: 83% vs 69%
 Disease-free survival ↑ HR 0.74, 5-year DFS 87% vs 65%
 Perineal wound complications: no difference
 IOP ↓ (OR 0.49), CRM positivity ↓ (OR 0.60)
 Perineal wound complications: no difference

Conclusion: ELAPE improves long-term survival without increasing wound morbidity. Consider broader use in low rectal cancer



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6. INTRODUCTION

6.1. Overview of the topic

6.1.1. *What is the topic?*

Rectal cancer is a major global health challenge, accounting for more than 700,000 new cases annually worldwide (1), with its incidence expected to increase to 3.2 million cases by 2040 (2). Surgical treatment remains the cornerstone of curative therapy for rectal cancer. TME is considered the gold standard for resectable disease (3), while APE remains the primary surgical option for distal rectal cancers where sphincter preservation is not feasible (4).

6.1.2. *What is the problem to solve?*

A major challenge in rectal cancer surgery is selecting the optimal surgical approach that maximizes oncological outcomes while minimizing functional impairment.

Following TME, several reconstructive options are available. Although EEA is technically straightforward, it has been associated with impaired bowel function in the early postoperative period (5,6). Alternative techniques, such as CJP and SEA, were developed to improve postoperative function; however, their advantages regarding long-term QoL remain uncertain (7,8), and evacuation difficulties have been reported (9,10). Consequently, the optimal method of reconstruction remains a subject of ongoing debate.

In patients requiring non-sphincter-preserving surgery, uncertainty exists regarding the extent of resection required to achieve the best oncological outcomes. Although ELAPE has been shown to reduce IOP and CRM positivity compared with conventional APE (11–13), it remains unclear whether these improvements translate into superior long-term oncological outcomes. Furthermore, concerns have been raised regarding the increased extent of perineal dissection, which may result in longer operative times and greater perineal wound morbidity (14). As a result, uncertainty persists regarding whether the improved specimen quality achieved by ELAPE translates into meaningful patient benefit.

6.1.3. What is the importance of the topic?

The importance of this topic stems from the growing number of rectal cancer patients and the increasing emphasis on survivorship and QoL following cancer treatment (2,15). Improvements in oncological therapies have resulted in a larger population of long-term survivors, making postoperative function, independence, and QoL increasingly relevant endpoints of treatment success (16). Furthermore, impaired postoperative function and reduced QoL may persist long after treatment, contributing to increased healthcare utilization, productivity loss, and ongoing societal burden among colorectal cancer survivors (17–19). Optimizing surgical techniques, therefore, has the potential to improve both clinical outcomes and healthcare resource utilization.

6.1.4. What would be the impact of our research results?

The results of this research provide clinically relevant evidence regarding two important decision points in rectal cancer surgery. First, by comparing different reconstructive techniques following TME, the findings help clarify whether more complex anastomotic configurations provide meaningful functional or QoL advantages over conventional EEA anastomosis (5–8). Second, by evaluating both long-term oncological outcomes and treatment-related morbidity following ELAPE and APE, this work helps determine whether improved specimen quality translates into measurable patient benefit (12,13). These findings may facilitate evidence-based selection of surgical techniques, enabling surgeons to optimize the balance between oncological outcomes, functional recovery, surgical morbidity, and QoL in patients with rectal cancer

7. OBJECTIVES

7.1. Study I

The objective of the first study was to compare the surgical, functional, and QoL outcomes associated with different reconstructive techniques following TME for rectal cancer. Specifically, the study aimed to evaluate whether EEA provides comparable outcomes to CJP, SEA, and transverse coloplasty (TCP), thereby identifying the most appropriate reconstructive strategy for patients undergoing sphincter-preserving surgery.

7.2. Study II

The objective of the second study was to compare ELAPE and APE in patients with distal rectal cancer for whom sphincter preservation was not feasible. The study aimed to determine whether the extended resection associated with ELAPE translates into superior long-term oncological outcomes, while assessing whether these advantages can be achieved without compromising postoperative recovery and wound healing.

8. METHODS

The protocols of both studies were prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022368907 for Study I and CRD42023412308 for Study II). Both systematic reviews and meta-analyses were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the PRISMA 2020 Statement.

8.1. Study I

1.1.1. Eligibility Criteria

Inclusion criteria were established using the PICO framework. Randomized controlled trials (RCT) involving adult patients undergoing TME for rectal cancer were eligible for inclusion. EEA served as the intervention, while CJP, SEA, and TCP were evaluated as comparator techniques. The primary outcomes of interest were anastomotic leakage (AL), postoperative bowel function, and QoL. Secondary outcomes included mortality, postoperative ileus, overall complication rates, and reintervention requirements.

1.1.2. Information Sources

Relevant studies were identified through a systematic search of MEDLINE (via PubMed), Embase, and CENTRAL on November 8, 2022. The search strategy was applied to all searchable database fields, and no language or additional filtering criteria were imposed

1.1.3. Search Strategy

The search key comprised three main domains: 1. TME, 2. types of anastomoses, and 3. the concept of randomization.

In full detail: procto* OR rect* OR TME OR "total mesorectal excision" OR "low anterior resection") AND (anastomosis, surgical OR anastomo* OR "end to end" OR "end-to-end" OR "side to end" OR "side-to-end" OR "end to side" OR "end-to-side" OR "J pouch" OR "J-pouch" OR "straight colorectal reconstruction" OR "straight anastomosis" OR "transverse coloplasty") AND (random* OR RCT).

1.1.4. Study Selection and Data Extraction

Study screening and selection were performed independently by two reviewers. After removing duplicate records using EndNote (20), titles and abstracts were screened, followed by full-text assessment of potentially eligible studies. The selection process was facilitated using the Rayyan platform (21). Agreement between reviewers was evaluated using Cohen's kappa coefficient (22), and any disagreements were resolved through discussion with a third reviewer. To identify additional relevant studies, forward and backward citation searches were also conducted using the Citationchaser tool (23). Data extraction was carried out independently by two reviewers using standardized Microsoft Excel spreadsheets. Discrepancies were resolved by consensus with the involvement of a third reviewer when necessary. In cases where multiple publications reported outcomes from the same study population, data were extracted from the most recent and comprehensive publication. Corresponding authors were contacted when essential data were missing.

The extracted variables included publication characteristics (first author, year of publication, country of origin, and DOI), study characteristics (study design, number of participating centers, follow-up duration, and sample size), patient demographics, and details of the investigated reconstructive techniques. Outcome data included AL, mortality, postoperative ileus, bowel function, and QoL measures reported at different follow-up intervals. Additional variables potentially influencing outcomes, such as the use of defunctioning stoma, neoadjuvant treatment, surgical approach, and anastomotic technique (hand-sewn or stapled), were also collected. When fistula or pelvic sepsis were reported separately, these events were incorporated into the analysis of AL.

1.1.5. Risk of Bias and Quality of Evidence Assessment

The methodological quality of the included RCT's was assessed using the revised Cochrane Risk of Bias tool (RoB 2) (24). Risk of bias was evaluated across five domains: the randomization process, deviations from intended interventions, completeness of outcome data, outcome measurement, and selective reporting of results. Potential publication bias was assessed using visual inspection of funnel plots and the modified Egger's test. The certainty of the evidence for each outcome was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework using the GRADEpro software. Risk-of-bias

assessment and evidence grading were performed independently by two reviewers. Any discrepancies were resolved through discussion, with the involvement of a third reviewer when consensus could not be reached.

1.1.6. Data Synthesis and Analysis

Despite adherence to RCT's, assuming considerable heterogeneity - e.g., differences in the “true” effect sizes among studies representing different populations – in medical meta-analyses due to the different settings of the included studies, employing a random-effects model was essential to account for diversity and derive meaningful pooled effect sizes.

Risk ratios (RR) with a 95% confidence interval (CI) were used as the effect size measure for dichotomous outcomes. For continuous variables, the mean difference (MD) was calculated with a 95% CI. As the QoL was assessed using different questionnaires, Hedges' g standardized mean difference (SMD) (25) with its 95% CI was used as the effect size measure. As QoL results were presented at various time points in the articles, a multivariate model was employed.

The meta-analysis findings were summarized on forest plots. Where applicable (the number of studies was large enough and not too heterogeneous), the prediction intervals of the results were also reported. Additionally, between-study heterogeneity was assessed using both Higgins&Thompson's I² statistics (26) and tau (T²), if applicable (eg. if more than 5 studies were included). The effect of potential outlier publications was explored using different influence measures and plots following the recommendation of Harrer et al (27). Results were considered statistically significant, if the pooled CI did not contain the null value.

All statistical analyses were made by R (28) using the meta (27) package for basic meta-analysis calculations and plots, and dmetar (29) package for additional influential analysis calculations and plots. For multivariate models, the package metafor (30) was also used.

1.2. Study II

1.2.1. Eligibility Criteria

Eligibility criteria were defined according to the PICO framework. The study population comprised adult patients with advanced low rectal cancer undergoing

curative-intent surgery. ELAPE was considered the intervention of interest, while APE served as the comparator. The primary endpoints were long-term oncological outcomes, including OS, DFS, and LRFS. Secondary outcomes encompassed intraoperative parameters, such as IOP, CRM involvement, circumferential resection margin length, blood loss, and operative time; postoperative outcomes, including 30-day mortality, overall morbidity, reoperation rate, and length of hospital stay; as well as perineal wound-related outcomes, including overall wound complications, wound infection, wound dehiscence, perineal hernia formation, and perineal pain.

1.2.2. Information Sources

A comprehensive literature search was performed on April 14, 2023, in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was applied across all searchable database fields without restrictions regarding language or other study characteristics.

1.2.3. Search Strategy

The search key comprised two main domains: population and the two types of surgeries: (Rectal neoplasms OR "rectal tumour") AND (ELAPE OR extralevator OR extra-levator OR levator OR abdominoperineal OR abdomino-perineal OR abdomino).

1.2.4. Study Selection and Data Extraction

The screening and study selection process was conducted independently by two reviewers. Duplicate records were identified and removed using EndNote (20) through a combination of automated and manual procedures. Following title and abstract screening in the Rayyan platform (21), potentially eligible articles underwent full-text assessment. Inter-reviewer agreement was evaluated using Cohen's kappa coefficient (22), and any discrepancies were resolved through discussion with a third reviewer. To maximize study identification, forward and backward citation searches were additionally performed using the Citationchaser tool (23).

Data extraction was carried out independently by two reviewers using standardized Microsoft Excel spreadsheets. Any disagreements were resolved by consensus with the involvement of a third reviewer when necessary. In cases where multiple publications reported data from overlapping patient populations, information was extracted from either the original publication or the study containing the most comprehensive dataset.

The extracted information included publication and study characteristics, patient demographics, duration of follow-up, and all outcomes specified in the eligibility criteria. Data regarding the number of patients and events in each treatment group were collected for all analyzed endpoints. Additional variables included preoperative and pathological TNM stage, neoadjuvant and adjuvant oncological treatments, surgical approach (open, laparoscopic, or robotic), methods of perineal reconstruction, and tumor height.

1.2.5. Risk of Bias and Quality of Evidence Assessment

The methodological quality of the included studies was evaluated using tools recommended by the Cochrane Collaboration. RCT's were assessed with the revised Cochrane Risk of Bias tool (RoB 2) (24), whereas non-randomized interventional studies were evaluated using the ROBINS-I instrument (31). Potential publication bias was explored through visual examination of funnel plots and by applying the modified Egger's test. The overall certainty of the evidence was determined according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (32) framework using the GRADEpro software. All assessments were performed independently by two reviewers, and any discrepancies were resolved through discussion with the involvement of a third reviewer when required.

1.2.6. Data Synthesis and Analysis

Considerable heterogeneity among the study populations was assumed, and random effects models were used within a frequentist framework. For dichotomous outcomes, the odds ratio (OR) was calculated from the total number of patients and events in each group. For continuous outcomes, the mean difference (MD) was derived from the sample size, mean, and standard deviation (SD). For time-to-event data, an HR with a 95% confidence interval (CI) was used, comparing ELAPE and APE groups. Two methods were applied: a classical random-effects meta-analysis for study HRs and an IPD-based random-effects Cox hazard model with Gaussian random effects. Survival probabilities were estimated at specific time points and pooled using a 3-level model. Additionally, pooled survival curves were estimated with Pandey's method (33). Results were summarized in tables, forest plots, and Kaplan-Meier survival curves. Heterogeneity was assessed by between-study variance (τ^2) and Higgins' I^2 (26). For

IPD-based outcomes, the standard error of the random effects distribution was reported. Small-study bias was evaluated using funnel plots and tests like Egger and Harbord (34). Outlier studies were checked using leave-one-out influence measures as suggested by Harrer et al. (27) R software (28) was used for all statistical analyses: meta (33), dmetar (29), and metafor (30) packages for meta-analysis; survival (33), survminer (35) and coxme (36) for IPD-based calculations; and MetaSurvival (33) for pooled curve estimates.

2. RESULTS

2.1. Study I

2.1.1. Study Search and Selection

29 studies out of 4459 were included in the analysis. The flowchart of selection is presented in Figure 1.

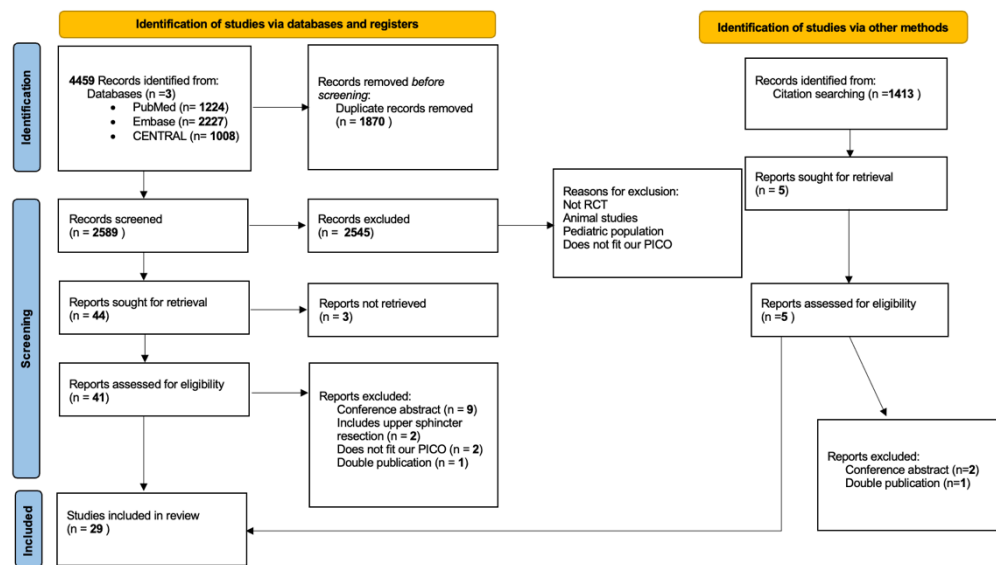


Figure 1. PRISMA 2020 flow chart detailing the search and selection process. (37)

2.1.2. Basic characteristics of included studies

All included studies were RCTs. Detailed baseline characteristics are presented in Table 1.

Regarding defunctioning stoma formation, 12 studies (7,38–48) reported stoma creation in all patients, while five studies (49–53) demonstrated a balanced distribution of stoma use between the study arms. In the study by Oya et al. (54), ileostomy was performed more frequently in the CJP group. Information on stoma formation was not reported in eight studies (8,55–61).

Regarding the surgical approach, four studies (41,43,48,58) employed only open surgery, whereas Liang et al. (49) used a purely laparoscopic technique. In five additional studies (7,42,47,50,52), the distribution of surgical approaches was balanced

between the intervention groups. Sixteen studies (8,38–40,44–46,51,53–57,59–61) did not provide details regarding the operative approach.

In most cases (7,38,42–44,46,47,49,50,53–58,60), only stapled anastomosis was performed. In studies employing hand-sewn anastomoses (39,40,45,48,52), their use was similarly distributed between the groups. Choen et al. (41) performed stapled anastomoses in the EEA group, while a mixed method was used in the CJP group. Four RCTs (8,45,59,61) did not specify the anastomotic technique employed.

Only two studies (49,54) excluded all patients who had received neoadjuvant therapy. In six studies (7,8,43,47,50,52), the use and type of neoadjuvant treatment were balanced between the study arms. In contrast, most RCTs (38,40–42,46,48,51,56) reported unequal distributions of neoadjuvant therapy between the intervention groups.

Table 1: Baseline characteristics of the studies included (a shortened version)

Nr.	First author	Year	Country	Intervention (I)			Comparison (C)			Presence of stoma		Neoadjuvant therapy (Ch=chemotherapy R=radiotherapy,C=combined)	
				Type	Nr. of patients (Females %)	Age	Type	Nr. of patients (%F)	Age	I	C	I	C
1	Ahmed et al.	2021	Pakistan	EEA	30 (23.3)	27.1 (5.5)*	SEA	30 (30)	28.6 (5.3)*	NA		NA	
2	Alvadipour et al.	2021	Iran	EEA	19 (57.9)	61 (21)*	CJP	20 (35)	52 (24.7)*	NA		Ch 15.7%	Ch 65%
							SEA	21 (52.3)	61 (24)*	NA		Ch 15.7%	Ch 4.7%
3	Brisinda et al.	2009	Italy	EEA	37 (45.9)	63.7 (9.2)*	SEA	40 (52.2)	67 (5.9)*	NA		NA	
4	Choen et al.	1995	Singapore	EEA	20 (25)	62.5(44-86)†	CJP	20 (35)	64.5 (38-83)†	100%		C 10%	C 5%
5	Choi et al.	2003	Korea	EEA	23 (56.5)	58 (41-80)†	CJP	24 (58.3)	61 (36-75)†	100%		NA	
6	Fazio et al.	2007	International	EEA	49 (5.3)	60.2 (12)*	TCP	47 (17.1)	59.6 (9.1)*	NA		NA	
7	Gavaruzzi et al.	2020	Italy	EEA	158 (39.8)	63 (55-72)¶	CJP	161 (44.7)	66 (58-72)¶	100%		Ch 0.6% R 11.4% C 57.6%	Ch 0.6% R 13% C 55.2%
8	Habeeb et al.	2022	Egypt	EEA	37 (54.1)	61.03 (13.9)*	SEA	37 (43.2)	62.58 (12.3)*	NA		C 100%	
9	Hallböök et al.	1996	Sweden	EEA	52 (48)	69 (29-82)†	CJP	45 (44.4)	67 (40-86)†	59%	71%	Ch 5.7% R 28.8%	Ch 8.8% R 15.5%
10	Hallböök et al.	1997	Sweden	EEA	23 (47.8)	70 (37-82)†	CJP	22 (54.5)	67 (40-84)†	100%		NA	
11	Hallböök et al.	1997	Sweden	EEA	23 (43.4)	70 (37-82)†	CJP	23 (47.8)	67 (40-84)†				
12	Ho et al.	1996	Singapore	EEA	16 (37.5)	61.2 (3.2)‡	CJP	17 (64.7)	61.2 (3.8)‡	100%		C 43.7%	C 52.8%
13	Ho et al.	2000	Singapore	EEA	17 (23.5)	61.1 (2)*	CJP	20 (40)	62.1 (2.7)*	100%		C 19.2%	C 38.1%
14	Ho et al.	2001	Singapore	EEA	19(10.5)	62.1 (2.3)‡	CJP	16 (31.2)	61.3 (3.2)‡				
15	Ho et al.	2002	Singapore	EEA	6 (16.6)	51.5 (1.9)‡	CJP	6 (16.6)	63.2 (4.5)‡				
16	Hida et al.	2004	Japan	EEA	18 (33)	NA	CJP	16 (35.7)	NA	NA		NA	
17	Lazorthes et al.	1997	France	EEA	19 (26.3)	59 (40-82)§	CJP	18 (33.3)	56 (42-75)§	100%		R 47.3%	R 55.5%
18	Liang et al.	2007	Taiwan	EEA	24 (41.6)	62.4 (9.8)*	CJP	24(45.8)	64.4 (10.4)*	12.5 %	16.7 %	0%	
19	Marti et al.	2018	Switzerland	EEA	112 (NA)	66.3 (32.3-90.9)†	CJP	112 (NA)	68.6 (30.9-85.5) †	90.3 %	90.7 %	Ch 70.7% R 6.06% C 4.04%	Ch 71.4% R 6.15% C 0%
							SEA	112 (NA)	67.2(32.3-88.9)†		95.12 %	Ch 69.4% R 3.1% C 3.1%	
20	Ortiz et al.	1995	Spain	EEA	19 (47.3)	67.3 (9.2)*	CJP	19 (31.5)	59.5 (14.2)*	100%		NA	
21	Oya et al.	2002	Japan	EEA	21 (61.9)	59 (42-80)†	CJP	21 (57.1)	61 (47-79)†	9.5%	57.1 %	0%	

22	Parray et al.	2014	India	EEA	20 (50)	47.8 (16.9)*	CJP	22 (50)	50.7 (8.8)*	NA		NA	
23	Parray et al.	2014	India	EEA	20 (45)	49.59 (19-75)§	TCP	22 (40)	53.6 (22-80) §	15%	18%	NA	
24	Planellas et al.	2020	Spain	EEA	35 (34.3)	68 (46-94)†	SEA	30 (43.3)	64 (27-81)†	28.6 %	30%	C 60%	C 56.6%
25	Pucciarelli et al.	2019	Italy	EEA	189 (39.6)	63 (54-72)#	CJP	190 (43.1)	66 (58-72)#	100%		Ch 0.5% R 10% C 60.8%	Ch 0.5% R 14.2% C 56.8%
26	Rasulov et al.	2020	Russia	EEA	38 (47.3)	58	SEA	30 (40)	60	100%		Ch 34.2% C 47.3%	Ch 43.3% C 46.6%
							CJP	22 (72.7)	57	100%		Ch 27.2% C 50%	Ch 27.2% C 50%
27	Ribi et al.	2019	International	EEA	99 (32.3)	66.3 (32.3-90.9) †	CJP	63 (39.7)	68.6 (30.9-85.5) †	NA		Ch 4% R 6.1% C 70.7%	Ch 0% R 6.3% C 71.4%
							SEA	95 (34.7)	67.2 (32.3-88.9) †	NA		Ch 3.2% R 3.2% C 69.5%	Ch 3.2% R 3.2% C 69.5%
28	Rybakov et al.	2016	Russia	EEA	40 (50)	63 (58-69)¶	SEA	41 (68)	61 (55-65)¶	100%		C 37.5%	C 36.5%
29	Sailer et al.	2002	Germany	EEA	32 (40.6)	67 (9)*	CJP	32(34.3)	64(11)*	100%		C 10%	C 5%

2.1.3. End-to-end anastomosis versus Colonic J Pouch

2.1.3.1. Surgical outcomes

No statistically significant differences were observed between the groups for any postoperative morbidity outcome. AL was reported in a total of 15 articles (38–40,42,44,46–49,51,52,54,56,60,61), with a RR of 1.03; CI: [0.84–1.26], see Figure 2. Concerning mortality, seven studies (39,40,44,48,51,52,61) were analyzed, and an RR of 0.77; CI: [0.30–1.98] was obtained. A total of six RCTs (41,47,48,51,52,54) reported instances of ileus, with a RR of 0.64; CI: [0.40–1.01]. For overall postoperative complications, the RR was 1.03; CI: [0.23–4.63], and for surgical reintervention, the RR was 1.18; CI: [0.67–2.07].

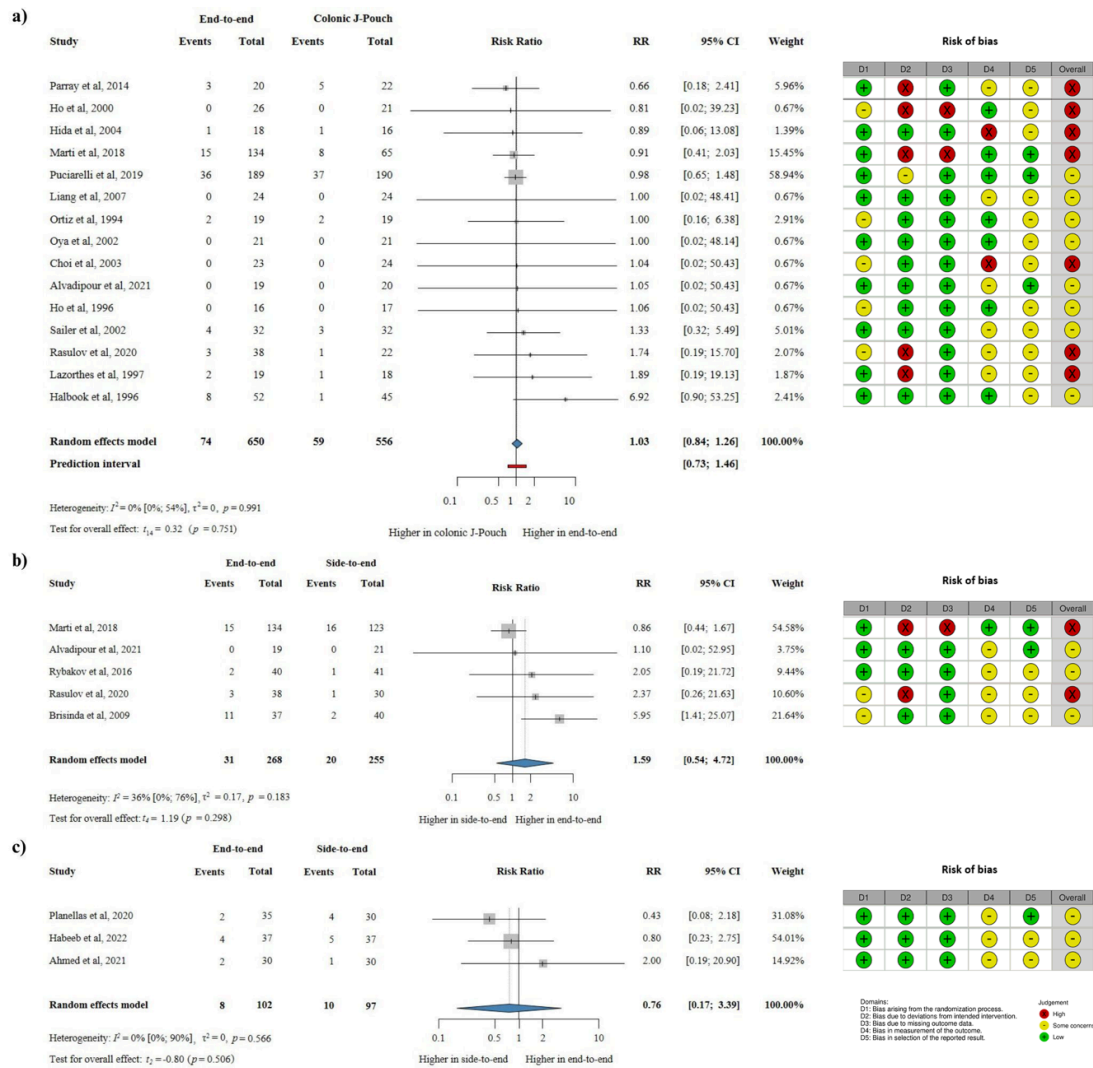
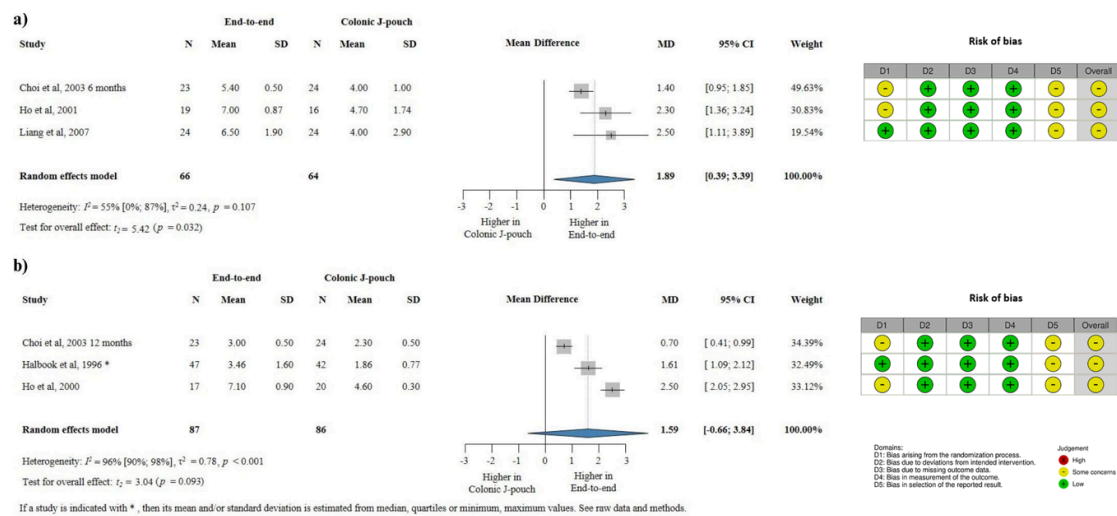


Figure 2: Forest plot and Risk of Bias assessment for the anastomotic leakage outcome in patients receiving end-to-end anastomosis, compared to a) colonic J-pouch; b)

side-to-end anastomosis; c) side-to-end anastomosis (subgroup for sigmoidectomy cases included).

2.1.3.2. Functional outcomes

Functional outcome was evaluated by the number of daily bowel movements and assessed at two time points (see Figure 3). At six months postoperatively, the EEA group had a slightly higher number of stools per day, with a MD of 1.89; CI: [0.39–3.39]. However, at one year, the MD was 1.59; CI: [(-)0.66–3.84].



(MD – mean difference; CI – confidence interval)

Figure 3: Forest plot and Risk of Bias assessment for the bowel movement outcome in patients receiving end-to-end anastomosis, compared to colonic J-pouch at a) six and b) 12 months postoperatively.

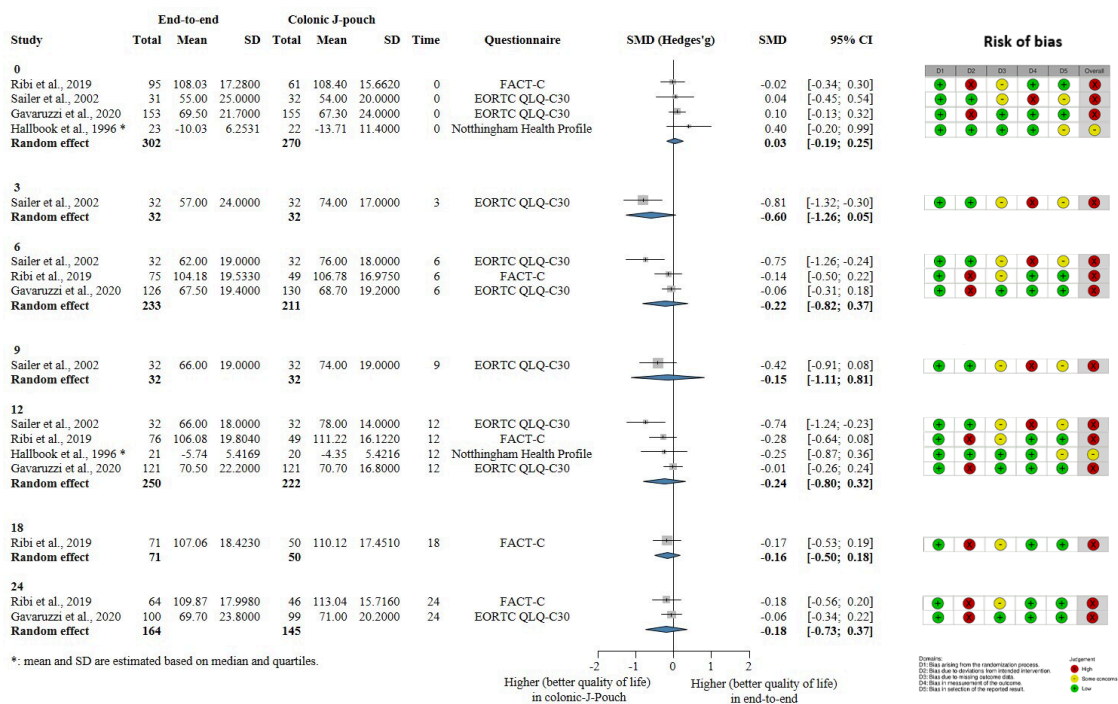
2.1.3.3. Quality of life

Four studies (7,8,45,48) were included in the multivariate analysis of QoL outcomes (Figure 4). QoL estimates were generated for seven predefined time points using a multivariate model that incorporated all available longitudinal data, thereby improving the precision and efficiency of the effect estimates.

At baseline, before surgery, no difference in QoL was observed between the groups (SMD: 0.03; 95% CI: -0.19 to 0.25). Only Sailer et al. (48) assessed QoL at three months postoperatively and reported a clinically small, but statistically non-significant, advantage for the CJP group (SMD: -0.81; 95% CI: -1.32 to 0.30).

At six months following surgery, data from three RCTs (7,8,48), yielded a pooled SMD of -0.22 (95% CI: -0.82 to 0.37), indicating no statistically significant difference between the groups. At nine months, a single study reported a modest improvement in QoL favoring CJP (SMD: -0.42 ; 95% CI: -0.91 to 0.08), although the result did not reach statistical significance.

One year after surgery, pooled data from the four RCTs demonstrated no significant difference in QoL between the groups (SMD: -0.24 ; 95% CI: -0.80 to 0.32). Long-term outcomes were reported less frequently, with QoL assessed at 18 months in one study (8) and at 24 months in two studies (7,8). At both time points, the observed effect sizes were small, suggesting no clinically meaningful difference in QoL between the two anastomotic techniques during later follow-up.



SMD – standardized mean difference; CI – confidence interval)

Figure 4: Forest plot and Risk of Bias assessment for the quality-of-life outcome in patients receiving end-to-end anastomosis compared to colonic J-pouch

2.1.4. End-to-end anastomosis versus Side-to-end anastomosis

2.1.4.1. Surgical outcomes

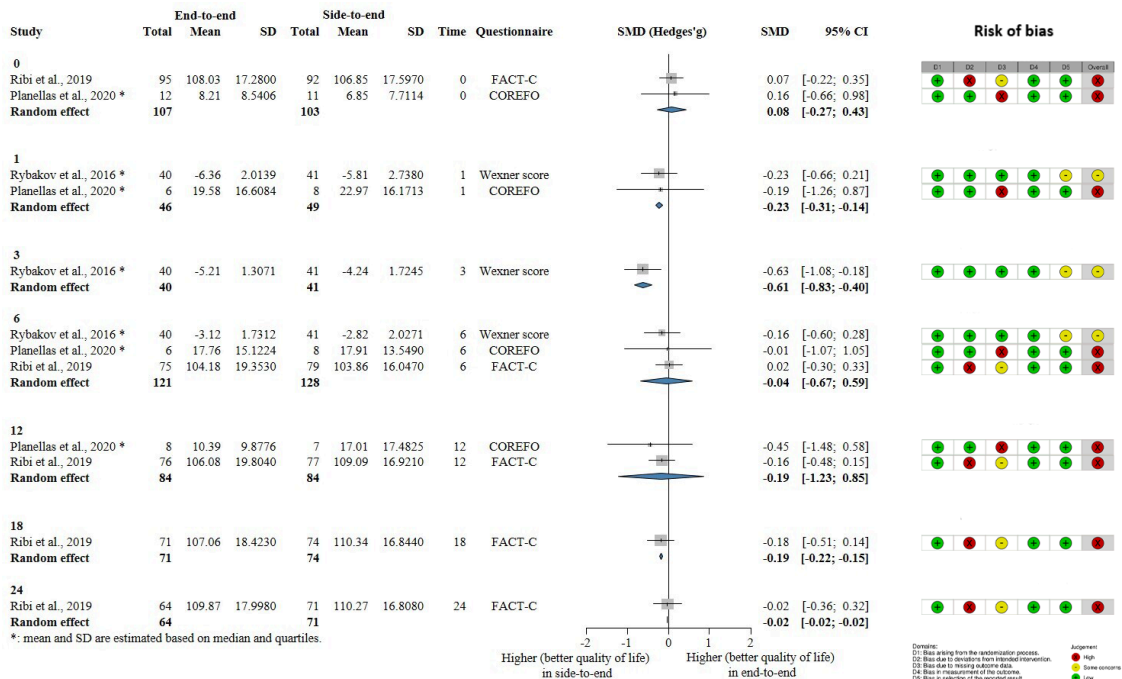
AL ratios were reported in eight articles (42,43,50,52,55–58); for forest plots, see Figure 2. In the five RCTs (42,43,52,56,57) where strictly rectum resection was performed, no statistically significant difference was found (RR: 1.59; CI: [0.54–4.72]). Three articles included cases of sigmoidectomy also, thus, a separate analysis was carried out, resulting in a RR of 0.76; CI: [0.17–3.39]. In the former, surgical reintervention ratios were investigated, resulting in an RR of 0.76; CI [0.03–18.71].

2.1.4.2. Functional outcomes

Due to limited data, quantitative analysis was not performed on daily bowel movements. Rybakov et al. 32) found that the slightly elevated number of stools observed in the EEA group was resolved at six months postoperatively. Rasulov et al. (42) concluded that at three months following surgery, there was no statistically significant difference between the two arms. The Egyptian study (58) showed a significant change in stool frequency following EEA.

2.1.4.3. Quality of life

Three articles (8,43,50) were included in our QoL analysis (see Figure 5). Predictions were made at seven time points. At baseline, based on two RCTs (8,50), no difference was found between the two types of anastomosis. At one and three months, only two (43,50) and one RCT (43) assessed patients' QoL. In the former, similar results were seen, and in the latter, a slightly better level of well-being was observed in the SEA group. At six months postoperatively, based on three articles (8,43,50), the SMD was -0.04; CI: [(-)0.67–0.59], resulting in a statistically non-significant finding. At the 12, 18, and 24 months time-points similar QoL was observed between the two reconstructive techniques.



(SMD – standardized mean difference; CI – confidence interval)

Figure 5: Forest plot and Risk of Bias assessment for the quality-of-life outcome in patients receiving end-to-end anastomosis compared to side-to-end anastomosis

2.1.5. Risk of Bias Assessment

RoB was assessed for all outcomes, and the individual results can be seen in Figures 2-5. 12 RCTs (7,8,38,40–42,44,48,50,52,60,61) had an overall high risk of bias. The primary source of bias arose from the inability to blind surgeons to the allocated intervention, which may have influenced outcome assessment and measurement. In addition, several studies were considered at high risk of bias due to deviations from the intended interventions. Specifically, following randomization, some patients were subsequently deemed unsuitable for CJP reconstruction; these individuals were either excluded from the analyses or reassigned to the EEA group, potentially compromising the benefits of random allocation. Finally, the long-term follow-up studies were frequently affected by substantial missing outcome data, resulting in an additional risk of bias.

2.1.6. Publication bias and heterogeneity

Comparing EEA to CJP, for the outcomes of AL (0%; CI: [0%–54%]), mortality (0%; CI: [0%–71%]), and ileus (0%; CI: [0%–75%]), the I^2 was low. When examining EEA versus SEA, the heterogeneity for AL (16%; CI: [0%–59%]) was low (29%; CI: [0%–93%]).

Publication bias assessment involved visual analysis of funnel plots, showing no potential small study bias for any evaluated outcomes.

In our sensitivity analysis, the impact of omitting the study by Choen et al. (41) was assessed on the comparison between CJP and EEA regarding postoperative ileus. Notably, omitting this study revealed a statistically significant increase in the incidence of ileus associated with CJP compared to EEA.

2.1.7. Certainty of evidence

In the comparison with CJP, for the outcomes of AL, mortality, ileus, and surgical reintervention the level of evidence was considered moderate, while for the overall postoperative complications, bowel movement, and QoL it was appraised as low. In the case of SEA, the outcome of AL was graded moderate and low for surgical reintervention and QoL.

2.2. Study II

2.2.1. Search and selection

Out of 12,171 studies screened, 38 were included in the final analysis. The selection process is illustrated in Figure 6.

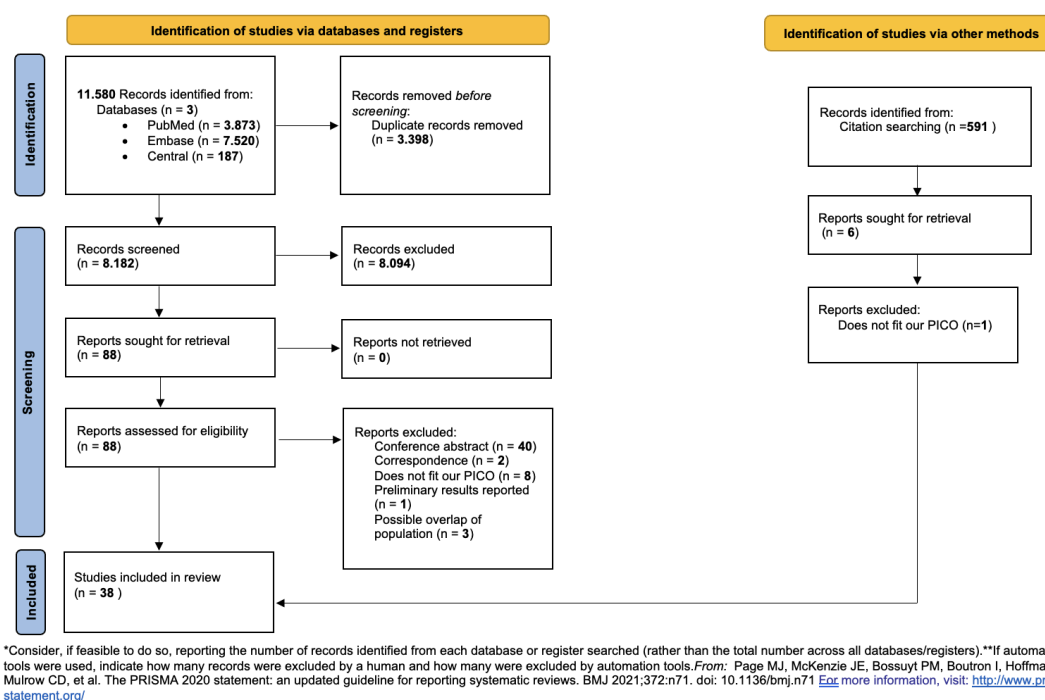


Figure 6: PRISMA 2020 flowchart representing the study selection process (37)

2.2.2. Basic characteristics of included studies

Baseline characteristics of the included studies are summarized in Table 2. Four studies were RCTs (12,62–64), one was a prospective case-control study (65), one was a propensity score-matched analysis (66), and one was a prospective cohort study (67); the remaining studies employed retrospective cohort designs.

The use of neoadjuvant therapy was generally well balanced between the study groups, although several studies (65,68–76) reported a higher proportion of patients receiving neoadjuvant treatment in the ELAPE cohort. Tumor height was also largely comparable across studies, with a small number (68–70,73,74) reporting lower tumor locations among patients undergoing ELAPE. With respect to the surgical approach, four studies (77–80) exclusively utilized laparoscopic procedures in both groups, while 14 studies (65,68–70,72–74,76,81–86) reported a balanced distribution of open and minimally invasive techniques between the treatment arms. Seven studies (66,75,87–91) described more frequent use of laparoscopic or robotic surgery in the ELAPE group, whereas Bianco et al. (64) reported greater use of these approaches in the APE cohort. West et

al. (92) had substantial missing data regarding the operative approach, and 11 (12,14,62,63,66,67,71,93–96) studies did not report this information.

Tumor staging was reported inconsistently across studies, with clinical, pathological, and post-neoadjuvant TNM classifications used interchangeably. This heterogeneity precluded a comprehensive comparison of baseline staging characteristics across the included studies. Nevertheless, the available data suggested that tumor stage was generally comparable between the ELAPE and APE groups.

Table 2: Baseline characteristics of the enrolled studies

Nr.	First author	Year	Country	ELAPE				APE			
				Nr. of patients (%F)	Age (years)	Tumor height (cm)	Oncological therapy	Nr. of patients (%F)	Age	Tumor height (cm)	Oncological therapy
1.	Aggarwal(14)	2018	India	21 (38,1)	50 (20-68)*	NA	NCRT –100%	50 (NA)	NA	NA	NCRT – 100%
2.	Asplund(82)	2012	Sweden	79 (44)	67 (35 – 89)*	4(0-8)*	NRT – 75,9% NCRT -18.9%	79 (30)	68 (38 – 85)*	4 (0-10)*	NRT – 83,5% NCRT – 6,3%
3.	Bianco(64)	2016	International	17 (52,4)	60 (90)†	2 (2-3)¶	NCRT –100%	17 (35,3)	64 (12) †	2 (1,75-4)¶	NCRT –100%
4.	Carpelean (87)	2018	Finland	42 (35,7)	61 (2)§	NA	NCRT – 66% NRT – 26,1% CT – 73,8%	27 (25,6)	67 (2) §	NA	NCRT -70,3% NRT – 22,2% CT – 62,96%
5.	Cesar (89)	2018	Brazil	22 (45)	58 ‡	0 (from dentate line)	NCRT –100%	67 (39)	57 ‡	1 (from dentate line)	NCRT –100%
6.	Colov (68)	2016	Denmark	245 (37)	68 (59-74)¶	0-5:90% 6-10:10%	NCRT – 71%	200 (37)	69 (63-77)¶	0-5:69% 6-10:31%	NCRT – 41%
7.	Danilov (78)	2020	Russia	62 (42)	60,3 (7,8)†	3,7 (1,2) †	NCRT – 66% CT – 38,7%	30 (40)	62,4 (8,2)†	3,6 (1,2) †	NCRT -63,3% CT – 40%
8.	Dsouza (83)	2020	India	57 (40,4)	46,37‡	NA	NCRT -96,5%	138 (31,9)	46,29‡	NA	NCRT -97,8%
9.	Güven (77)	2019	Turkey	42(41)	58 (7,1) †	3,4 (1,1) †	NCRT –100%	62(45)	59,4 (4,2) †	3,2 (0,7) †	NCRT-100%
10.	Han (12)	2012	China	35 (42,8)	63 (44-81)*	3 (2-7)*	NCRT -28,5%	32 (34,3)	68 (32-84)*	3(2-5)*	NCRT -28,1%
11.	Hanif (67)	2016	UK	24 (38)	68 (37-87)*	NA	NRT – 20,8%	48 (31)	69 (41-82)*	NA	NRT – 18,7%
12.	How(94)	2013	Ireland	10 (40)	58 (48-83)*	4,4 ‡	NCRT – 80% NRT – 20%	10(20)	66 (51-79)*	4,7 ‡	NCRT – 90% NRT – 10%
13.	Kamali (84)	2017	UK	27 (33,3)	67,8‡	NA	NCRT -81,5%	20 (14,2)	66,9‡	NA	NCRT -71,4%
14.	Klein (69,70)	2015	Denmark	301 (36)	68 (60-75)¶	0-5:88,7% 6-10:8,6% >10:0,6%	NCRT – 70%	253 (36)	69 (63-77)¶	0-5:62,8% 6-10:32% >10:2,7%	NCRT – 45%
15.		2016									
16.	Liu (97)	2020	UK	30 (26,6)	68 ‡	NA	NCRT -53,3%	30(43,3)	67,8 ‡	NA	NCRT -46,6%
17.	Murashko (88)	2017	Russia	42 (57)	60,3(44-73)*	NA	NRT – 59,5% NCRT – 7%	48 (31)	69 (41-82)*	NA	NRT – 45,8% NRCT – 8%
18.	Nessar (71)	2016	Turkey	25 (32)	60,3 (13,%)†	NA	NCRT – 36%	56 (34)	56,8 (14,1) †	NA	NCRT -10,7%
19.	Ortiz (66)	2014	Spain	457 (28,4)	<65:35 % 65-75:30% >75:35 %	0-5:96% 6:4%	NCRT – 76%	457 (29,9)	<65:34% 65-75:30% >75:35%	0-5:95% 6:5%	NCRT -75,7%
20.	Othman (63)	2020	Egypt	20	NA	2 (0.1-4)*	NCRT – 85%	20	NA	3 (1-4)*	NCRT – 85%
21.	Pai (81)	2016	India	42(11,9)	46 ¥	NA	NCRT – 88%	78 (32)	47 ¥	NA	NCRT -79,5%
22.	Papp (90)	2020	Hungary	38 (34,2)	66,5(33-85)*	2(0-8)*	NCRT – 60%	35(42,9)	68 (39-82)*	2 (0-10)*	NCRT -68,5%

23.	Park (85)	2016	Korea	13 (30,7)	55 (48-58) ¶	0-5:92,3% >5:7,7%	NCRT -76,9%	26 (46,15)	65(58-76) ¶	0-5:92,3% >5:7,7%	NCRT -96,1%
24.	Perdawood (72)	2014	Denmark	68 (34)	68 (42-85)*	4(1-6)*	NCRT -85,3%	39 (31)	69 (58-88)*	3(1-6)*	NCRT -48,7%
25. 26.	Prytz (73,74)	2014 2016	Sweden	518 (40)	68 (61-76) ¶	3,4 ‡	NCRT -30,6% NRT - 88%	209 (44)	71 (63-79) ¶	6,6 ‡	NCRT -15,3% NRT - 68,9%
27.	Qi (80)	2019	China	53(39,6)	60,2 (7,96) †	3,6 (1,1) †	NCRT -100% CT - 37,7%	58(43,1)	57,3 (11,1) †	3,2 (1,06) †	NCRT -17,2% CT -43,1%
28.	Seshadri (62)	2017	India	10 (30)	55,8 (11,7) †	1,4 (1,07) †	NCRT -100%	10 (30)	56,6 (11,9) †	1,3 (0,8) †	NCRT -100%
29.	Shen (75)	2019	China	106 (36,8)	60,7(52-70) ¶	3,1 (2-4) ¶	NCRT-42,4% CT - 43,4% RT - 8,49%	88 (42)	63,1(56-73) ¶	3,7(2,8-4,9) ¶	NCRT -28,4% CT - 31,8% RT - 6,8%
30.	Stelzner (93)	2011	Germany	28 (32,1)	66 (44-79)*	2,5(0-8)*	NCRT -100%	46 (19,6)	64 (44-82)*	3(0-9)*	NCRT - 100%
31.	Stelzner (95)	2016	Germany	36 (36,1)	65 (44-79)*	2(0-5)*	NCRT -88,8% NRT - 8,3% NCT -2,7% CT - 36,1%	36 (9)	64 (45-82)	4(0-6)*	NCRT -97,2% NRT - 0% NCT - 2,7% CT - 33,3%
32.	Ulusoy (86)	2022	Skopje	15 (33,3)	59,7 (17) †	NA	NA	52 (36,5)	65,5 (10) †	NA	NA
33.	Van Oostendorp (96)	2020	International	17(35,3)	62 (14) †	NA	NA	8 (12,5)	70,3 (7,1) †	NA	NA
34.	Vaughan-Shaw (65)	2012	UK	16 (56,25)	71 (49-88)*	NA	NCRT -56,2% NRT - 43,8%	10 (50) 10 (20)	72 (52-87)* 72,5(46-89)*	NA	NCRT - 35% NRT - 45%
35.	Wang (12)	2015	China	23 (46,8)	57,3 (12,2) †	3 (1,3) †	NCRT -21,7% RT - 39,13%	25 (52)	56,8 (11,9) †	3 (1,45) †	NCRT - 20% RT - 44%
36.	Wang (79)	2022	China	94 (44,6)	59,6 (11,9) †	NA	NCRT -47,8%	83 (55,4)	58,3 (10,8) †	NA	NCRT -50,6%
37.	West (92)	2010	International	176 (31,8)	66 (58-73) ¶	1,5(0,2-2) ¶	RT - 73,86% CT - 47,72%	124 (29,8)	68 (57 - 75) ¶	2(0,3-3) ¶	RT - 72,58% CT - 38,7%
38.	Zhang (76)	2022	China	68 (36,8)	61,3 (11,5) †	3 (2-3,5)*	NCRT -45,6% CT- 70,5%	46 (34,8)	64,8 (11,1) †	3 (2-4)*	NCRT -19,5% CT - 60,8%

Grey filling means a study is a randomized controlled study; ELAPE: extralevator abdominoperineal excision; APE: abdominoperineal excision; NA: not available; %F: percentage of female patients; NCRT: neoadjuvant chemoradiotherapy; NRT: neoadjuvant radiotherapy; NCT: neoadjuvant chemotherapy; RT: adjuvant radiotherapy; CT: adjuvant chemotherapy; * median (range min-max); † mean (SD); ¶ median (IQR min-max); § mean (SEM); ‡ mean; ¥ median

2.2.3. Long-term oncological outcomes

2.2.3.1. Overall survival

Although OS was reported in 10 studies, only seven (12,75,76,78,80,86,91) provided extractable data because of poor Kaplan–Meier curve quality; qualitative findings from the excluded studies are summarized at the end of this subsection.

Patients undergoing ELAPE had approximately a 47% lower risk of death than those receiving APE over the entire follow-up period (HR: 0.54, CI: 0.40–0.73 from IPD – see Figure 7; for sensitivity analysis, see Figure 8).

At 12 months, the two groups' estimated survival probabilities were similar: 98% (CI: 0.92–0.99) for APE and 97% (CI: 0.90–0.99) for ELAPE. However, by 24 months, a divergence emerged, with survival declining slightly in both groups but remaining higher in the ELAPE cohort (93% for ELAPE (CI: 0.80–0.97) vs 86% for APE (CI: 0.68–0.95)). The clinically relevant difference was observed at 5 years, where the ELAPE group showed a relevantly better survival rate of 83% (CI: 0.53–0.95) compared to 69% (CI: 0.40–0.88) for APE. See Figure 9.

Carpelan et al. (87) reported mean follow-up times of 3.2 years for ELAPE and 5.8 years for APE, with no significant OS difference ($p = 0.8173$). Klein et al. (70) found 4-year OS rates of 74% for APE and 77% for ELAPE ($p = 0.59$). Similarly, Prytz et al. (74) observed no difference in 3-year OS between the two groups.

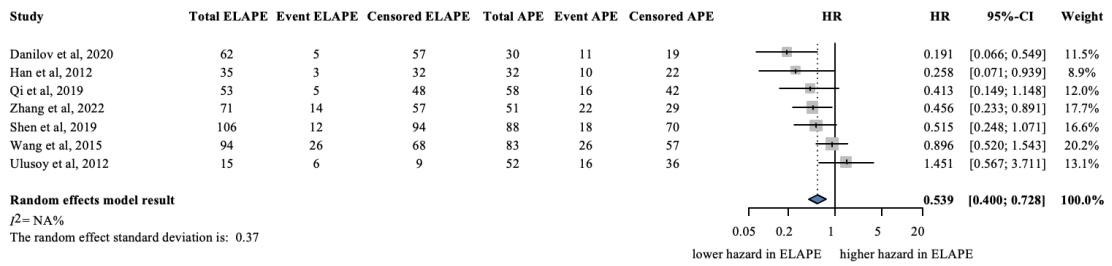


Figure 7: Forest plots representing overall survival following ELAPE vs. APE - IPD-based analysis.

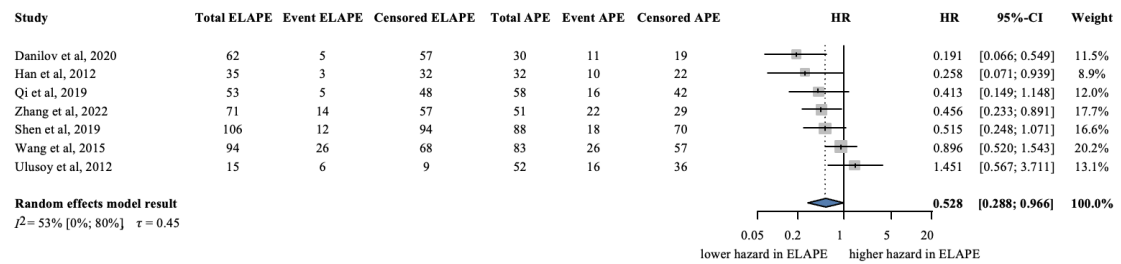


Figure 8: Forest plots representing overall survival following ELAPE vs. APE using “classical” analysis

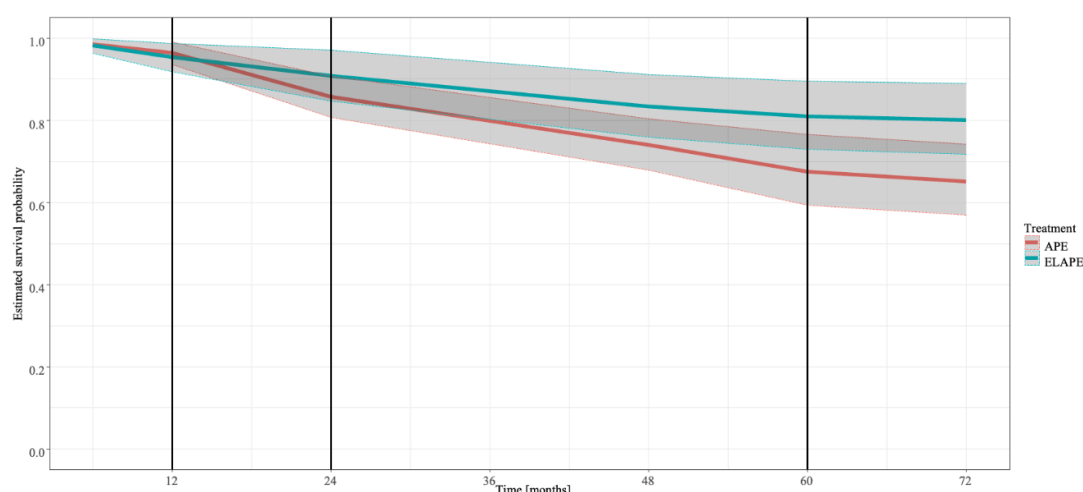


Figure 9: Estimated survival probabilities at given times following ELAPE vs. APE

2.2.3.2. Disease-free survival

Data from five articles (12,75,78–80) showed a 26% lower risk of DFS in the ELAPE group over the entire follow-up period (HR: 0.74, CI: 0.55–0.99 from IPD – see Figure 10; for sensitivity analysis, see Figure 11).

At 12 months, the estimated DFS probability was slightly higher for ELAPE (98%, CI: 0.87–1.00) compared to APE (96%, CI: 0.79–0.99). By 24 months, the gap widened, with DFS at 78% (CI: 0.50–0.93) for APE and 89% (CI: 0.68–0.97) for ELAPE. At 5 years, ELAPE demonstrated a notably higher DFS of 87% (CI: 0.50–0.98), while APE had a DFS of 65% (CI: 0.24–0.92) – see Figure 11.

Carpelan et al. (87) observed mean follow-up times of 3.2 years for ELAPE and 5.8 years for APE, with no significant difference in DFS ($p = 0.6311$). Klein et al. (70) found 4-year DFS rates of 67% for APE and 66% for ELAPE ($p = 0.82$).

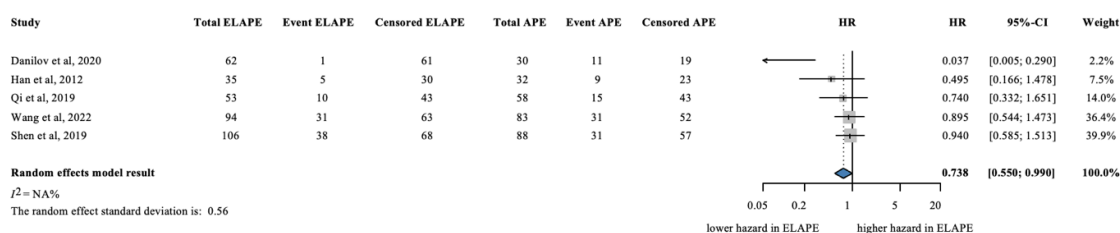


Figure 10: Forest plots representing disease free survival following ELAPE vs. APE using IPD-based analysis.

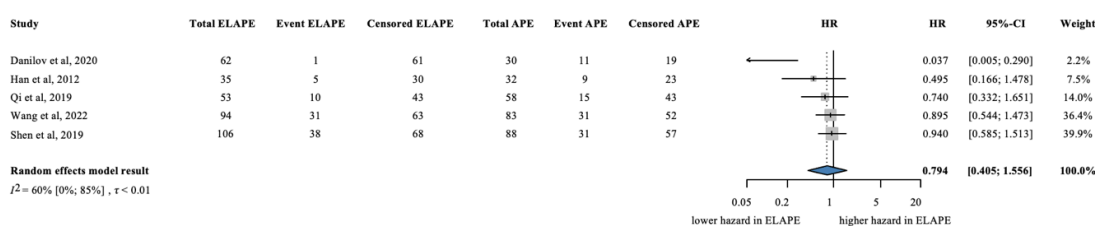


Figure 11: Forest plots representing disease-free survival following ELAPE vs. APE using “classical” analysis.

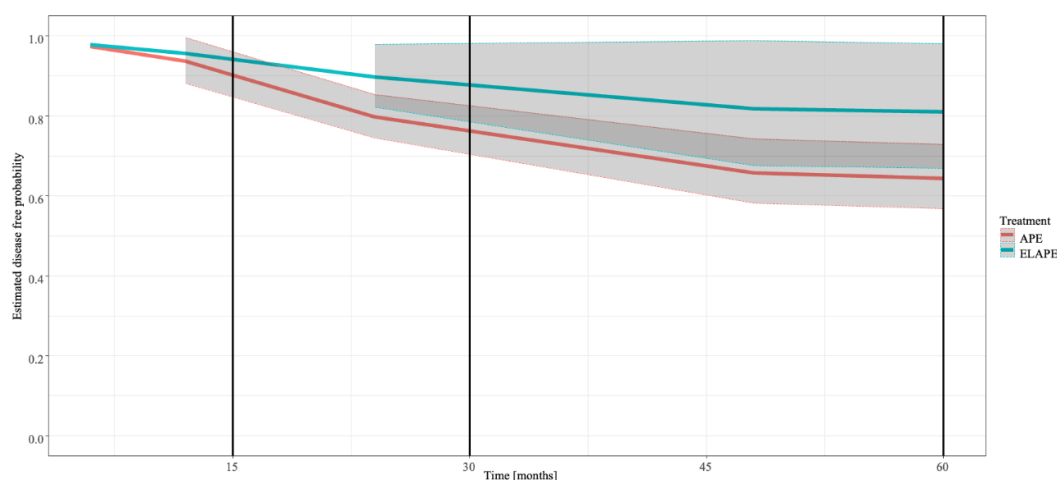


Figure 12: Estimated DFS probabilities at given times following ELAPE vs. APE

2.2.3.3. Local recurrence-free survival

Data from four studies (66,75,76,79) suggested a 33% lower risk of LR in the ELAPE group over the entire follow-up period, but the results did not reach statistical significance (HR: 0.67, CI: 0.45–1.00 from IPD – see Figure 13; HR: 0.67, CI: 0.2–2.25 from aggregated data – see Figure 14).

At 12 months, the estimated LRFS probability was slightly higher for ELAPE (98%, CI: 0.89–1.00) compared to APE (96%, CI: 0.78–0.99). By 24 months, the advantage of ELAPE became more pronounced (96%, CI: 0.68–1.00 for ELAPE vs. 87%, CI: 0.46–0.98 for APE). At 5 years, ELAPE maintained a higher LRFS (81%, CI: 0.02–1.00) compared to APE (72%, CI: 0.02–1.00), though the wide confidence intervals indicate uncertainty in these estimates. For more details, see Figure 15.

Carpelan et al. (87) reported local recurrence rates of 7% for ELAPE and 19% for APE ($p = 0.2473$), suggesting a lower recurrence risk with ELAPE. In contrast, Prytz et al. (74) found higher 3-year local recurrence rates for ELAPE compared to APE, with a relative risk of 4.91 (median follow-up: 3.43 years).

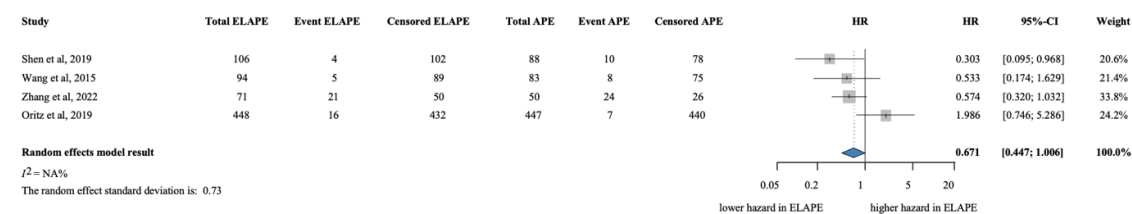


Figure 13: Forest plots representing local recurrence free survival following ELAPE vs. APE using IPD-based analysis.

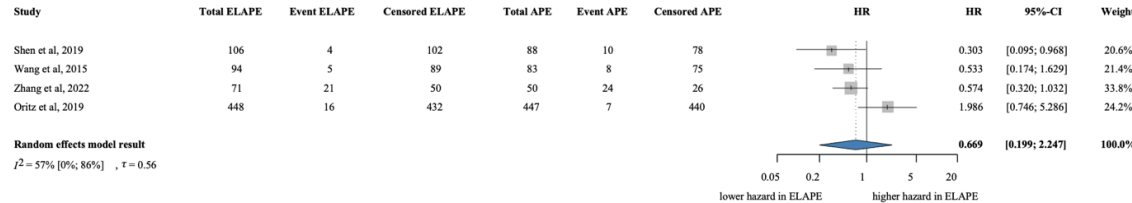


Figure 14: Forest plots representing local recurrence free survival following ELAPE vs. APE using “classical” analysis.

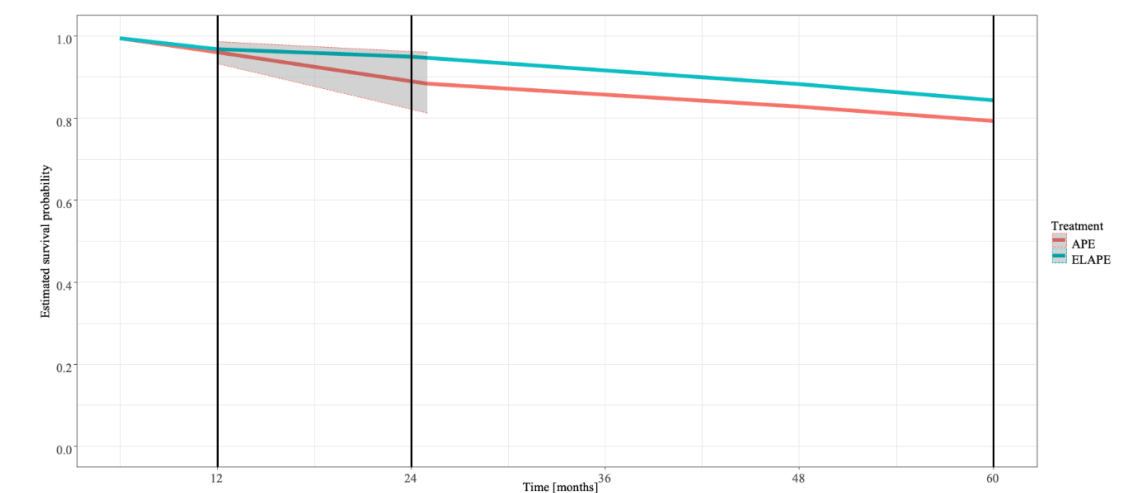


Figure 15: Estimated LRFS probabilities at given times following ELAPE vs. APE

2.2.4. Intraoperative parameters

ELAPE significantly reduced IOP (OR: 0.49; CI: 0.34–0.72), with an even greater effect in RCTs (OR: 0.22; CI: 0.07–0.73), corresponding to 78% lower odds of perforation compared to APE.

ELAPE was associated with lower CRM positivity (OR: 0.60; CI: 0.40–0.90), with an even greater reduction in the RCT subgroup (OR: 0.15; CI: 0.06–0.42), corresponding to 85% lower odds compared with APE.

ELAPE resulted in less blood loss (MD: -54.68 ml; CI: -95.42 – -13.93 ml), but a longer operative time by about one hour (MD 61.72 min; CI: 38.7 – 84.76 min), compared to APE. See table 3.

2.2.5. Postoperative parameters

Analysis of mortality, overall complications, reoperations, and hospital stay revealed no significant differences between ELAPE and APE. For further details see table 3.

2.2.6. Perineal wound complications

Analysis of overall perineal wound complications and infections revealed no significant differences. While the OR of 1.72 may suggest a higher rate of perineal wound dehiscence with ELAPE, the confidence interval (CI: 0.96 – 3.09), indicates no statistically significant difference. Perineal hernia occurrence was similar (OR: 0.84; CI: 0.37 – 1.87). However, perineal pain was more frequently reported in ELAPE patients (OR: 3.59; CI: 1.1 – 11.74). See table 3.

Table 3: Results of secondary outcomes

Outcome of interest	Nr. of studies included	Nr. of patients (ELAPE/APE)	MD/OR (95% CI)	Study heterogeneity	
				I ² (95% CI)	τ
Intraoperative parameters					
IOP	27	2241/1932	0.49 (0.34; 0.72)	39% (3%; 62%)	0.25
IOP – subgroup of RCT’s only	4	82/79	0.22 (0.07; 0.73)	0% (0%; 85%)	0
Positive CRM	30	2423/2116	0.60 (0.40; 0.90)	64% (47%; 76%)	0.5
Positive CRM – subgroup of RCT’s only	4	82/79	0.16 (0.06; 0.42)	0% (0%; 85%)	0
Blood loss	14	1365/946	-54.68 (-95.42; -13.93)	77% (62%; 86%)	1748.03
Operative time	15	1179/816	61.73 (38.70; 84.76)	88% (81%; 92%)	1287.56
Postoperative parameters					

Mortality	18	1567/1325	0.90 (0.64; 1.26)	0% (0%; 50%)	0
Mortality – subgroup of RCT's only	3	62/59	0.45 (0.03; 5.76)	0% (0%; 90%)	0
Overall complications	8	1209/937	1.06 (0.69; 1.63)	40% (0%; 73%)	0.11
Reoperation	8	1171/997	1.18 (0.84; 1.66)	0% (0%; 68%)	0
Hospital stay	11	791/694	0.11 (-2.53; 2.75)	94% (91%; 96%)	13.14
Perineal wound complications					
Overall complications	13	1173/1244	1.39 (0.81; 2.40)	72% (50%; 84%)	0.51
Infection	19	1045/1052	1.02 (0.69; 1.50)	40% (0%; 65%)	0.24
Infection – subgroup of RCT's only	3	72/69	0.82 (0.13; 5.06)	0% (0%; 90%)	0
Dehiscence	9	603/712	1.72 (0.96; 3.09)	29% (0%; 67%)	0.14
Perineal hernia	13	789/803	0.84 (0.37; 1.87)	33% (0%; 65%)	0.43
Perineal pain	5	386/388	3.59 (1.10; 11.74)	44% (0%; 79%)	0.41

ELAPE: extralevator abdominoperineal excision; APE: abdominoperineal excision; MD: mean difference; OR: odds ratio; CI: confidence interval; IOP: intraoperative perforation; CRM: circumferential resection margin; RCT: randomized controlled trial

2.2.7. Risk of bias assessment

Most included studies demonstrated an overall moderate RoB. Three studies (67,71,89) had a serious RoB, while one study (66) exhibited a low RoB. From the four RCTs included, three (12,63,64) had an overall low RoB, while one (62) showed some concerns in the randomization process.

2.2.8. Publication bias and heterogeneity

Visual analysis of funnel plots showed no potential small study bias for any evaluated outcomes. While heterogeneity was low in the RCT subgroup analyses, considerable between-study heterogeneity was observed in the pooled analyses of observational studies.

2.2.9. Certainty of evidence

The certainty of evidence was low to very low for most outcomes with concerns regarding risk of bias, inconsistency, and imprecision. However, intraoperative outcomes showed moderate certainty in RCT subgroups.

3. DISCUSSION

3.1. Summary of Findings, International Comparisons (including all studies)

The present doctoral thesis synthesizes the best available evidence regarding two key surgical decisions in the management of rectal cancer. Although these decisions concern different stages of treatment, both directly influence postoperative recovery, long-term oncological outcomes, and patients' QoL. The first study evaluated whether EEA provides outcomes comparable to alternative reconstructive techniques following TME, while the second investigated whether the more radical ELAPE improves outcomes compared with APE. Collectively, these studies emphasize that surgical decision-making should extend beyond technical feasibility and consider both oncological efficacy and postoperative functional recovery.

The results of the first study indicate that EEA has similar 30-day complication rates to other approaches, except for the rate of ileus, which seems to favor EEA. The mild bowel dysfunction following EEA resolves within a year. No significant difference was found in the patients' QoL compared with either CJP or SEA at the studied time points. The latest clinical practice guideline (3) on managing rectal cancer suggests that a colonic reservoir may be an option during TME. However, the results show that EEA yields similar results, thereby eliminating the necessity for pouch formation.

The findings are largely consistent with previous systematic reviews. Hüttner et al. (5), similarly reported no significant differences in postoperative surgical outcomes between reconstructive techniques, although they observed modest short-term functional advantages for CJP reconstruction. In the network meta-analysis, an individual comparison of EEA to SEA was not performed. McKechnie et al. (98) suggested that SEA reduced AL (RR 0.37; 95% CI [0.15–0.93], $p=0.04$, $I^2=0\%$); however, this association was not confirmed in the present analysis. These differences may arise from the inclusion of Marti et al.'s (52) supplementary data in the results, which account for 40% of the included studies. Likewise, the findings differ from those of Zaman et al. (99), who reported superior functional outcomes after CJP reconstruction and higher leakage rates following EEA, but they included retrospective cohort studies in their analysis. Surprisingly, in this analysis, the risk of developing ileus following EEA was lower by 36% compared to CJP, although due to the low number of study participants,

this investigation did not reveal statistical significance. More recent evidence also demonstrated that only TCP was associated with increased leakage rates, whereas differences between end-to-end, colonic J-pouch, and side-to-end reconstruction remained minimal (6). Unlike previous reviews, the present study quantitatively synthesized patient-reported QoL outcomes and demonstrated no clinically meaningful differences between reconstructive techniques.

All prior reviews divided the follow-up duration for evaluating functional outcomes into three categories, namely early (<8 months), intermediate (8 – 18 months), and late (>18 months postoperatively) periods, in accordance with the 2008 Cochrane Review (100). This study, however, assessed bowel function at 6 and 12 months, corresponding to the American Society of Clinical Oncology Resource-Stratified Guideline's post-treatment surveillance schedule (101). Assessing the findings, the benefit of EEA can be observed earlier than 18 months, as at one year following surgery, there is no significant difference between EEA and CJP regarding stool frequency. Nevertheless, the more recent RCTs did not provide a separate analysis of daily bowel movements, as they primarily relied on various QoL questionnaires to assess patient well-being, therefore, these were not included in the analysis. Thus, all meta-analyses published since 2008 have largely reproduced the same findings, utilizing studies that appeared over a decade ago.

In contrast, when sphincter preservation was not feasible, the findings supported a more radical surgical approach. ELAPE was associated with improved long-term OS and DFS compared with APE. These survival benefits were accompanied by significantly lower rates of IOP and CRM positivity, supporting the concept that a more cylindrical specimen and improved pathological clearance translate into better oncological outcomes. Although LRFS also favoured ELAPE, statistical significance was not reached, most likely because of the limited number of available survival events and the restricted amount of extractable individual patient data.

The oncological findings partly differ from previous meta-analyses. Earlier reviews consistently demonstrated lower IOP rates following ELAPE but failed to detect significant improvements in CRM positivity (102,103). In contrast, both pathological outcomes reached statistical significance in the present study and remained consistent in randomized subgroup analyses. Furthermore, previous reviews reported conflicting

oncological results. Negoï et al. (102) found no difference in one-year OS but observed improved three-year OS with ELAPE. Qi et al. (103) reported a significantly lower LR rate for ELAPE contradicting Negoï et al., who found no such benefit. These discrepancies stem from methodological differences, particularly the reliance on ORs, which fail to account for event timing. Our meta-analysis overcomes these limitations by using HRs for a time-dependent evaluation of all three key oncological outcomes over a longer, five-year follow-up period. Additionally, incorporating IPD minimizes biases and enhances statistical power.

Perineal wound complications did not differ significantly, countering concerns that the larger perineal defect and use of reconstruction techniques in ELAPE might increase these risks (82). In the APE group, perineal closure was primarily performed with direct suturing, while ELAPE required various reconstructive approaches, including mesh placement (both synthetic and biological), Vertical Rectus Abdominis Myocutaneous flap, gluteus maximus myocutaneous flap, V-Y advancement flap, and gracilis flap. Despite these differences, complication rates remained comparable, likely because the use of well-vascularized flaps or biological mesh in ELAPE may counteract the effect of the larger perineal defect by improving tissue coverage and reducing closure tension. Additionally, enhancements in perioperative care in more recent ELAPE cohorts, including standardized antibiotic prophylaxis and more structured postoperative wound management, may also contribute to comparable outcomes.

Perineal pain was significantly more frequent in ELAPE (OR 3.59), representing an important postoperative morbidity that should be weighed against the potential oncological advantages. This increased pain burden is likely related to the more extensive perineal dissection and the more frequent use of coccygectomy in ELAPE.

ELAPE surgery is approximately one hour longer than APE. This difference is largely due to the prone jackknife position used during the perineal dissection in ELAPE. After completing the abdominal phase, the intubated patient must be repositioned, which is a time-consuming process. Many surgeons are more familiar with the lithotomy position, while the prone approach changes the anatomical view and requires more cautious dissection. However, with increasing experience and familiarity, we anticipate that operative times for ELAPE will decrease in the future.

The lower intraoperative blood loss associated with ELAPE likely reflects the greater use of laparoscopic or robotic approaches, which reduce venous oozing through improved visualisation and the tamponade effect of pneumoperitoneum. The standardized cylindrical dissection of ELAPE, which remains outside the levator musculature and sphincter complex, may also limit bleeding from the pelvic floor. Lower conversion rates and the greater involvement of specialist colorectal surgeons may further contribute to this finding.

Taken together, the findings of this thesis demonstrate that surgical decision-making in rectal cancer should remain individualized according to the operative objective. When restorative surgery is feasible, simpler reconstructive techniques appear sufficient to achieve excellent functional recovery and QoL without compromising safety. Conversely, when abdominoperineal excision is required, a more radical dissection may provide meaningful long-term oncological benefits while maintaining acceptable postoperative morbidity. These findings support a tailored surgical approach that balances technical complexity, functional outcomes, perioperative morbidity, and oncological efficacy.

3.2. Strengths

3.2.1. Study I

All included articles were RCTs, allowing better control over the confounding factors and offering a homogeneous pool of evidence. A meticulous methodology was adhered to throughout every stage of this meta-analysis, which includes risk-of-bias and GRADE assessment. To the knowledge available, this is the first meta-analysis that synthesized QoL data following TME. This study shows that assessing only bowel movement or intestinal function doesn't necessarily associate with an improved quality of life.

3.2.2. Study II

A rigorous systematic review methodology was applied, including comprehensive risk-of-bias assessment and certainty of evidence evaluation with the GRADE approach. In contrast to many previous meta-analyses, the study incorporated hazard ratios and reconstructed individual patient data for survival analyses, allowing more accurate

estimation of long-term oncological outcomes. Furthermore, predefined subgroup analyses of randomized controlled trials were performed for several outcomes, enabling assessment of the consistency of results across different study designs.

3.3. Limitations

3.3.1. Study I

The greatest limitation of the study is the high risk of bias due to the quasi-randomization of patients ineligible for pouch formation during surgery. Additionally, the limited sample size and use of multiple questionnaires led to limited publication bias assessment, and high heterogeneity in bowel movement and quality of life analysis.

3.3.2. Study II

The main limitations are the predominance of non-randomized studies, the lack of long-term follow-up studies, and the lack of possibility for adjusting confounding factors. Additionally, the poor quality of some Kaplan-Meier curves resulted in the exclusion of data from two major studies with large sample sizes.

4. CONCLUSIONS

4.1. Study I

EEA is as effective as other techniques with lowered ileus rates. The slight, temporary impairment in bowel movement does not impact overall QoL, since at six and 12 months postoperatively, patient well-being is similar compared to CJP or SEA.

4.2. Study II

ELAPE offers clinically relevant oncological advantages over APE, with improved OS, DFS, LRFS, and reduced rates of IOP and CRM positivity. Despite the extended resection, perineal wound complications were similar between the two techniques.

5. IMPLICATIONS FOR PRACTICE

5.1. Study I

The findings of this meta-analysis support the routine use of EEA following TME, as it provides comparable postoperative morbidity, bowel function, and QoL to alternative reconstructive techniques while demonstrating a lower incidence of postoperative ileus. Given its technical simplicity and reduced dependence on additional stapling devices, EEA may be particularly advantageous in healthcare systems with limited resources or in regions with a high incidence of rectal cancer. These findings suggest that routine construction of more complex colonic reservoirs may not be necessary for the majority of patients.

5.2. Study II

Current clinical guidelines (3,104) recommend ELAPE mainly for bulky, locally advanced tumors with levator involvement; however, our results challenge this restrictive approach. The consistent oncological advantages observed suggest that ELAPE may provide benefits across tumor stages, supporting broader indications. Surgeons should balance these benefits with transparency about potential postoperative issues, such as perineal pain.

6. IMPLICATIONS FOR RESEARCH

6.1. Study I

Further investigations are needed, with a proper randomization process, utilizing larger sample sizes, to comprehensively examine the long-term QoL outcomes of patients, while employing a standardized questionnaire for consistent measurement. Increasing the sample size in future studies may enhance statistical power and enable the strengthening of clinically relevant differences, particularly regarding the risk of ileus in CJP compared to EEA. Additionally, incorporating cost-effectiveness analyses would provide additional perspectives for future decision-making.

6.2. Study II

Future research should include RCTs with long-term follow-up, use multivariate survival models for more nuanced insights, and explore ELAPE across different TNM stages to refine patient selection. To support reproducibility, anonymized datasets should be shared for external validation.

7. IMPLICATIONS FOR POLICY MAKERS

7.1. Study I

The findings of this study have implications for healthcare policy, guideline development, and resource allocation. Given the comparable postoperative outcomes and quality of life achieved with EEA, routine use of more technically demanding reconstructive techniques may not be justified in all patients undergoing TME. Clinical practice guidelines should therefore acknowledge EEA as an evidence-based reconstructive option rather than promoting routine pouch formation. In addition, because EEA requires fewer stapling devices and is technically less demanding, its broader implementation may reduce healthcare costs and improve access to high-quality rectal cancer surgery, particularly in resource-constrained healthcare systems. Policymakers should also encourage standardized reporting of functional and QoL outcomes to facilitate future evidence synthesis and benchmarking across institutions.

7.2. Study II

The results of this study suggest that current recommendations restricting ELAPE primarily to bulky or locally advanced tumors may warrant re-evaluation as additional evidence emerges. The observed improvements in oncological outcomes support consideration of broader indications within future clinical guidelines while recognizing the need for careful patient selection. Policymakers should promote standardized surgical quality assurance programs, including the routine reporting of CRM status, IOP, and long-term oncological outcomes, to facilitate continuous evaluation of surgical performance. Furthermore, support for multicentric prospective registries and RCTs would strengthen the evidence base required for future guideline updates and health policy decisions.

8. FUTURE PERSPECTIVES

The future of rectal cancer care relies on continued progress in prevention, early diagnosis, surgical innovation, and evidence-based practice. Expanding colorectal cancer screening programs and improving participation rates remain essential, as earlier detection increases the likelihood of curative treatment, facilitates sphincter-preserving surgery, and improves long-term oncological outcomes and quality of life.

Further progress in rectal surgery should focus on greater standardization of operative techniques, pathological assessment, and outcome reporting. Uniform reporting of oncological, functional, and patient-reported outcomes would improve the comparability of studies and strengthen the evidence supporting clinical decision-making. At the same time, treatment strategies should become increasingly individualized, balancing oncological safety with postoperative function and quality of life according to tumour characteristics and patient factors.

Technological advances, including robotic surgery, artificial intelligence, and advanced imaging, are expected to further improve surgical precision, training, and quality assurance. However, their widespread implementation should continue to be supported by high-quality clinical evidence.

Finally, international collaboration through multicentre registries, standardized data collection, and the sharing of anonymized individual patient data will facilitate more robust research and accelerate the development of evidence-based guidelines. Ultimately, the future of rectal cancer surgery lies in combining standardized, patient-centred, and data-driven care to achieve the best possible outcomes for patients worldwide.

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10. BIBLIOGRAPHY

10.1. Publications Related to the Thesis

1. **Kávási, Sarolta Beáta;** Iov, Diana-Elena; Rancz, Anett; Zolcsák, Ádám; Veres, Dániel Sándor; Lenti, Katalin; Miheller, Pál; Hegyi, Péter; Ábrahám, Szabolcs
End-to-end anastomosis provides similar quality-of-life, compared with other reconstructive techniques six months following total mesorectal excision: Systematic review and meta-analysis
EUROPEAN JOURNAL OF SURGICAL ONCOLOGY (2024) – IF: 2,9
Publication:35181225 Journal Article (Survey paper) Scientific
Journal subject: Scopus - Surgery Rank: D1
Journal subject: Scopus - Medicine (miscellaneous) Rank: Q1
Journal subject: Scopus - Oncology Rank: Q2
2. **Kávási, Sarolta Beáta;** Floria, Diana-Elena; Rancz, Anett; Sándor Veres, Dániel; Faluhelyi, Nándor; Miheller, Pál; Hegyi, Péter; Ábrahám, Szabolcs
Extralevator Abdominoperineal Excision Improves Overall Survival Compared to Standard Abdominoperineal Excision: A Systematic Review and Meta-Analysis **ANNALS OF GASTROENTEROLOGICAL SURGERY (2026) – IF: 3,3**
Publication:36886333
Journal subject: Scopus - Surgery Rank: D1
Journal subject: Scopus - Gastroenterology Rank: Q1

10.2. Publications not Related to the Thesis

1. Floria, Diana-Elena; Obeidat, Mahmoud; **Kávási, Sarolta Beáta;** Teutsch, Brigitta; Veres, Dániel Sándor; Hagymási, Krisztina; Hegyi, Péter; Drug, Vasile-Liviu; Erőss, Bálint
Systematic review and meta-analysis: proton pump inhibitors slightly decrease the severity of chronic cough
SCIENTIFIC REPORTS (2024) – IF: 3,9
Publication:34896347
Journal subject: Scopus - Multidisciplinary Rank: Q1

2. Floria, Diana-Elena; Obeidat, Mahmoud; Váncsa, Szilárd; **Kávási, Sarolta Beáta**; Földvári-Nagy, László; Hegyi, Péter; Veres, Dániel Sándor; Drug, Vasile-Liviu; Erőss, Bálint

Proton pump inhibitors are not associated with an increased risk of Clostridioides difficile infection: a systematic review and meta-analysis of randomized controlled trials

GUT MICROBES (2025) – IF: 11

Publication:36376104

Journal subject: Scopus - Gastroenterology Rank: D1

Journal subject: Scopus - Infectious Diseases Rank: D1

Journal subject: Scopus - Microbiology (medical) Rank: D1

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