A report on treatment options in advanced rectal carcinoma for Universitätsklinikum Schleswig-Holstein/Campus Kiel

Kleijnen Systematic Reviews Ltd

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LIST OF ABBREVIATIONS

AL	Anastomotic leakage
APR	Abdominoperineal resection
AR	Anterior resection
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
DFS	Disease-free survival
DS	Diverting stoma
DARE	Database of Abstracts of Reviews of Effects
FAQ	Frequently asked question
HA	Hartman procedure
HR	Hazard ratio
HTA	Health technology assessment
ISR	intersphincteric resection
KSR	Kleijnen Systematic Reviews Ltd
LAR	Low anterior resection
LARS	Low Anterior Resection Syndrome
LHP	Low Hartman procedure
MA	Meta-analysis
MD	Mean difference
ME	Mesorectal excision
N/A	Not applicable
NICE	National Institute for Health and Care Excellence (UK)
NR	Not reported
OR	Odds ratio
OS	Overall survival
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Transparent Reporting of Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomised controlled trial
RFS	Recurrence-free survival
RR	Risk ratio
SDM	Shared decision making
SF-36	Short form-36
SMD	Standardised mean difference
SP	Sphincter preservation
SPS	Sphincter-preserving surgery
SR	Systematic review
TME	Total mesorectal excision

UK	United Kingdom
UKSH	Universitätsklinikum Schleswig-Holstein
UAR	Ultra-low anterior resection

1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews Ltd (KSR) has prepared an evidence report with a synthesis of the evidence of the relevant treatment options for advanced rectal carcinoma: surgery with permanent colostoma or sphincter-preserving surgery (SPS).

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed with surgeons at Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. These questions reflect the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Systematic reviews (SRs), clinical practice guidelines (CPGs) and primary research papers evaluated in this report aim to inform clinicians, patients, researchers, and health policy makers on relevant evidence pertaining to surgery with permanent colostoma or sphincter-preserving surgery for patients with advanced rectal carcinoma.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients with rectal carcinoma in the lower/middle third of the rectum (up to 12 cm from the anocutaneous line)	Patients for whom one of the named options is not feasible due to a position or size of the tumour or due to comorbidities
Intervention/ comparator	1. a. Low (& potentially ultra-low) anterior resection or inters-phincteric resection with sphincter preservation with a temporary stoma by means of TME b. Stoma reversal/closure i.e., second surgery* 2. Low Hartmann Procedure (LHP) with permanent stoma by means of TME** 3. Miles surgery i.e., abdominoperineal resection (APR) with sphincter elimination and permanent stoma	Anterior resection
Outcomes	• Reoperation • Rehospitalisation rate • Length of hospitalisation • Local tumour recurrence • Recurrence of stoma (for 1a and 1b.) • Mortality • 30-days mortality • Quality of life • Long-term management of stoma • Anastomotic leakage (for 1a. and 1b.)	N/A

	Included	Excluded
	• Stoma-related complications (e.g., durability, hernia, dysfunction, infection, prolapse) • Infections e.g., pelvic sepsis, pelvis abscess, abdominal abscess • Other complications i.e., non-surgical (re)interventions • Low anterior resection syndrome	
Study design	Systematic reviews, clinical practice guidelines, primary research	Narrative reviews; expert opinions; letters' overviews of reviews
* = with restoring the natural colon passage ** = without restoring the natural colon passage Main focus of decision aid is on adults but KSR will check whether or not age and comorbidities are effect modifiers. KSR = Kleijnen Systematic Reviews N/A = not applicable; TME = total mesorectal excision		

2.2 FREQUENTLY ASKED QUESTIONS

The following frequently asked questions (FAQs) were identified:

1. What does the treatment involve?
2. Will I need a permanent stoma? If not: when will the temporary stoma be rediverted? Will I need another hospitalisation/surgery then?
3. How will treatment influence my tumour, i.e., oncological outcomes, risk for local tumour recurrence?
4. Will the treatment prolong my life?
5. What are the long-term and short-term risks or side effects-related to surgery and/or stoma, e.g., complications impacting current/further treatments?
6. Could complications impact current or further treatments?
7. How will treatment or potential complications impact my quality of life?

2.3 LITERATURE SEARCHES

Literature searches were conducted on 5 May 2021 to identify systematic reviews on sphincter-preserving surgery in patients with advanced rectal carcinoma, including colostomy and ileostomy. This updates a previous report conducted in December 2020, and extends its scope to include additional surgical procedures including Hartmann procedure and ileostomy reversal/closure (see also Table 3).

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range to 2015-2021. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched in May 2021 from 2015 to the most recent date available:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 5 of 12, May 2021
- KSR Evidence (Internet) (https://ksrevidence.com/): 2015 - 5.5.21
- Health Technology Assessment (HTA) database (https://www.crd.york.ac.uk/CRDWeb/): 2015 to 31 Mar 2018
- Epistemonikos (Internet) (https://www.epistemonikos.org/): 2015 - 5.5.21
- International HTA Database (Internet) (https://database.inahta.org/): 2015 - 5.5.21

The following resources were searched in December 2020 for the previous report. An update search of these resources was not considered to be necessary:

- Database of Abstracts of Reviews of Effects (DARE) (CRD): 2015 to 31 Mar 2015
- TRIP database (internet) (https://www.tripdatabase.com/): 2015-17/10/2020
- NICE Evidence (www.evidence.nhs.uk): 2015-17/12/2020
- NICE Guidance (www.nice.org.uk): 2015-17/12/2020
- ECRI Guidelines Trust (https://guidelines.ecri.org/): 2015-17/12/2020

Full details of all search strategies are presented in Appendix 1.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

For this evidence report, searches for systematic reviews, guidelines and/or primary studies were supplemented by targeted web searches to find information for the more narrative aspects of FAQs. The bibliographies of included studies and review articles were also checked for additional relevant articles.

2.5 STUDY SELECTION AND DATA EXTRACTION

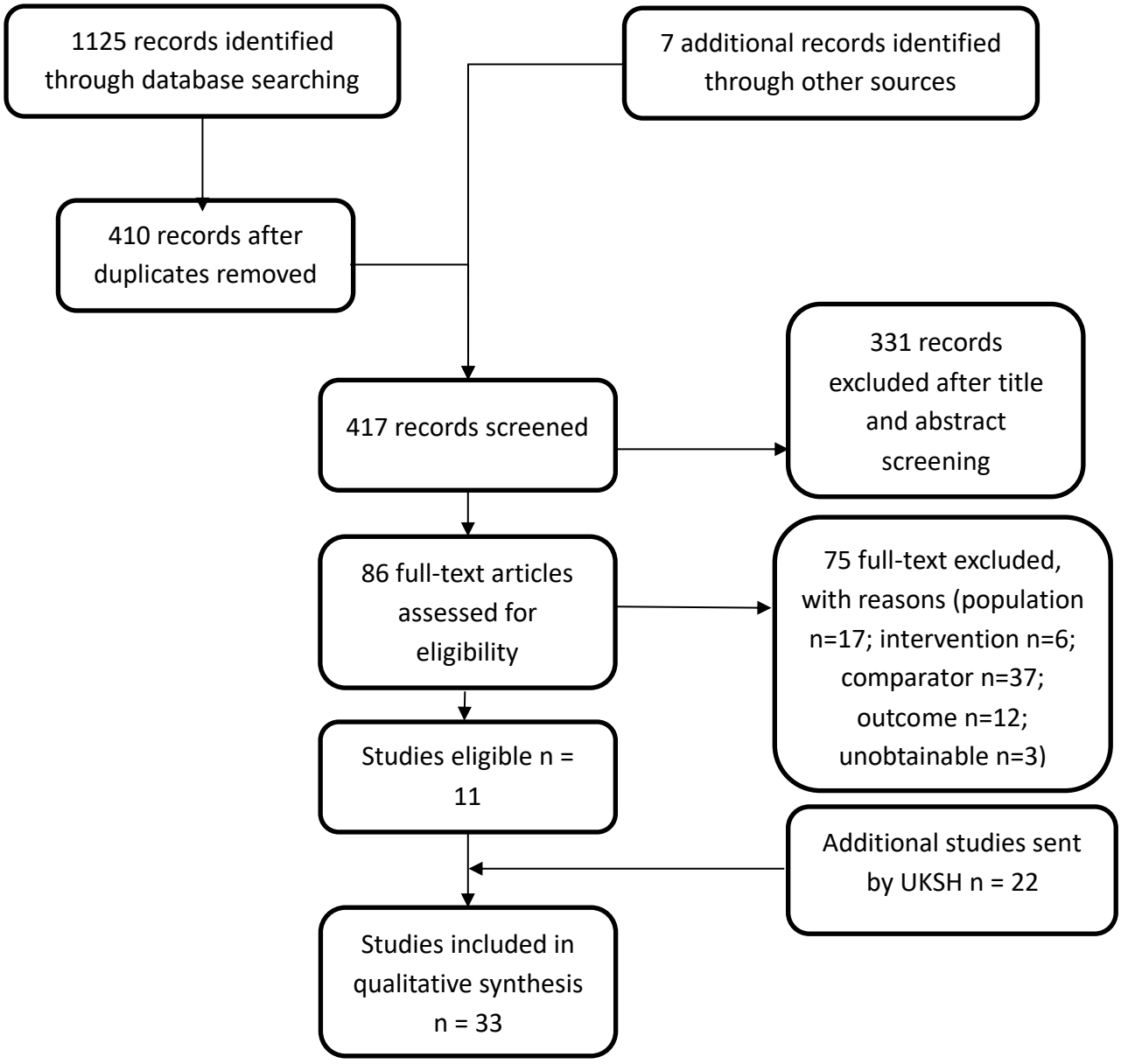
Titles and abstracts of all records identified by the electronic searches were screened by two independent reviewers with any disagreements settled through consensus. For potentially eligible studies, full-text versions were obtained, and screened by these same two independent reviewers against the pre-specified inclusion and exclusion criteria. For each study, one reviewer extracted the data, and another validated the entries. Again, any disagreements were resolved through discussion and consensus.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted in December 2020 (subsequently updated in May 2021) to identify all relevant SRs, HTAs, or CPGs as well as primary studies. Originally, a total of 352 records were retrieved from the electronic literature searches and 773 in May 2021; and seven identified through supplementary searches. After the removal of duplicate records, 417 titles and abstracts were screened by two reviewers. After screening of 86 full-text papers, eleven met the inclusion criteria. Twenty-two additional publications were provided by the UKSH team. Those mainly observational studies were not identified by our initial searches geared towards SRs, HTAs, or CPGs. A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[1]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Overall, fifteen systematic reviews (SRs), two clinical practice guidelines (CPGs), two randomised clinical trials (RCTs) and fourteen observational studies were eligible for inclusion. Table 2 summarises the sources of evidence used to answer the seven FAQs. The SRs and CPGs included mixed evidence from RCTs and observational studies. Quantitative evidence from direct comparisons, i.e. surgery with permanent colostoma or sphincter-preserving surgery was available to answer the FAQs 3, 4, 5 and 7. Quantitative evidence from indirect comparisons was available to answer the FAQs 1, 2, 5 and 6. FAQs 5 and 6 were conceptually similar and thus merged together.

Table 2: Evidence sources

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I need a permanent stoma? if not: when will the temporary stoma be rediverted? Will I need another hospitalisation/surgery then?	FAQ3: How will treatment influence my tumour? i.e., oncological outcomes, risk for local tumour recurrence?	FAQ4: Will the treatment prolong my life?	FAQ5: What are the both long and short-risks or side effects-related to surgery and/or stoma?	FAQ6: How far may complications impact current or further treatments?	FAQ7: How will treatment or potential complications impact my quality of life?
AWMF2019[2]	CPG	APR LAR	✓				✓	✓	
Arunachalam 2016[3]	SR	TME			✓		✓	✓	
Bazzel 2016[4]	SR	LAR (SPS)	✓						
Clausen 2021[5]	SR	AR or LAR early closure AR or LAR standard closure					✓	✓	
Cornish 2007[6]	SR	AR (SPS) APR							✓
Cong 2015[7]	SR	AR or LAR (SPS)					✓	✓	
Croese 2018[8]	SR	LAR (SPS)/Stoma					✓	✓	
Fernandez-Martinez 2020[9]	SR	APR							✓

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I need a permanent stoma? if not: when will the temporary stoma be rediverted? Will I need another hospitalisation/surgery then?	FAQ3: How will treatment influence my tumour? i.e., oncological outcomes, risk for local tumour recurrence?	FAQ4: Will the treatment prolong my life?	FAQ5: What are the both long and short-risks or side effects-related to surgery and/or stoma?	FAQ6: How far may complications impact current or further treatments?	FAQ7: How will treatment or potential complications impact my quality of life?
		LAR (SPS)							
Garg 2019[10]	SR	LAR (SPS)					✓	✓	
Holmgren 2017[11]	Obs. study	AR/SPS or permanent stoma					✓	✓	
Jonker 2016[12]	Obs. study	LAR (SPS) LHP					✓	✓	
Keane 2017[13]	SR	LAR (SPS)/Stoma					✓	✓	
Keane 2020[14]	SR	LAR (SPS)/Stoma					✓	✓	
Kim 2013[15]	Obs. study	APR LAR (SPS)				✓	✓	✓	
Kim 2021[16]	Obs. study	LAR (SPS)/Stoma					✓	✓	
Lee 2021[17]	Obs. study	APR LAR (SPS)					✓	✓	
Lindgren 2011[18]	RCT	LAR/ SPS or permanent stoma		✓					
Lozano 2015[19]	Obs.	AR (SPS)			✓	✓	✓	✓	

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I need a permanent stoma? if not: when will the temporary stoma be rediverted? Will I need another hospitalisation/surgery then?	FAQ3: How will treatment influence my tumour? i.e., oncological outcomes, risk for local tumour recurrence?	FAQ4: Will the treatment prolong my life?	FAQ5: What are the both long and short-risks or side effects-related to surgery and/or stoma?	FAQ6: How far may complications impact current or further treatments?	FAQ7: How will treatment or potential complications impact my quality of life?
	study	APR							
Mak 2017[20]	Obs. study	UAR (SPS)		✓					
Malik 2018[21]	SR	LAR/Stoma					✓	✓	
Molina Rodríguez 2011[22]	Obs. study	APR					✓	✓	
		LHP							
Montedori et al. 2010 [23]	SR	LAR (SPS)/Stoma					✓	✓	
NICE[24]	CPG	ME/SPS	✓						
Omidvari 2013[25]	Obs. study	APR			✓	✓			
		LAR (SPS)							
Pachler 2012[26]	SR	AR (SPS)	✓						✓
Peng 2020[27]	SR	APR				✓			
		LAR (SPS)							
Popiolek 2020[28]	Obs. study	APR				✓	✓		
		LHP							
Schneider 2016[29]	RCT	Stoma					✓	✓	

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I need a permanent stoma? if not: when will the temporary stoma be rediverted? Will I need another hospitalisation/surgery then?	FAQ3: How will treatment influence my tumour? i.e., oncological outcomes, risk for local tumour recurrence?	FAQ4: Will the treatment prolong my life?	FAQ5: What are the both long and short-risks or side effects-related to surgery and/or stoma?	FAQ6: How far may complications impact current or further treatments?	FAQ7: How will treatment or potential complications impact my quality of life?
Sverrisson 2015[30]	Obs. study	APR LHP				✓	✓		
Sverrisson 2018[31]	Obs. study	APR LHP				✓	✓		
Wang 2015[32]	SR	APR LAR (SPS)			✓	✓	✓		
Yeom 2017[33]	Obs. study	APR LAR (SPS)			✓				
Zeman 2020[34]	Obs. study	LAR (SPS)/Stoma					✓	✓	

APR = abdominoperineal resection; AR = anterior resection; CPG = clinical practice guidelines; LAR = low anterior resection; LHP = Low Hartman's procedure; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; Obs. study = observational study; RCT = randomised controlled trial; SP = sphincter preserving surgery; SR = systematic review; TME = total mesorectal excision; ; UAR = ultra-low anterior resection.

3.3 FAQ 1: What does the treatment involve?

This section covers the three treatment options of advanced rectal carcinoma. Two surgical options: both involving permanent colostomy, one of them being abdominoperineal resection (APR) (including elimination of sphincter and anus), the other one being the so-called low-Harmanns procedure (with sphincter and anus preservation). The third option is a sphincter-preserving surgery (low anterior resection/intersphincteric resection with sphincter preservation) that involves a protective stoma for a limited period of time. The protective stoma is also called diversion or temporary stoma. This type of stoma aims to reduce the risk of anastomotic leakage following the first surgery. To re-divert this type of stoma, a second surgery is required, i.e., stoma closure. All options are summarized in Table 3. It is worth emphasising that the type of surgery also depends on the location or size of the tumour as well as the existing comorbidities.[4] These two surgical options are described in Table 3.

Table 3: Description of treatments for advanced rectal carcinoma

Surgery with sphincter removal and end-stoma (Abdominoperineal Resection - APR)
Abdominoperineal resection (APR) is a surgical procedure that involves removal of the anus, the rectum and part of the sigmoid colon with affected cancerous cells.[4] This surgical technique is designed for all patients in whom sphincter preservation might be difficult and this surgery is a relevant treatment option especially in patients with deep tumour location (<3-4 cm from the aneocutaneous line).[24] The end of the remaining colon is brought out on the surface of the abdomen permanently as an opening, called a colostomy.[35] A stoma appliance is then worn at all times to collect stool and gas from the colostomy. The recovery time in a hospital following the APR ranges from five to seven days. In clinical practice, APR is performed by means of low anterior resection (LAR)/anterior resection (AR), or total mesorectal excision (TME)- all considered equally effective when compared with sphincter-preserving surgery described below.[2]
Sphincter preserving surgery with end-stoma (Low Hartmann Procedure – LHP)
The Hartmann procedure or low Hartman procedure (LHP) involves a tumour resection, creation of an end-stoma, and the distal rectal stump is closed by stapled sutures or hand-sewn (and the sphincter is preserved; and the resulting pouch becomes a blind segment of colon from the anus to the sealed stump).[28, 37] LHP remains a valid option when a low colorectal anastomosis is contraindicated because of previous faecal incontinence, advanced age, or extensive metastatic diffusion of the cancer.[22] Some surgeons prefer LHP to avoid the potentially lethal complication of anastomotic leakage.[12]
Sphincter-preserving surgery with temporary stoma and stoma re-diversion (SPS)
Sphincter-preserving surgery (SPS) includes removing the sigmoid colon and middle or upper rectum, with a low colorectal anastomosis (a surgical connection by stitching or stapling) to avoid a permanent colostomy.[4] The procedure has become the usual treatment for cancers of the low and mid rectum except for those cancers very close to

the anal sphincter.[26] It is performed by specially trained/experienced physicians under local or general anaesthesia.[2] The most common goals of SPS include local control, long-term survival, preservation of bladder, and sexual function; and maintenance or improvement in quality of life.[4] In clinical practice, SPS is performed by means of low anterior resection (LAR)/anterior resection (AR), intersphincteric resection (ISR), or total mesorectal excision (TME). A protective or diversion/temporary stoma is commonly performed during SPS to protect colorectal anastomosis form leaking; and both colostomy and/or ileostomy (the end of the small intestine brought out on the surface of the abdomen) are equally effective. Stoma closure is another operation performed to reverse the ileostomy or colostomy so that intestinal continuity of bowel movements is restored. The procedure (which involves incising the area around the stoma and reattaching the upper section to the remaining section of the colon) is carried out usually after at least 3 months (and up to a few years) following the initial colostomy surgery but this also depends on individual's health state.[36] Any information on the stoma system/type or position is given by the attending physician and a suitably trained nurse at the earliest convenience; self-help groups can be useful as well.[2]

3.4 FAQ 2: Will I need a permanent stoma despite sphincter-preserving surgery (SPS)?

This section explains whether a specific type of surgery, i.e. sphincter-preserving low anterior resection (LAR) is a risk factor for permanent stoma. Two studies provided quantitative data pertaining to this outcome, and both reported similar findings. One observational study (Mak et al. 2017) of 194 patients who underwent sphincter-preserving ultra-low anterior resection (UAR) for low rectal cancer evaluated the occurrence of permanent stoma over time and associated risk factors.[20] It reported that 23.7% of patients needed a permanent stoma following sphincter-preserving surgery (SPS) at a median follow-up of 15 months. Advanced disease, prior chemoradiotherapy, anastomotic-related complications (anastomotic leakage) and disease progression (local recurrence) were the main reasons for permanent stoma in these patients. The certainty of the evidence was very low for this FAQ due to high risk of bias and indirectness (see Table 4).

In a multicentre trial (Lindgren et al. 2011), 234 patients undergoing LAR (SPS) of the rectum were randomly assigned to a group with stomas (n=116) or a group without stoma (n=118).[18] The authors reported that overall, 19% (45/233) of the patients required a permanent stoma at a follow-up of 6 years. The certainty of the evidence was very low due to high risk of bias and indirectness (see Table 4).

Table 4: FAQ 2 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Need for permanent stoma							
Mak 2017[20]	1 (Obs. study)	15 months^	46/194 (23.7%) UAR (SPS)	Inestimable	Inestimable	Very low (high risk of bias and indirectness)	
Lindgren 2011[18]	1 RCT	72 months (range: 42–108)	45/233 (19.4%) LAR with stoma	188/233 (80.6%) LAR without stoma	Inestimable	Very low (high risk of bias and indirectness)	Difference in favour of stoma but data of low quality ⇩

^ median value
CI = confidence interval; Obs. study = observational study; RCT = randomised controlled trial; SPS = sphincter-preserving surgery; UAR = ultra-low anterior resection

3.5 FAQ 3: How will treatment influence my tumour?

This section explains how specific types of surgery, i.e. LAR or APR will influence the patients' tumour; and whether the surgery influences the risk for local tumour recurrence.

Local recurrence

The systematic review by Wang et al. 2015 searched six electronic databases and included studies of any design comparing APR and LAR (SPS).[32] It included 10 observational studies (for this outcome/FAQ) in the meta-analysis. Risk of bias was assessed using the Cochrane risk of bias tool for randomised controlled trials (RCTs) which was not appropriate for observational study designs. They reported higher odds of local recurrence following APR (13.2%) compared with LAR (8.7%) (odds ratio (OR) = 1.67; 95% confidence interval (CI) 1.27 to 2.20) at five years follow-up. The certainty of the evidence was low for this FAQ due to high risk of bias (see Table 5). One multicentre observational study compared oncologic outcomes of 1,343 patients who underwent AR (SPS) (n=973) or APR (n=370) for low rectal cancer.[19] Based on Cox regression analysis, they reported no difference in local cancer recurrence between AR and APR at 60 months follow-up (hazard ratio (HR) = 1.68; 95% CI 0.87 to 3.23). Arunachalam et al. 2016 aimed to evaluate the evidence regarding technical parameters, oncological outcomes, morbidity, and mortality after TME.[3] They searched two electronic databases and included cohort studies of TME. The review included 15 studies with a total of 449 patients. Risk of bias was assessed using the Newcastle-Ottawa scale. The authors reported 4 local recurrences (1.5%) and 12 patients (5.6%) with metastatic disease.[3] The certainty of the evidence was low or very low for this FAQ due to high risk of bias and imprecision or indirectness (see Table 5).

Table 5: FAQ 3 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Local recurrence							
Arunachalam 2016[3]	15 observational studies	Median= 14.7	4 (2.5%) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
Wang 2015[32]	10 observational studies	5 years	295/2,234 (13.2%) APR	336/3,820 (8.8%) LAR (SPS)	OR = 1.67; 95% CI 1.27 to 2.20^^	Low (high risk of bias)	Difference in favour of LAR but data of low quality ⇗
Lozano 2015[19]	1 observational study	60 months	APR (inestimable)	AR (SPS) (inestimable)	HR = 1.68; 95% CI 0.87 to 3.23^	Very low (high risk of bias; imprecision)	No difference shown ⇔

^ = Cox regression analysis; also patients with low and mid rectal cancer were included. ^^ = own re-calculation with RevMan 5.4.1 (please refer to Appendix 2). APR = abdominoperineal resection; AR = anterior resection; CI = confidence interval; LAR = low anterior resection; OR = odds ratio; TME = total mesorectal excision; SPS = sphincter-preserving surgery

3.6 FAQ 4: WILL THE TREATMENT PROLONG MY LIFE?

This section explains whether specific types of surgery, i.e. surgery with permanent colostoma or sphincter-preserving surgery will prolong patients' lives using mainly direct evidence.

Disease free survival (DFS)

One retrospective study compared local control and survival rates following APR or LAR (SPS) in 153 patients with newly histologically diagnosed adenocarcinoma located at low and middle third of the rectum.[25] Based on log rank test, the study authors reported no difference in DFS between LAR and APR at five years follow-up 54.4% versus 60.7%, respectively. The certainty of the evidence was very low in this study due to high risk of bias and imprecision (see Table 6).

Another retrospective study compared oncologic outcomes following APR or LAR (SPS) in 804 patients with adenocarcinoma of the rectum (≤ stage III), a distal tumour margin located within 6 cm of the anal verge, an Eastern Cooperative Oncology Group performance status of 0 or 1.[15] The authors reported no difference in DFS between LAR and APR at five years follow-up 83% versus 75.1% respectively based on very low certainty of the evidence (see Table 6).

In this SR, Peng et al. 2020 aimed to compare the outcomes of APR and LAR (SPS).[27] The authors searched three electronic databases and included all comparative studies. The SR and MA included 12 studies with a total of 2438 patients. Risk of bias was assessed using the Newcastle-Ottawa scale. The authors reported no difference between APR and LAR in disease free survival at 5 years follow-up (HR = 0.98; 95% CI 0.79 to 1.20) based on very low certainty of the evidence (see Table 6).[27]

Overall survival (OS)

One retrospective study reported no difference in OS between LAR (SPS) and APR at five years follow-up 68.7% versus 84% respectively.[25] The certainty of the evidence was very low in this study due to high risk of bias and imprecision (see Table 6).

By pooling data from 11 observational studies, Wang et al. 2015 reported lower mortality following APR (62.2%) compared with LAR (SPS) (70.6%) (OR = 0.58; 95% CI 0.44 to 0.77) at five years follow-up.[32] The certainty of the evidence was low for this FAQ due to high risk of bias and heterogeneity (see Table 6).

Kim et al. 2013 reported no differences in OS between LAR (SPS) and APR at five years follow-up 87.7% versus 83% respectively.[15] This was based on very low certainty of the evidence (see Table 6).

Lozano et al. 2015 reported no difference in OS in APR compared with AR (SPS) at 60 months follow-up (HR = 1.37; 95% CI 1.00 to 1.86).[19] The certainty of the evidence was very low for this FAQ due to high risk of bias and imprecision (see Table 6).

Peng et al. 2020 also reported no difference between APR and LAR (SPS) in overall survival at 5 years follow-up (HR = 1.12; 95% CI 0.70 to 2.14) based on very low certainty of the evidence (see Table 6).[27]

Recurrence-free survival (RFS)

Yeom et al. 2017 retrospectively reviewed the medical records of 409 patients with very low rectal cancer (i.e., tumours within 3 cm from the anal verge) undergoing LAR (SPS) and APR.[33] The authors reported that the mode of surgery did not affect the recurrence type at five years (APR 84.2% versus 70.2% LAR). The certainty of the evidence was very low due to high risk of bias and imprecision (see Table 6).

Table 6: FAQ 4 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Disease free survival							
Omidvari 2013[25]	1 observational study	5 years	(60.7%) APR	(54.4%) LAR (SPS)	RR = 0.83; 95% CI 0.53 to 1.29^^	Very low (high risk of bias and imprecision)	No difference shown ⇔
Kim 2013[15]	1 observational study	5 years	(75.1%) APR**	(83.1%) LAR (SPS)**	Inestimable	Very low (high risk of bias and imprecision)	No difference shown ⇔
Peng 2020[27]	8 observational studies	5 years	APR (inestimable)	LAR (SPS) (inestimable)	HR = 0.98; 95% CI 0.79 to 1.20	Very low (high risk of bias, inconsistency)	No difference shown ⇔
Overall survival							
Omidvari 2013[25]	1 observational study	5 years	(84%)* APR	(68.7%)* LAR (SPS)	RR = 0.53; 95% CI 0.25 to 1.12^^	Very low (high risk of bias and imprecision)	No difference shown ⇔
Wang 2015[32]	11 observational studies	5 years	1,769/2,844 (62.2%) APR	2,615/3700 (70.7%) LAR (SPS)	OR = 0.58; 95% CI 0.44 to 0.77^^	Low (high risk of bias and inconsistency)	Difference in favour of APR but data of low quality ⇗
Kim 2013[15]	1 observational study	5 years	(83%) APR**	(87.7%) LAR (SPS)**	Inestimable	Very low (high risk of bias and imprecision)	No difference shown ⇔
Lozano 2015[19]	1 observational study	60 months	APR (inestimable)	AR (SPS) (inestimable)	HR = 1.37; 95% CI 1.00 to 1.86^	Very low (high risk of bias; imprecision)	Difference in favour of AR but data of very low

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
							quality ⇗
Peng 2020[27]	8 observational studies	5 years	APR (inestimable)	LAR (SPS) (inestimable)	HR = 1.12; 95% CI 0.70 to 2.14	Very low (high risk of bias, inconsistency)	No difference shown ⇔
Recurrence-free survival							
Yeom 2017[33]	1 observational study	5 years	APR (84.2%)	(70.2%) LAR (SPS)	Inestimable	Very low (high risk of bias and imprecision)	No difference shown ⇔

* = percentages are predictive values based on Kaplan–Meier estimator; ** = includes all cancer stages; ^ = Cox regression analysis; ^^ = own re-calculation with RevMan 5.4.1 (please refer to Appendix 2). APR = abdominoperineal resection; AR = anterior resection; CI = confidence interval; HR = hazard ratio; LAR = low anterior resection; NR = not reported; OR = odds ratio; RR = risk ratio; SPS = sphincter-preserving surgery

3.7 FAQ 5 & 6: What are the long-term and short-term risks or side effects-related to surgery and/or stoma, e.g. complications impacting current/further treatments?

This section discusses long-term and short-term risks or side effects related to all types of surgeries and/or stoma using both direct and indirect evidence. Surgery and stoma types are directly related to each other. In general, different surgeries lead to different types of stoma, i.e., APR leads to a permanent stoma (the anal sphincter is being removed) whereas SPS (the anal sphincter is being preserved) in most instances (but not always, depending on a surgeons' preference and specific surgery situation) is done with a diversion stoma. It is a temporary type of stoma that prevents the occurrence of anastomotic leakage (described below) by diverting the faecal stream and keeping the anastomosis free of faecal material.[23] Stoma reversal/closure is another operation performed to reverse that temporary stoma so that intestinal continuity of bowel movements is restored.

Anastomotic leakage (AL) following SPS and diversion stoma

Cong et al. 2015 aimed to systematically review studies of AL requiring laparotomy and the associated rate of diverting stoma (DS) in anterior resection (AR) or LAR (SPS) for rectal cancer.[7] The authors searched Medline for articles published since 2000 and included 37 mainly observational studies. The quality of the primary studies was not critically appraised. The authors reported no differences between the two procedures in reducing AL (OR=1.12; 95% CI 0.99 to 1.27). However, there was a higher number of deaths (following anastomotic leakage) in AR (1.1%) compared with LAR (0.35%, for combined estimates of DS and no-DS).[7] It is also worth noting that diversion stoma is often recommended to avoid AL.[2] The certainty of the evidence was low for this FAQ due to high risk of bias and inconsistency (see Table 7).

The systematic review by Garg et al. 2019 searched the literature up to October 2016 and included randomised controlled trials (RCTs) that compared DS with no stoma (no-DS) in LAR of the rectum.[10] Risk of bias was not critically assessed. The authors included four RCTs and concluded there were lower rates of AL following DS compared with no-DS (RR=0.26; 95% CI 0.15 to 0.45). The certainty of the evidence was low for this FAQ due to unclear risk of bias and indirectness (see Table 7).

The systematic review by Montedori et al. 2010 [23] aimed to determine the efficacy of protective diversion stoma in LAR for rectal carcinoma. Three databases (Medline, Embase and the Cochrane Library) for RTCs comparing the use of stoma versus no-stoma. When compared with controls, the use of stoma was associated with less anastomotic leakage (RR=0.33; 95% CI 0.21 to 0.53). The certainty of the evidence was low for this FAQ due to unclear or high risk of bias and indirectness (see Table 7).

Arunachalam et al. 2016 reported that 7.3% of patients undergoing TME had anastomotic leakage at median follow-up of 14.7 months. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

The SR by Clausen et al. 2021 [5] aimed to evaluate the safety of early ileostomy closure compared with standard closure in patients undergoing AR or LAR (SPS). Three databases (Medline, Embase and the Cochrane Library) and three trial registers were searched for RTCs comparing early ileostomy closure versus standard closure. Risk of bias was assessed using the Cochrane risk of bias tool for randomised controlled trials (RCTs). Data from 6 RCTs were pooled, and no differences between early ileostomy closure versus standard closure in reducing the risk of anastomotic leakage were found (RR= 0.96; 95% CI 0.38 to 2.46). The certainty of the evidence was very low for this outcome due to unclear or high risk of bias and imprecision (see Table 7).

In their observational study, Zeman et al. 2020 assessed the risk of permanent stoma after LAR in 286 rectal cancer patients with or without loop ileostomy.[34] The authors reported lower risk of anastomotic leakage following DS compared with patients without DS (5% vs 23.8%; OR = 0.17; 95% CI 0.06 to 0.44).[34] The certainty of the evidence was low for this outcome due to high risk of bias and imprecision (see Table 7).

Reoperation

Cong et al. 2015 reported that there were higher odds of reoperation following anastomotic leakage in AR (SPS) (6.5%) compared with LAR (SPS) (4.2%) (OR= 1.60; 95% CI 1.35 to 1.90).[7] The certainty of the evidence was very low for this FAQ due to high risk of bias and inconsistency (see Table 7). Garg et al. 2019 reported that there were lower reoperation rates in LAR of the rectum following DS compared with no-DS (risk ratio (RR) = 0.33; 95% CI 0.21 to 0.51). The certainty of the evidence was low for this FAQ due to unclear risk of bias and indirectness (see Table 7).

Montedori et al. 2010 reported that when compared with controls, the use of diversion stoma was associated with lower reoperation rates (RR=0.28; 95% CI 0.17 to 0.48).[23] The certainty of the evidence was low for this FAQ due to unclear or high risk of bias and indirectness (see Table 7).

In their observational study, Molina Rodríguez et al. 2011 aimed to compare the postoperative outcomes of a series of patients with low rectal cancer who have undergone either low Hartmann resection (LHP) or APR.[22] Of 172 patients, 41 underwent LHR (23.8%) and 131 underwent APR (76.2%) and were included the analysis. The authors reported lower risk of reoperations following APR compared with LHP at 60 days follow-up (3.8% vs 14.6%; OR = 4.32; 95% CI 1.24 to 15.00).[22] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

In their observational study, Popiolek et al. 2020 aimed to compare LHP with intersphincteric APR, in patients operated with total mesorectal excision for mid-rectal cancer.[28] Of 64 patients 34 underwent LHP (53.1%) and 30 underwent APR (46.9%) and were included the analysis. Similarly, the authors reported lower risk of reoperations following APR compared with LHP at follow-ups ranging from 3 to 24 months (3% vs 24%;

OR = 8.92; 95% CI 1.04 to 76.24).[28] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

In their observational study, Jonker et al. 2016 aimed to assess whether avoiding an anastomosis by performing LHP is associated with lower complication rates than LAR (SPS) with and without diversion ileostomy.[12] Of 4288 patients, 1194 (27.8%) underwent LHR and 866 (20.1%) had LAR without diversion ileostomy and the remaining 2228 (51.9%) had LAR with diversion ileostomy. The authors reported higher risk of reoperations following LAR without diversion ileostomy compared with LHP (16.5% vs 7.3%; OR = 2.56; 95% CI 1.92 to 3.41); but no difference between LHP and LAR with diversion ileostomy (OR = 1.12; 95% CI 0.85 to 1.47).[12] The certainty of the evidence was low for this outcome due to high risk of bias (see Table 7).

The SR by Clausen et al. 2021 [5] found no differences between early ileostomy closure compared with standard closure (RR= 1.35; 95% CI 0.62 to 2.96). The certainty of the evidence was very low for this FAQ due to unclear or high risk of bias and imprecision (see Table 7).

In their observational study, Sverrisson et al. 2015 aimed to report postoperative complications and analyse risk factors in rectal cancer patients operated with LHP. [30] Of 624 patients, 64% underwent AR (SPS), 25% had APR and 11% had LHR. The authors found no differences in reoperations between APR and LHP (7% vs 4%; OR = 0.61; 95% CI 0.17 to 2.26) based on very low certainty evidence.

Arunachalam et al. 2016 reported that 7.5% of patients undergoing TME had reoperations at median follow-up of 14.7 months. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

Metastases

Kim et al. 2013 reported no difference between APR compared with LAR (SPS) in the incidence of lung metastases.[15] This was based on very low certainty of the evidence (see Table 7).

Lozano et al. 2015 reported no differences between APR and AR (SPS) in reducing metastases at 60 months follow-up (HR = 1.31; 95% CI 0.98 to 1.76).[19] The certainty of the evidence was very low for this FAQ due to high risk of bias and imprecision (see Table 7).

Arunachalam et al. 2016 reported that 7.9% of patients undergoing TME had distant metastases at median follow-up of 14.7 months. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

Deaths

Lozano et al. 2015 reported no differences between APR and AR (SPS) in reducing mortality rates at 60 months follow-up 2.9% versus 4.8% respectively (OR = 0.60; 95% CI 0.33 to

1.10).[19] The certainty of the evidence was very low for this FAQ due to high risk of bias and imprecision (see Table 7).

30-days mortality

Popiolek et al. 2020 reported no deaths at 30-days following either APR or LHP.[28] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Jonker et al. 2016 reported lower risk of mortality at 30-days following LAR with or without diversion ileostomy compared with LHP (OR = 0.40; 95% CI 0.25 to 0.65) and (0.39; 95% CI 0.20 to 0.77) respectively.[12] The certainty of the evidence was low for this outcome due to high risk of bias (see Table 7).

In their observational study, Sverrisson et al. 2018 aimed to describe the postoperative surgical complications in patients with rectal cancer undergoing Hartmann's procedure.[31] Of 10,940 patients, 13% underwent the procedure (62% had LHR). The authors reported that 53 patients (4%) died at 30 days. There was no comparator group for this outcome. The certainty of the evidence was very low for this outcome due to high risk of bias (see Table 7).

Sverrisson et al. 2015 found no differences in 30-days mortality between APR and LHP (0% vs 3%; OR = 11.81; 95% CI 0.56 to 249.39) based on very low certainty evidence. [30]

Arunachalam et al. 2016 reported that 0.2% of patients undergoing TME died at 30-days. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

60-days mortality

Molina Rodríguez et al. 2011 reported no differences in 60-days mortality between APR and LHP (3% vs 7.3%; OR = 2.51; 95% CI 0.54 to 11.69).[22] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

90-days mortality

Popiolek et al. 2020 reported no differences in 90-days mortality between APR and LHP (0% vs 3%; OR = 2.73; 95% CI 0.11 to 69.60).[28] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Sverrisson et al. 2018 reported that 87 patients (6%) died at 90 days following Hartman's procedure. There was no comparator group for this outcome. The certainty of the evidence was low for this outcome due to high risk of bias (see Table 7).

Length of hospital stay

Peng et al. 2020 reported shorter length of hospital stay (in days) following LAR (SPS) compared with APR (MD = -2.98; 95% CI -3.54 to -2.43 shorter) based on very low certainty of the evidence (see Table 7).[27]

Popiolek et al. 2020 reported shorter length of hospital stay (in days) following APR compared to Hartman's procedure (MD = -4.30; 95% CI -8.52 to -0.08 shorter).[28] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Molina Rodríguez et al. 2011 reported no differences in length of hospital stay (in days) between APR and LHP (MD = -0.20 in days; 95% CI -3.43 to 3.03).[22] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Jonker et al. 2016 reported no differences in length of hospital stay following LAR with or without diversion ileostomy compared with LHP.[12] The certainty of the evidence was low for this outcome due to high risk of bias (see Table 7).

Arunachalam et al. 2016 reported a median length of hospital stay of 7.3 days (range: 3-41) following TME. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

Surgical complications

By pooling data from seven observational studies, Wang et al. 2015 reported higher risk of complications following APR (24.1%) compared with LAR (SPS) (22.9%) (RR = 1.09; 95% CI 1.03 to 1.15) at five years follow-up.[32] However, caution is advised when interpreting these analyses as there were several inconsistencies in the primary analyses by Wang et al. 2015.[32] The certainty of the evidence was very low for this FAQ due to high risk of bias (see Table 7).

Schneider et al. 2016 aimed to determine risk factors for operative revision after ileostomy closure; and reported an additional post hoc analysis of a prospective trial.[29] The authors reported that six out of 114 patients (5.3%) required an immediate reoperation (small bowel perforation, complete bowel obstruction, anastomotic leakage, postoperative ileus, deep wound infection) due to surgical complications directly related to the ileostomy reversal.[29]

Sverrisson et al. 2015 reported higher risk of complications i.e., mainly perineal wound infections, pelvic hematoma, pelvic abscess following APR compared with LHP (32% vs 13%; OR = 3.15; 95% CI 1.45 to 6.84) based on very low certainty evidence.[30]

Overall complications

Sverrisson et al. 2018 reported that 41% of patients suffered from overall complications. There was no comparator group for this outcome; and the length of follow-up was not reported. The certainty of the evidence was very low for this outcome due to high risk of bias (see Table 7).

Peng et al. 2020 reported lower complications rate following LAR (SPS) compared with APR (OR = 0.76; 95% CI 0.59 to 0.99) based on very low certainty of the evidence (see Table 7).[27]

Holmgren et al. 2017 investigated the permanent stoma prevalence, factors influencing stoma outcome and complication rates following stoma reversal surgery.[11] This was an observational study carried out between 2007 and 2013 using the Swedish Colorectal Cancer Registry. The authors reported an overall complications rate of 31% (71/229) following stoma reversal at a median follow-up of 1331 days.[11] Those complications included bowel obstruction, anastomotic failure, intra-operative complications, incisional hernia, cardiac arrest, respiratory insufficiency, stroke, sepsis or/and abscess formation. The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Pelvic abscess

Popiolek et al. 2020 reported no differences between APR compared to Hartman's procedure in pelvic abscesses (10% vs 21%; OR = 0.43; 95% CI 0.10 to 1.83) at follow-up ranging form 3-24 months.[28] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Molina Rodríguez et al. 2011 reported lower rate of pelvic abscess following APR compared to LHP at 60-days follow-up (OR = 0.23; 95% CI 0.06 to 0.89).[22] The certainty of the evidence was very low for this outcome due to high risk of bias and imprecision (see Table 7).

Sverrisson et al. 2015 reported slightly elevated risk of pelvic abscess following LHP compared with APR (OR = 0.21; 95% CI 0.02 to 2.38) based on very low certainty evidence.[30]

Arunachalam et al. 2016 reported that 6.8% of patients had pelvic abscess following TME. There was no comparison group for this outcome.[3] The certainty of the evidence was very low for this outcome due to high risk of bias and indirectness (see Table 7).

Intra-abdominal abscess or infections

Jonker et al. 2016 reported lower rate of pelvic abscess following LAR with or without diversion ileostomy compared with LHP (OR = 0.53; 95% CI 0.38 to 0.73; and OR = 0.43; 95% CI 0.27 to 0.69).[12] The certainty of the evidence was low for this outcome due to high risk of bias (see Table 7).

Sverrisson et al. 2018 reported that 122 patients (8%) had pelvic abscess following LHP. There was no comparator group for this outcome. The certainty of the evidence was very low for this outcome due to high risk of bias (see Table 7).

Malik et al. 2018 undertook a SR of RCTs reporting the incidence of stoma related complications in adults.[21] Three electronic databases (Medline, CINAHL and the Cochrane Library) were searched for relevant literature. The authors included a total of 18 trials, involving 1,009 patients (majority with colorectal cancer). The incidence of stoma related complications ranged from 2.9% to 81.1%; and was the highest for end colostomy median 62.6% (range: 2 to 100), compared with median 14.3% (range: 2.9 to 62.2) for loop ileostomy and median 26.3% (range: 13.9 to 100) for loop colostomy. Peristomal skin complications were more common in loop colostomy and loop ileostomy (32.3%; range: 18.4 to 46.2 in loop colostomy, and 14.0%; range: 5.6 to 37.8% in loop ileostomy) compared

to end colostomy (3,6%; range: 2.4 to 4.8%). Parastomal hernia (median=59.3%; range: 41.5 to 88.2) on the other hand, a complication that usually occurs after the first postoperative month, was the most common complication for end colostomy (59.3%; range: 41.5 to 88.2%). This complication was only 2,4% (range: 0 to 13,3%) in loop ileostomy and 0% (range: 0 to 5,6%) in loop colostomy. Another complication seemed also more common in end colostomy compared to loop ileostomy: stoma ischaemia (0%; range: 0 to 3.3% in loop ileostomy compared to 5.9%; range: 2.0 to 7.3% in end colostomy or 2.6%; range: 2.6 to 2.6% in loop colostomy). For stoma prolapse, there was higher a higher incidence following loop colostomy (7.9%; range: 5.6 to 41%) compared with end colostomy (4.1%; range: 3.2 to 4.9%) or loop ileostomy (0%; range: 0 to 5.4%). Other complications seemed similar in both groups: stoma retraction and stoma stenosis all in the median range between 0 and 5%. Early complications, such as high output stoma, peristomal irritation, stoma infection, ischaemia and retraction, typically occur within one month of surgery. Parastomal hernia, stoma prolapse and stenosis are examples of late complications, which tend to occur after the first postoperative month. These conditions may impact on quality of life or even require further surgery.

Low Anterior Resection Syndrome (LARS) following SPS

Low Anterior Resection Syndrome (LARS) which may follow SPS can be defined as a myriad of symptoms including incontinence, frequency, urgency, or feelings of incomplete emptying, all adversely impacting (QoL).[8] Croese et al. 2018 summarised the reported prevalence and risk factors of LARS which includes incontinence (to faeces and flatus), urgency, diarrhoea, frequency and clustering of bowel motions.[8] They reported the estimated prevalence of major LARS of 41% (95% CI 34-48; 11 studies) at more than 12 months follow-up.[8] A low anastomotic height or history of radiotherapy were found to be major risk factors, however only studies using the LARS score were included in their review. The LARS score is a validated scoring system which considers impact of bowel dysfunction (incontinence for flatus, incontinence for liquid stools, frequency, clustering, and urgency) on patients' overall quality of life.[8] A range between 30 to 42 indicates major LARS, 21 to 29 indicates minor LARS, and less than 21 indicates no LARS.

The SR by Keane et al. 2017 aimed to describe the instruments and outcome measures used in studies of bowel dysfunction after LAR (SPS) and identify major themes used in the assessment of LARS.[13] The authors searched Medline, Embase, CINAHL, and Cochrane Library for publications between 1986 and July 2016. One hundred and twenty-eight studies were included in the synthesis. The review found a substantial variation in the reporting of functional outcomes after LAR. Of those 128 studies, most frequently reported outcomes were incontinence (97%), stool frequency (80%), urgency (67%), evacuatory dysfunction (47%), gas–stool discrimination (34%) and a measure of QoL (80%).[13] The authors concluded that most studies have focused on incontinence, omitting other symptoms that correlate with patients' quality of life (adversely affected by LARS).[13]

The SR by Keane et al. 2020 aimed to compare bowel function and QoL outcomes between patients undergoing LAR with and without the formation of a diverting ileostomy.[14] The authors searched Medline, Embase, Scopus, CINAHL, and Cochrane Library for publications between 2007 and 2018; and included seven studies (of those three RCTs) of variable, mainly low quality. The authors reported higher risk of major LARS following diversion ileostomy compared with no ileostomy (OR = 1.96; 95% CI 1.10 to 3.48.[14] The certainty of the evidence was low for this outcome due to high risk of bias and imprecision (see Table 7).

In their observational study, Kim et al. 2021 aimed to identify risk factors associated with LARS.[16] Two hundred and eighty-three patients who underwent AR, LAR or ISR for colorectal cancer with a median follow-up of 24 months were analysed. The authors found that LARS was prevalent in 43.3% of patients; and the more severe the symptoms of LARS, the lower global health status, QoL, or emotional function were reported.[16] Preoperative radiotherapy, low anastomosis, and complications were independent risk factors for LARS.[16]

Patients' preferences

Because SPS can be associated with the above-described LARS, there is a few patients who prefer APR to LAR (SPS). In their qualitative study, Lee et al. 2021 included ambulatory patients without colorectal cancer at a single high-volume academic colorectal referral centre (patients with prior stoma or cancer were excluded).[17] Participants were presented with a hypothetical scenario describing a low rectal cancer and their preferences for functional and oncologic outcomes following APR and SPS were recorded. APR was the preferred option in 18% of patients owing to the impairments in anorectal function associated with LARS.

Table 7: FAQs 5 and 6 – Evidence synthesis

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Anastomotic leakage							
Arunachalam 2016[3]	15 observational studies	Median= 14.7	(7.3%) TME[$]	None	Inestimable	Very low (high risk of bias and indirectness)	
Clausen 2021[5]	6 (RCTs)	NR	9/269 (3.3%) AR or LAR (SPS) early closure	9/259 (3.4%) AR or LAR (SPS) standard closure	RR= 0.96; 95% CI 0.39 to 2.39*	Low (unclear or high risk of bias and imprecision)	No difference shown ⇔
Cong 2015[7]	15+22 (RCTs and observational studies)	NR	1,222/12,376 (9.9%) for AR (SPS)	338/3,802 (8.9%) for LAR (SPS)	OR=1.12; 95% CI 0.99 to 1.27*	Low (high risk of bias and high heterogeneity)	No difference shown ⇔
Garg 2019[10]	4 (RCTs)	NR	13/356 (3.7%) for LAR (SPS) with DS	52/334 (15.6%) for LAR (SPS) without DS	RR=0.26; 95% CI 0.15 to 0.45	Low (unclear risk of bias and indirectness)	Difference in favour of DS but data of low quality ⇗
Montedori 2010 [23]	6 (RCTs)	NR	21/332 (6.3%) LAR (SPS) with DS	62/316 (19.6%) LAR (SPS) without DS	RR=0.33; 95% CI 0.21 to 0.53	Low (unclear or high risk of bias and indirectness)	Difference in favour of DS but data of low quality ⇗
Zeman 2020[34]	Observational study	Range: 46-50 months	5/101 (5%) LAR (SPS) with DS	44/185 (23.8%) LAR (SPS) without DS	OR = 0.17; 95% CI 0.06 to 0.44*	Very low (high risk of bias and imprecision)	Difference in favour of DS but data of very low quality

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
							⇗
Reoperation							
Cong 2015[7]	15+22 (RCTs and observational studies)	NR	813/12,376 (6.6%) for AR (SPS)	160/3,802 (4.2%) for LAR (SPS)	OR= 1.60; 95% CI 1.35 to 1.90*	Very low (unclear risk of bias and high heterogeneity)	Difference in favour of LAR but data of very low quality ⇗
Garg 2019[10]	5 (RCTs)	NR	23/390 (5.9%) for LAR (SPS) with DS	69/378 (18.3%) for LAR (SPS) without DS	RR=0.33; 95% CI 0.21 to 0.51	Low (unclear risk of bias and indirectness)	Difference in favour of LAR with DS but data of low quality ⇗
Montedori et al. 2010 [23]	6 (RCTs)	NR	13/332 (3.9%) LAR (SPS) with DS	51/316 (16.1%) LAR (SPS) without DS	RR=0.28; 95% CI 0.17 to 0.48	Low (unclear or high risk of bias and indirectness)	Difference in favour of DS but data of low quality ⇗
Molina Rodríguez 2011[22]	1 observational study	60 days	5/131 (3.8%) APR	6/41 (14.6%) LHP	OR = 4.32; 95% CI 1.24 to 15.00*	Very low (high risk of bias; imprecision)	Difference in favour of APR but data of very low quality ⇗
Popiolek 2020[28]	1 observational study	3 and 24 months	1/30 (3%) APR	8/34 (24%) LHP	OR = 8.92; 95% CI 1.04 to 76.24*	Very low (high risk of bias; imprecision)	Difference in favour of APR but data of very low quality ⇗

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Jonker 2016[12]	1 observational study	NM	139/866 (16.5%) LAR (SPS) without DS	83/1194 (7.3%) LHP	OR = 2.56; 95% CI 1.92 to 3.41*	Low (high risk of bias)	Difference in favour of LHP but data of low quality ⇗
Jonker 2016[12]	1 observational study	NM	172/2228 (8.1%) LAR (SPS) with DS	83/1194 (7.3%) LHP	OR = 1.12; 95% CI 0.85 to 1.47*	Low (high risk of bias)	No difference shown ⇔
Clausen 2021[5]	6 (RCTs)	NR	16/269 (5.9%) AR or LAR early closure	10/259 (3.8%) AR or LAR standard closure	RR= 1.35; 95% CI 0.62 to 2.96	Low (unclear or high risk of bias and imprecision)	No difference shown ⇔
Sverrisson 2015[30]	1 observational study	NR	11/159 (7%) APR	3/69 (4%) LHP	OR = 0.61; 95% CI 0.17 to 2.26*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Arunachalam 2016[3]	15 observational studies	Median= 14.7	34 (7.5%) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
Metastases							
Kim 2013[15]	1 observational study	NR	APR (15.9%)	LAR (SPS) (10%)	Inestimable	Very low (high risk of bias; imprecision)	No difference shown ⇔
Lozano 2015[19]	1 observational study	60 months	APR (inestimable)	AR (SPS) (inestimable)	HR = 1.31; 95% CI 0.98 to 1.76^	Very low (high risk of bias; imprecision)	No difference shown ⇔

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Arunachalam 2016[3]	15 observational studies	Median= 14.7	12 (7.9%) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
Death							
Lozano 2015[19]	1 observational study	60 months	29/973 (3.0%) APR	18/370 (4.9%) AR (SPS)	OR = 0.60; 95% CI 0.33 to 1.10*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Cong 2015[7]	21 studies (RCTs and observational studies)	NR	79/6,952 (1.1%) for AR (SPS)	13/3,668 (0.35%) for LAR (SPS)	OR = 3.23; 95% CI 1.79 to 5.82*^^	Low (unclear risk of bias and indirectness)	Difference in favour of LAR but data of low quality ⇗
30-days mortality							
Popiolek 2020[28]	1 observational study	3 and 24 months	0/30 (0%) APR	0/34 (0%) LHP	Inestimable	Very low (high risk of bias; imprecision)	No difference shown ⇔
Jonker 2016[12]	1 observational study	NM	11/866 (1.3%) LAR (SPS) without DS	38/1194 (3.2%) LHP	OR = 0.39; 95% CI 0.20 to 0.77*	Low (high risk of bias)	Difference in favour of LAR but data of low quality ⇗
Jonker 2016[12]	1 observational study	NM	29/2228 (1.3%) LAR (SPS) with DS	38/1194 (3.2%) LHP	OR = 0.40; 95% CI 0.25 to 0.65*	Low (high risk of bias)	Difference in favour of LAR but data of low quality ⇗

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Sverrisson 2018[31]	1 observational study	NM	53/1452 (4%) LHP	None	Inestimable	Very low (high risk of bias)	
Sverrisson 2015[30]	1 observational study	NR	0/159 (0%) APR	2/69 (3%) LHP	OR = 11.81; 95% CI 0.56 to 249.39*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Arunachalam 2016[3]	15 observational studies	Median= 14.7	2 (0.8%) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
60-days mortality							
Molina Rodríguez 2011[22]	1 observational study	60 days	4/131 (3%) APR	3/41 (7.3%) LHP	OR = 2.51; 95% CI 0.54 to 11.69*	Very low (high risk of bias; imprecision)	No difference shown ⇔
90-days mortality							
Popiolek 2020[28]	1 observational study	3 and 24 months	0/30 (0%) APR	1/34 (3%) LHP	OR = 2.73; 95% CI 0.11 to 69.60*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Sverrisson 2018[31]	1 observational study	NM	87/1452 (6%) LHP	None	Inestimable	Very low (high risk of bias and indirectness)	
Length of hospital stay							
Peng 2020[27]	3 observational studies	NM	N/A/321 LAR (SPS)	N/A/338 APR	MD = -2.98 in days; 95% CI -3.54 to -2.43 shorter	Very low (high risk of bias, imprecision)	Difference in favour of LAR but data of very low quality ⇗
Popiolek	1 observational	3 and 24	Median = 10	Median = 12 (range:	MD = -4.30 in days;	Very low (high risk	Difference in

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
2020[28]	study	months	(range:7-30) APR	7-43) LHP	95% CI -8.52 to -0.08 shorter*	of bias; imprecision)	favour of APR but data of very low quality ⇗
Molina Rodríguez 2011[22]	1 observational study	60 days	Mean = 12.2 (range:5-41) APR	Mean = 12.4 (range: 1-41) LHP	MD = -0.20 in days; 95% CI -3.43 to 3.03*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Jonker 2016[12]	1 observational study	NM	Median = 9 LAR (SPS) without DS	Median = 9 LHP	Inestimable	Low (high risk of bias)	No difference shown ⇔
Jonker 2016[12]	1 observational study	NM	Median = 9 LAR (SPS) with DS	Median = 9 LHP	Inestimable	Low (high risk of bias)	No difference shown ⇔
Arunachalam 2016[3]	15 observational studies	Median= 14.7	Median = 7.3 (range:3-41) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
Surgical complications (not otherwise specified)							
Wang 2015[32]	7 observational studies	5 years	257/1,063 (24.2%) APR	521/2,271 (22.9%) LAR (SPS)	RR = 1.09; 95% CI 1.03 to 1.15*	Very low (high risk of bias; inconsistency)	Difference in favour of LAR but data of very low quality ⇗
Schneider 2015[29]	1 RCT	3 months	6/114 (5.3%)	None	Inestimable	Very low (high risk of bias and indirectness)	

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Sverrisson 2015[30]	1 observational study	NR	51/159 (32%) APR	9/69 (13%) LHP	OR = 3.15; 95% CI 1.45 to 6.84*	Very low (high risk of bias; imprecision)	Difference in favour of LHP but data of very low quality ⇗
Overall complications							
Holmgren 2017[11]	1 observational study	Median: 1331 days (range: 34–2906 days)	71/229 AR (31%)	None	Inestimable	Very low (high risk of bias)	
Sverrisson 2018[31]	1 observational study	NM	594/1452 (41%) LHP	None	Inestimable	Very low (high risk of bias)	
Peng 2020[27]	5 observational studies	NM	212/567 (37.3%) LAR (SPS)	219/504 (43.4%) APR	OR = 0.76; 95% CI 0.59 to 0.99	Very low (high risk of bias, inconsistency)	Difference in favour of LAR but data of very low quality ⇗
Pelvic abscess							
Popiolek 2020[28]	1 observational study	3 and 24 months	3/30 (10%) APR	7/34 (21%) LHP	OR = 0.43; 95% CI 0.10 to 1.83*	Very low (high risk of bias; imprecision)	No difference shown ⇔
Molina Rodríguez 2011[22]	1 observational study	60 days	4/131 (3%) APR	5/41 (12.2%) LHP	OR = 0.23; 95% CI 0.06 to 0.89*	Very low (high risk of bias; imprecision)	Difference in favour of APR but data of very

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
							low quality ⇩
Sverrisson 2015[30]	1 observational study	NR	1/159 (1%) APR	2/69 (3%) LHP	OR = 0.21; 95% CI 0.02 to 2.38*	Very low (high risk of bias; imprecision)	Difference in favour of APR but data of very low quality ⇩
Arunachalam 2016[3]	15 observational studies	Median= 14.7	19.4 (6.8%) TME	None	Inestimable	Very low (high risk of bias and indirectness)	
Intra-abdominal abscess or infections							
Jonker 2016[12]	1 observational study	NM	24/866 (2.8%) LAR (SPS) without DS	74/1194 (6.2%) LHP	OR = 0.43; 95% CI 0.27 to 0.69*	Low (high risk of bias)	Difference in favour of LAR without DS but data of low quality ⇩
Jonker 2016[12]	1 observational study	NM	75/2228 (3.4%) LAR (SPS) with DS	74/1194 (6.2%) LHP	OR = 0.53; 95% CI 0.38 to 0.73*	Low (high risk of bias)	Difference in favour of LAR with DS but data of low quality ⇩
Sverrisson 2018[31]	1 observational study	NM	122/1452 (8%) LHP	None	Inestimable	Very low (high risk of bias)	

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Peristomal skin complications							
Malik 2018[21]	18 RCTs	Range: 2 to 60 months	Median = 32.3% (range: 18.4 to 46.2%) for loop colostomy	Median = 3.6% (range: 2.4 to 4.8%) for end colostomy	Inestimable	Low (unclear risk of bias and indirectness)	Difference in favour of end colostomy but data of low quality ⇗
Parastomal hernia							
Malik 2018[21]	18 RCTs	Range: 2 to 60 months	Median = 0% (range: 0 to 5.6%) for loop colostomy	Median = 59.3% (range: 41.5 to 88.2%) for end colostomy	Inestimable	Low (unclear risk of bias and indirectness)	Difference in favour of loop colostomy but data of low quality ⇗
Stoma ischaemia							
Malik 2018[21]	18 RCTs	Range: 2 to 60 months	Median = 2.6% (range: 2.6 to 2.6%) for loop colostomy	Median = 5.9% (range: 2 to 7.3%) for end colostomy	Inestimable	Low (unclear risk of bias and indirectness)	Difference in favour of loop colostomy but data of low quality ⇗
Stoma prolapse							
Malik 2018[21]	18 RCTs	Range: 2 to 60 months	Median = 7.9% (range: 5.6 to 41%) for loop colostomy	Median = 4.1% (range: 3.2 to 4.9%) for end colostomy	Inestimable	Low (unclear risk of bias and indirectness)	Difference in favour of end colostomy but data of low

Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
							quality ⇩
Low Anterior Resection Syndrome (LARS) following sphincter preserving surgery (without end stoma)							
Croese 2018[8]	11 observational studies	12 months	Major LARS 41% (90%CI 0.34 to 0.48) for LAR (SPS)	No Lars 35% for LAR (SPS)	Inestimable	Low (unclear risk of bias and indirectness)	
Keane 2020 [14]	7 studies (3 RCTs)	Range: 3-50 months	43/84 (51.1%) for ileostomy LAR	46/143 (32.1%) no ileostomy LAR	OR = 1.96; 95% CI 1.10 to 3.48	Low (high risk of bias and imprecision)	Difference in favour of no ileostomy but data of low quality ⇩
Kim 2021[16]	1 observational study	24 months	Major LARS all patients 123/283 (43.4%); AR: 10/123 (8.1%); LAR: 82/123 (66.6%); UAR: 31/123 (25.2%)	No LARS all patients 101/283 (35.6%); AR: 42/101 (41.5%); LAR: 48/101 (47.5%); UAR: 11/101 (10.8%)	Inestimable	Low (unclear risk of bias and indirectness)	

* own re-calculation with RevMan 5.4.1 (please refer to the Appendix 2). ** Median time from surgery to survey. ^ = Cox regression analysis. ^^ please note the estimate includes combined numbers of diversion stoma and no- diversion stoma. $ = 9.1% estimate cited in the text (7.3% chosen from the table 5 of that paper). AR = anterior resection; CI = confidence interval; DS = diverting stoma; HA = Hartmann procedure; LAR = low anterior resection; LARS = Low Anterior Resection Syndrome; LHP = low Hartmann procedure; MD = mean difference; N/A = not applicable; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; SPS = sphincter-preserving surgery; UAR = ultralow anterior resection.

3.8 FAQ 7: How will treatment impact my quality of life?

A large Cochrane SR of 35 studies involving 5,127 participants could not draw conclusions whether the quality of life (QoL) of patients with a colostomy after APR was poorer than for patients undergoing a SPS.[26] The authors suggested that both types of surgeries adversely affect the patients' QoL, however in a different way i.e., they experience different symptoms. Patients undergoing APR (without sphincter preservation) typically have less diarrhoea, constipation, gastrointestinal problems, but worse bodily perception and mental health. In contrast, SPS patients scored better in physical or social functioning, general health, energy and vitality, had less fatigue or pain, but have more constipation, diarrhoea and worse emotional health. It is worth noting that these findings were sometimes contradictory and both APR and SPS patients suffer poorer health or global QoL. This review included mainly observational evidence and recommended larger, better designed and executed prospective studies to answer this question.[26] However, Fernandez-Martinez et al. 2020[9] included three observational studies comparing LAR (SPS) (n=96) versus APR (n=70). They reported no differences in global QoL between the two groups at an average follow-up of 12 months based on low certainty evidence standardised mean difference (SMD = 0.01; 95% CI -0.30 to 0.33).[9] The authors also reported that patients following APR suffer worse physical function, bodily image perception, sexual function or urinary dysfunction. In contrast, in patients following SPS, higher faecal incontinence, frequent defecation and poorer QoL were reported.[9] Based on low certainty evidence, no difference was shown between the two treatment options in improving global health measured with QLQ-30 (a quality-of-life instrument for use in international clinical trials in oncology; the scale ranges from zero to 100, with higher scores representing a better QoL) at follow-ups of up to two years (mean difference (MD) = -0.61; 95% CI -3.53 to 2.31) based on eight observational studies comparing AR (SPS) (n=774) versus APR (n=369).[6] Based on four observational studies comparing AR (SPS) (n=236) versus APR (n=170), no difference was shown between the two treatment options in general quality of life (measured with SF-36; similarly the scale ranges from zero to 100, with higher scores representing a better QoL) at follow-ups of up to two years (MD= -7.49; 95% CI -19.4 to 4.44; see Table 8).[6]

Table 8: FAQ 7 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
General quality of life * **	Cornish 2007[6]	4 observational studies	Up to 2 years	AR (SPS) (n=236)	APR (n=170)	MD= -7.49; 95% CI -19.4 to 4.44	Low (high risk of bias and imprecision)	No difference shown ⇔
Global health **	Cornish 2007[6]	8 observational studies	Up to 2 years	AR (SPS) (n=774)	APR (n=369)	MD= -0.61; 95% CI -3.53 to 2.31	Low (high risk of bias and imprecision)	No difference shown ⇔
Global quality of life	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= 0.01; 95% CI -0.30 to 0.33*	Low (high risk of bias and imprecision)	No difference shown ⇔
Quality of life (physical functioning)	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= 0.22; 95% CI -0.36 to 0.81*	Low (high risk of bias and imprecision)	No difference shown ⇔
Quality of life (role functioning)	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= -0.04; 95% CI -0.51 to 0.43*	Low (high risk of bias and imprecision)	No difference shown ⇔
Quality of life (emotional functioning)	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= 0.03; 95% CI -0.58 to 0.63*	Low (high risk of bias and imprecision)	No difference shown ⇔
Quality of life (cognitive functioning)	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= -0.19; 95% CI -0.51 to 0.12*	Low (high risk of bias and imprecision)	No difference shown ⇔

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Quality of life (social functioning)	Fernandez-Martinez 2020[9]	3 observational studies	12 months	LAR (SPS) (n=96)	APR (n=70)	SMD= 0.18; 95% CI -0.29 to 0.66*	Low (high risk of bias and imprecision)	No difference shown ⇔

* own re-calculation with RevMan 5.4.1 (please refer to the appendix 2). ** measured with The European Organization for Research and Treatment of Cancer QLQ-30. *** measured with short form-36 (SF-36). CI = confidence interval; MD = mean difference; NR = not reported; RCT = randomised controlled trial; SMD = standardised mean difference

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

In general, low or very low certainty evidence suggests conflicting evidence and inconsistent findings for most FAQs/outcomes.

There was no direct evidence comparing any of the surgical techniques against one another in increasing the risk of a permanent stoma. However, based on very low certainty evidence, two studies reported that between 19% and 23.7% of the patients needed a permanent stoma following SPS at 72 and 15 months follow-ups respectively.[18, 20]

There was conflicting evidence of both low and very low certainty suggesting either lower odds of local cancer recurrence following LAR (SPS) when compared with APR or showing no difference between APR and AR (SPS).

There was a relatively large body of direct evidence that provided data for FAQ 4. Two studies showed that there were no differences between LAR and APR in DFS at five years follow-up.[15, 25] Four studies compared APR with LAR in improving OS with conflicting results.[15, 19, 25, 32] Pooled estimates from 11 studies showed favourable effects of APR in improving OS at five years follow-up.[32] This was however based on low certainty evidence (highly heterogeneous and of unclear risk of bias).[32] Based on very low certainty evidence, one study showed that there were no differences between LAR and APR in RFS at five years follow-up.[33] This is in line with the German S3 guideline which also suggests that lack of difference between group depends on patient-specific profile or disease progression/development.[2]

Findings were rather inconsistent for short and long-term AEs of the surgical procedures. For instance, for anastomotic leakage and reoperation rates, both direct and indirect evidence was available and comparable results for AR, or LAR are presented. However, LAR with diverting stoma had lower rates of anastomotic leakage and reoperation compared to patients without diverting stoma based on low certainty evidence.[10, 23] It is worth remembering that stoma closure (the second surgery) is often required following the creation of a diversion stoma. That second operation itself carries an elevated risk of wound sepsis, postoperative bleeding, small bowel obstruction, pulmonary infection, reoperation, complications or LARS when compared with no diversion stoma.[38] For metastases, one study showed no differences between APR and AR (SPS) at 60 months follow-up.[19] Another study showed higher incidence of lung metastases following APR, compared with LAR but this is based on very low certainty evidence.[15] Similarly there was a lower complications rate following LAR compared with APR at five years follow-up based on highly heterogeneous data of high risk of bias.[32] For mortality, one study showed no differences between APR and AR at 60 months follow-up based on very low certainty evidence.[19] In general, there is a highly variable incidence of stoma-related complications (of all types of stoma). Unfortunately, it is unclear why e.g., end colostomy is linked to more complications (of all types) compared with loop colostomy or loop ileostomy. The clinical and methodological

heterogeneity of the included trials as well as different diagnostic methods being cited as the main reasons.[21]

Three of the included studies evaluated LARS.[8, 13, 16] While there are differences in operationalisation (defining the measurement) and conceptualisation (defining the concept itself) of LARS, on average more than 40% of patients after SPS experience it which can negatively impact one's psychological, social and physical QoL. Several existing risk factors for LARS have been identified including the history of radiotherapy, low anastomosis, and SPS-related complications. Recent CPG found no evidence for the optimal management of LARS recommending further research.[39]

Two studies consistently showed no differences between APR and LAR or AR for quality of life measured with the European Organisation for Research and Treatment of Cancer QLQ-30 or short form-36 questionnaire at follow-ups ranging between 12-24 months.[6, 9] The quality of the evidence was low in both studies.

For a comparison of German S3 guideline and findings of this review, please see Table 9 below. For each recommendation/ statement, an indication is given whether our report is in line with that recommendation along with a referral to the relevant section of the report.

Effect modifiers

In the study by Jonker et al. 2016, older age (>70), a history of myocardial infarction and chronic obstructive pulmonary disease were associated with higher risk of 30-day or in-hospital mortality after LAR and LHP (OR = 4.12; 95 CI 1.55 to 10.9 for 71-80 years old; OR = 5.99; 95% CI 2.07 to 17.4 for > 80 years old), (OR = 2.59; 95% CI 1.36 to 4.93) and (OR = 1.87; 95% CI 1.02 to 3.41) respectively.[12] Chronic obstructive pulmonary disease was also a risk factor for reoperation (OR = 1.45; 95% CI 1.04 to 2.01).[12] Similarly, higher age was a risk factor for intraabdominal infection in patients undergoing LHP (OR = 0.98; 95% CI 0.96 to 0.99).[31] However, in Sverrisson et al. 2015, age was not a risk factor for pelvic-perineal complications (OR = 1.02; 95% CI 0.99 to 1.05).[30]

Table 9: Comparison of German S3 guideline and findings of this review

From AWMF2019[2]	Text of recommendation/statement [strength of recommendation, level of evidence, consensus][*]	Evidence in this report
7.37	For deep tumours infiltrating the anal tube/ the sphincter where sphincter preservation is not possible, the abdominal-perineal extirpation should be "cylindrical" including resection of the levator ani. [B; 3b; consensus]	In line with the PICO; please refer to the section 3.3 of the report.
7.39	For radical surgery of rectal carcinoma with TME and deep anastomosis a deviation stoma should be used temporarily. [expert consensus; strong consensus]	In line with the PICO; please refer to the section 3.7 of the report.
7.40	Colostomy and ileostomy are equivalent deviation stoma. [expert consensus; strong consensus]	In line with the PICO; please refer to the section 3.3 of the report.
7.41	Adding a stoma should be discussed at the earliest convenience with patient undergoing surgery. [expert consensus; strong consensus]	In line with the PICO; please refer to the section 3.3 of the report.
7.42	The stoma position should be drawn pre-operatively. [expert consensus; consensus]	Some information given in the Table 3, section 3.3 of the report.

[*] Tables 3 to 5 of the guideline describe strength of recommendation, level of evidence, and consensus.[2] Briefly, strength of recommendation is classified as A (strong recommendation), B (recommendation), O (option), strength of recommendation not reported for statements; levels of evidence range from 1a ("SR (with homogeneity) of RCTs)" to 5 ("Expert opinion with explicit critical appraisal or based on physiology, bench research or 'first principles'"), level of evidence not reported for expert consensus; consensus range from strong consensus (agreement of >95% of participants) to no consensus (agreement of <50% of participants). PICO = participants, intervention, comparators, outcomes; RCT = randomised controlled trial; SR = systematic review; TME = total mesorectal excision

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report was developed using evidence from SRs, CPG and observational studies. Several strengths of this report need to be noted. These include comprehensive searches of the available evidence without date or language restrictions, as well as coverage of a wide range of FAQs and outcomes of interest.

However, some limitations should also be noted. Firstly, there was an unequal distribution of data under FAQ 5 and 6, hence it was decided to merge those under one umbrella outcome for conceptual clarity. Secondly, the treatment's influence on the tumour and the need for permanent stoma were the clinical areas where the least evidence was found hence increasing uncertainties in these areas. Thirdly, there was heterogeneity of populations and cancer sites studied, diversity of surgical procedures, comparators; and study designs used. The majority of outcomes were based on low or very low certainty evidence. The main reasons for downgrading were unclear or high risk of bias of the primary studies, inconsistency (statistical heterogeneity), indirectness (heterogeneity of populations, interventions or comparators) and imprecision (small sample sizes).

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APPENDIX 1: SEARCH STRATEGIES

Cochrane Database of Systematic Reviews (CDSR) (Wiley): 2015 - Iss 5, May 2021
https://www.cochranelibrary.com/
Date searched: 5.5.21
Records found: 24

#1 MeSH descriptor: [Rectal Neoplasms] explode all trees 1866
#2 (rectal* or rectum* or anal or anus) NEAR/3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) 5626
#3 #1 or #2 5626
#4 MeSH descriptor: [Colostomy] explode all trees 178
#5 MeSH descriptor: [Ileostomy] explode all trees 200
#6 MeSH descriptor: [Colonic Pouches] explode all trees 53
#7 (low NEXT anterior NEXT resect*) OR LAR OR (intersphinct* NEXT resect*) or (inter NEXT sphinct* NEXT resect*) OR ISR OR colostom* OR ileostom* OR stoma* OR (colon* NEAR/2 pouch*) 29407
#8 (mesorectal NEXT excision*) or (meso NEXT rectal NEXT excision*) or TME or TaTME 989
#9 (Hartmann* or LH) NEAR/2 (procedure* or operation* or resection* or pouch*) 111
#10 proctosigmoidectom* or (procto NEXT sigmoidectom*) or rectosigmoidectom* or (recto NEXT sigmoidectom*) 20
#11 MeSH descriptor: [Proctectomy] explode all trees 147
#12 proctectom* 114
#13 (abdominoperineal or "abdomino-perineal") NEAR/3 (resect* or amputat* or extirpat* or excis*) 343
#14 Miles NEAR/2 (surgery or operation*) 20
#15 (rectum* or rectal*) NEAR/3 (resect* or amputat* or extirpat* or excis*) 1500
#16 sphincter* NEAR/2 preserv* 249
#17 (discontinuity NEXT resection*) 1
#18 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 31250
#19 #3 and #18 with Cochrane Library publication date Between Jan 2015 and May 2021, in Cochrane Reviews 24

KSR Evidence: 2015 - 5.5.21
https://ksrevidence.com/
Date searched: 5.5.21
Records found: 273

1 (rectal* or rectum* or anal or anus) NEAR/3 (cancer* or neoplas* or oncolog* or malignan* or tumour* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) in All text 764 results

2 "low anterior resect*" or LAR or "intersphinct* resect*" or "inter-sphinct* resect*" or ISR or colostom* or ileostom* or stoma or stomas or stomat* or (colon* NEAR/2 pouch*) in All text 815 results
3 "mesorectal excision*" or "meso-rectal excision*" or TME or TaTME in All text 113 results
4 (Hartmann* or LH) NEAR/2 (procedure* or operation* or resection* or pouch*) in All text 39 results
5 proctosigmoidectom* or "procto-sigmoidectom*" or rectosigmoidectom* or "recto-sigmoidectom*" in All text 0 results
6 proctectom* in All text 13 results
7 (abdominoperineal or "abdomino-perineal") NEAR/3 (resect* or amputat* or extirpat* or excis*) in All text 46 results
8 Miles NEAR/2 (surgery or operation*) in All text 0 results
9 (rectum* or rectal*) NEAR/3 (resect* or amputat* or extirpat* or excis*) in All text 226 results
10 sphincter* NEAR/2 preserv* in All text 32 results
11 "discontinuity resection*" in All text 0 results
12 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 in All text 1089 results
13 #1 and #12 in All text 273 results
Filtered by: PUBLICATION DATE 2021, 2020, 2019, 2018, 2017, 2016, 2015

Health Technology Assessment (HTA) database: 2015 - 31.3.18
https://www.crd.york.ac.uk/CRDWeb/
Date searched: 5.5.21
Records found: 3

1 MeSH DESCRIPTOR Rectal Neoplasms EXPLODE ALL TREES 230
2 ((rectal* or rectum* or anal or anus) and (cancer* or neoplas* or oncolog* or malignan* or tumour* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*)) 594
3 #1 OR #2 594
4 MeSH DESCRIPTOR Colostomy EXPLODE ALL TREES 33
5 MeSH DESCRIPTOR Ileostomy EXPLODE ALL TREES 28
6 MeSH DESCRIPTOR Colonic Pouches EXPLODE ALL TREES 32
7 ("low anterior resect*" or LAR or "intersphinct* resect*" or "inter-sphinct* resect*" or ISR or colostom* or ileostom* or stoma or stomas or stomat* or (colon* and pouch*)) 302
8 ("mesorectal excision*" or "meso-rectal excision*" or TME or TaTME) 35
9 ((Hartmann* or LH) and (procedure* or operation* or resection* or pouch*)) 63
10 (proctosigmoidectom* or "procto-sigmoidectom*" or rectosigmoidectom* or "recto-sigmoidectom*") 3
11 MeSH DESCRIPTOR Proctectomy EXPLODE ALL TREES 27
12 (proctectom*) 6

13 ((abdominoperineal or "abdomino-perineal") and (resect* or amputat* or extirpat* or excis*)) 33
14 (Miles and (surgery or operation*)) 25
15 ((rectum* or rectal*) and (resect* or amputat* or extirpat* or excis*)) 227
16 (sphincter* and preserv*) 12
17 ("discontinuity resection*") 0
18 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 575
19 #3 AND #18 221
20 (#19) IN HTA FROM 2015 TO 2021 3

Epistemonikos: 2015 - 5.5.21
https://www.epistemonikos.org/
Date searched: 5.5.21
Records found: 449

#1 (title:((rectal* OR rectum* OR anal OR anus) AND (cancer* OR neoplas* OR oncolog* OR malignan* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR adenom* OR lesion*)) OR abstract:((rectal* OR rectum* OR anal OR anus) AND (cancer* OR neoplas* OR oncolog* OR malignan* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR adenom* OR lesion*)))
#2 (title:("low anterior resect*" OR LAR OR "intersphinct* resect*" OR "inter-sphinct* resect*" OR ISR OR colostom* OR ileostom* OR stoma OR stomas OR stomat* OR (colon* AND pouch*)) OR abstract:("low anterior resect*" OR LAR OR "intersphinct* resect*" OR "inter-sphinct* resect*" OR ISR OR colostom* OR ileostom* OR stoma OR stomas OR stomat* OR (colon* AND pouch*))) OR (title:("mesorectal excision*" OR "meso-rectal excision*" OR TME OR TaTME) OR abstract:("mesorectal excision*" OR "meso-rectal excision*" OR TME OR TaTME)) OR (title:((Hartmann* OR LH) AND (procedure* OR operation* OR resection* OR pouch*)) OR abstract:((Hartmann* OR LH) AND (procedure* OR operation* OR resection* OR pouch*))) OR (title:(proctosigmoidectom* OR "procto-sigmoidectom*" OR rectosigmoidectom* OR "recto-sigmoidectom*") OR abstract:(proctosigmoidectom* OR "procto-sigmoidectom*" OR rectosigmoidectom* OR "recto-sigmoidectom*")) OR (title:(proctectom*) OR abstract:(proctectom*)) OR (title:((abdominoperineal OR "abdomino-perineal") AND (resect* OR amputat* OR extirpat* OR excis*)) OR abstract:((abdominoperineal OR "abdomino-perineal") AND (resect* OR amputat* OR extirpat* OR excis*))) OR (title:(Miles AND (surgery OR operation*)) OR abstract:(Miles AND (surgery OR operation*))) OR (title:((rectum* OR rectal*) AND (resect* OR amputat* OR extirpat* OR excis*)) OR abstract:((rectum* OR rectal*) AND (resect* OR amputat* OR extirpat* OR excis*))) OR (title:(sphincter* AND preserv*) OR abstract:(sphincter* AND preserv*)) OR (title:("discontinuity resection*") OR abstract:("discontinuity resection*")) 05-05-2021 11:03:14 +01:00

#3 #1 and #2

International HTA Database: 2015 - 5.5.21
https://database.inahta.org/
Date searched: 5.5.21
Records found: 26

19 #18 AND #3 26
18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 28
17 "discontinuity resection*" 0
16 sphincter* and preserv* 0
15 (rectum* or rectal*) and (resect* or amputat* or extirpat* or excis*) 20
14 Miles and (surgery or operation*) 0
13 (abdominoperineal or "abdomino-perineal") and (resect* or amputat* or extirpat* or excis*) 0
12 proctectom* 0
11 "Proctectomy"[mhe] 0
10 proctosigmoidectom* or "procto-sigmoidectom*" or rectosigmoidectom* or "recto-sigmoidectom*" 0
9 (Hartmann* or LH) and (procedure* or operation* or resection* or pouch*) 1
8 "mesorectal excision*" or "meso-rectal excision*" or TME or TaTME 3
7 "low anterior resect*" or LAR or "intersphinct* resect*" or "inter-sphinct* resect*" or ISR or colostom* or ileostom* or stoma or stomas or stomat* or (colon* and pouch* 1
6 "Colonic Pouches"[mhe] 1
5 "Ileostomy"[mhe] 0
4 "Colostomy"[mhe] 3
3 #2 OR #1 103 May 05 2021 9:29 AM
2 (rectal* or rectum* or anal or anus) and (cancer* or neoplas* or oncolog* or malignan* or tumour* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) 100
1 "Rectal Neoplasms"[mhe] 25

Database of Abstracts of Reviews of Effects (DARE) (CRD): 2015 to 31 March 2015
https://www.crd.york.ac.uk/CRDWeb/
Searched: 17.12.20

1 MeSH DESCRIPTOR Rectal Neoplasms EXPLODE ALL TREES 230
2 (((rectal* or rectum* or anal or anus) NEAR3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*))) IN DARE, HTA FROM 2015 TO 2020 8
3 #1 OR #2 235
4 MeSH DESCRIPTOR Colostomy EXPLODE ALL TREES 33
5 MeSH DESCRIPTOR Ileostomy EXPLODE ALL TREES 28
6 MeSH DESCRIPTOR Colonic Pouches EXPLODE ALL TREES 32
7 (low anterior resect* OR LAR OR Intersphinct* resect* OR ISR OR colostom* OR ileostom* OR stoma* OR ostom* OR (colon* NEAR2 pouch*)) IN DARE, HTA FROM 2015 TO 2020 19
8 #4 OR #5 OR #6 OR #7102

9 #3 AND #8 12
10 * IN DARE FROM 2015 TO 2020 2587
11 #9 AND #10 0

TRIP Database: up to 2020/12/17
https://www.tripdatabase.com/
Searched 17.12.20

Limited to 2015 onwards

Keywords	**Hits**
(title:rect* cancer)(title:colostom* OR ileostom* OR ostom*) from:2015	40
Total	40
Total SRs	1
Guidelines	0

NHS Evidence (www.evidence.nhs.uk): up to 17.12.20
Searched 17.12.20

Search term – limited to guidance / systematic reviews, 2015-2020	**Hits**
Colostom*	71
Ileostom*	85
Total	156

NICE Guidance (www.nice.org.uk): up to 17.12.20
Searched: 17.12.20

Searched in Guidance, Advice and Quality standards
Searched 'Rectal Cancer' – 41
Searched 'colostomy' – 22
Searched 'ileostomy' – 10

ECRI (www.guidelines.ecri.org): up to 17.12.20
Searched 17.12.20

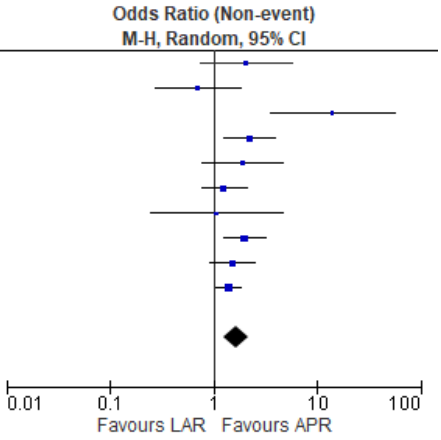
Search terms	**Hits**
'rectum cancer OR rectal cancer OR ostomy OR colostomy OR ileostomy'	20
Total restricted to 2015 onwards	20

APPENDIX 2: RE-CALCULATIONS WITH REVMAN 5.4.1

Local recurrence (please also refer to table 5)

Study or Subgroup	LAR Events	LAR Total	APR Events	APR Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Chambers 2010	7	93	10	70	5.7%	2.05 [0.74, 5.68]
Chuwa 2006	50	677	5	93	6.3%	0.71 [0.28, 1.83]
Heald 1997	3	105	9	31	3.4%	13.91 [3.48, 55.59]
Kim 2012	18	402	38	402	12.0%	2.23 [1.25, 3.97]
Law 2001	14	123	10	51	7.0%	1.90 [0.78, 4.61]
Li 2006	27	244	48	355	13.7%	1.26 [0.76, 2.08]
Li 2009	6	53	3	25	3.1%	1.07 [0.24, 4.67]
Marr 2005	48	355	43	181	14.9%	1.99 [1.26, 3.15]
Nagtegaal 2005	46	453	30	205	14.0%	1.52 [0.93, 2.48]
Wibe 2004	117	1315	99	821	20.0%	1.40 [1.06, 1.86]
Total (95% CI)		**3820**		**2234**	**100.0%**	**1.67 [1.27, 2.20]**
Total events	336		295			

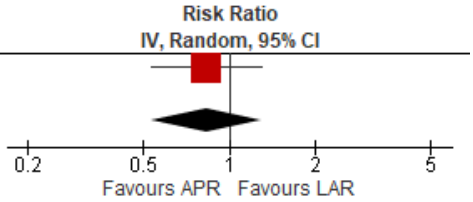
Heterogeneity: Tau² = 0.08; Chi² = 16.70, df = 9 (P = 0.05); I² = 46%
Test for overall effect: Z = 3.64 (P = 0.0003)



Disease free survival (please also refer to table 6)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Omidvari 2013	-0.1849	0.2258	100.0%	0.83 [0.53, 1.29]
Total (95% CI)			**100.0%**	**0.83 [0.53, 1.29]**

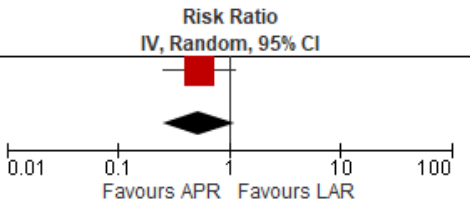
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



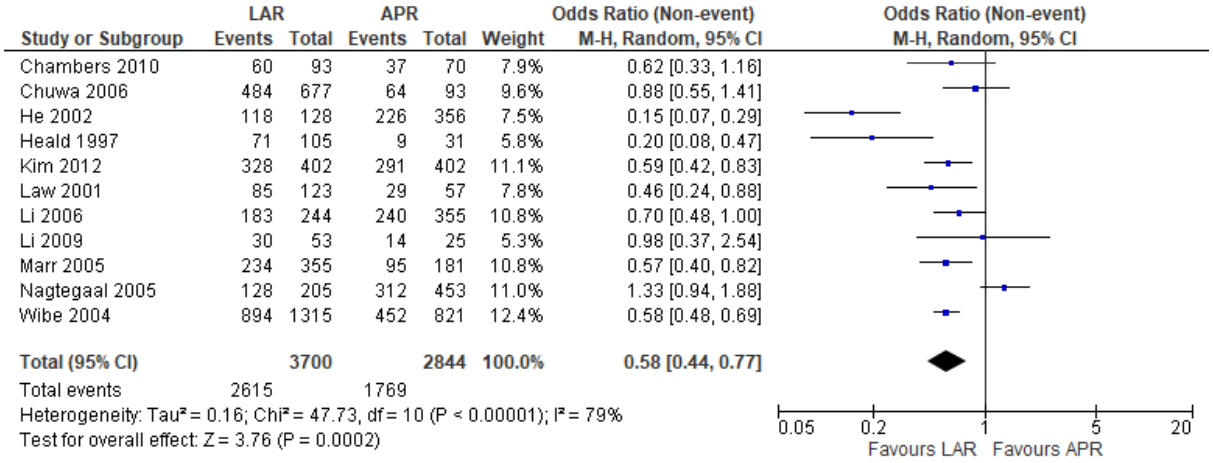
Overall survival (please also refer to Table 6)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Omidvari 2013	-0.6286	0.3768	100.0%	0.53 [0.25, 1.12]
Total (95% CI)			**100.0%**	**0.53 [0.25, 1.12]**

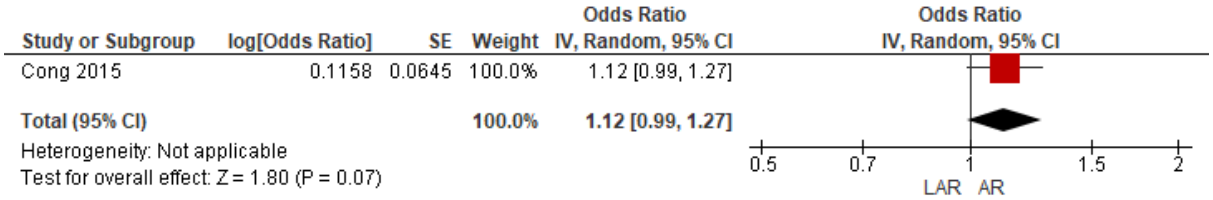
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.10)

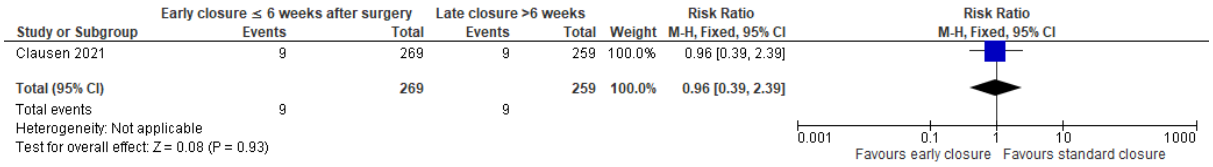


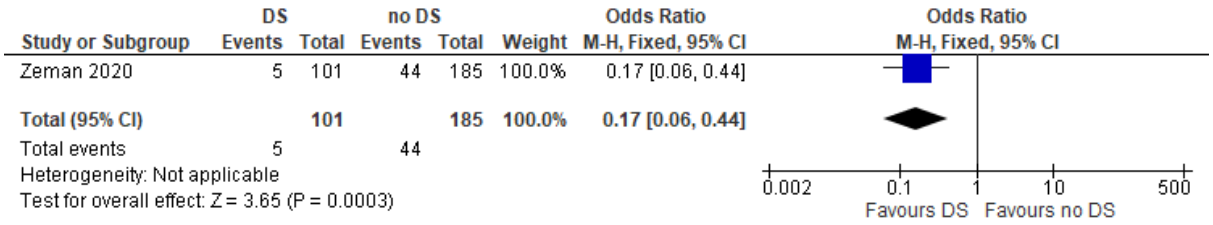
Overall survival-recalculated (please also refer to Table 6)



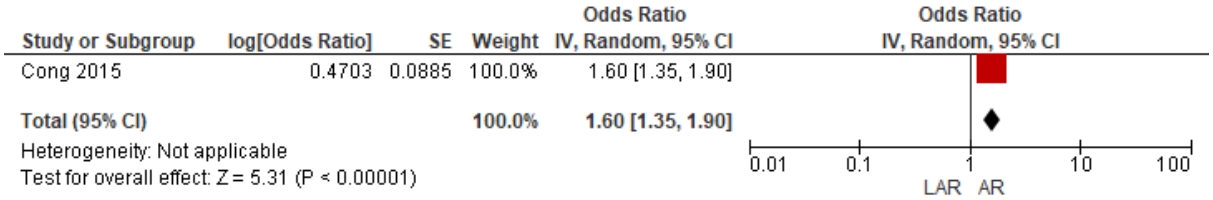
Anastomotic leakage (please also refer to Table 7)

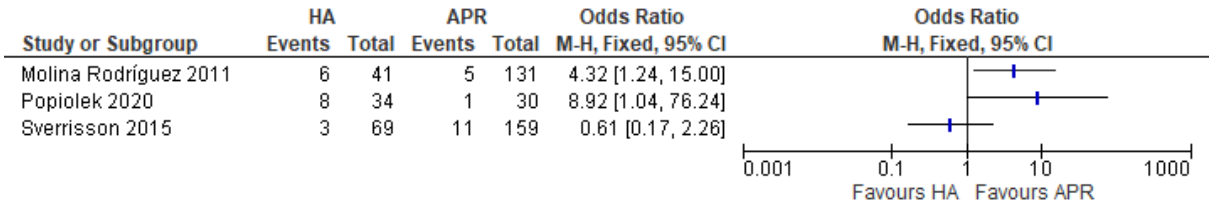


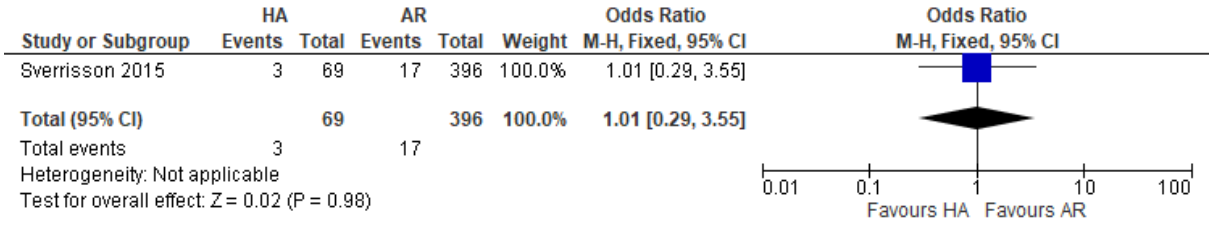


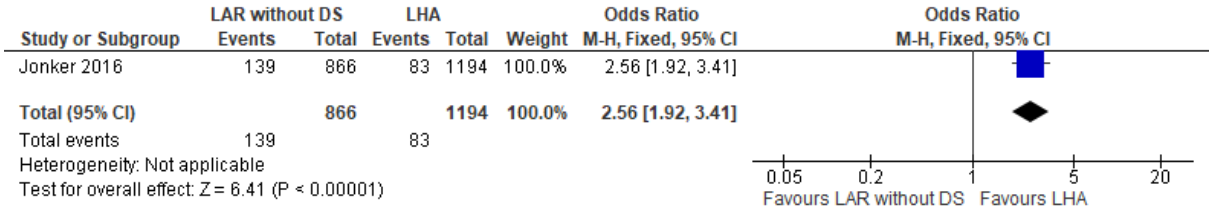


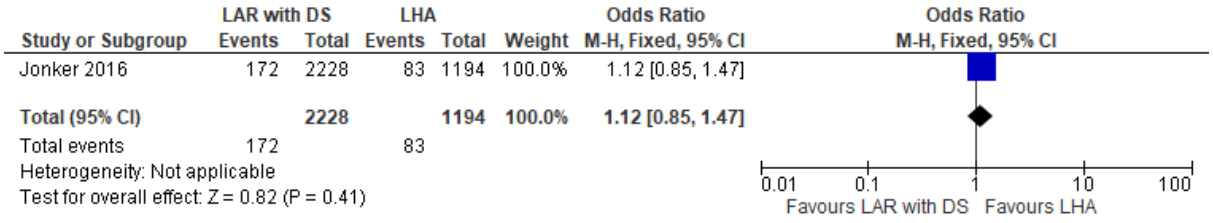
Reoperation (please also refer to Table 7)



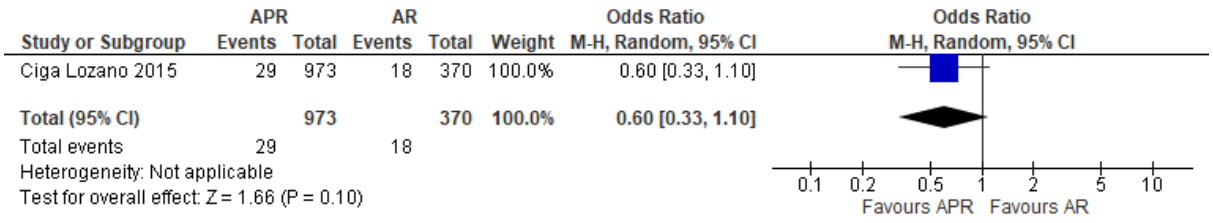


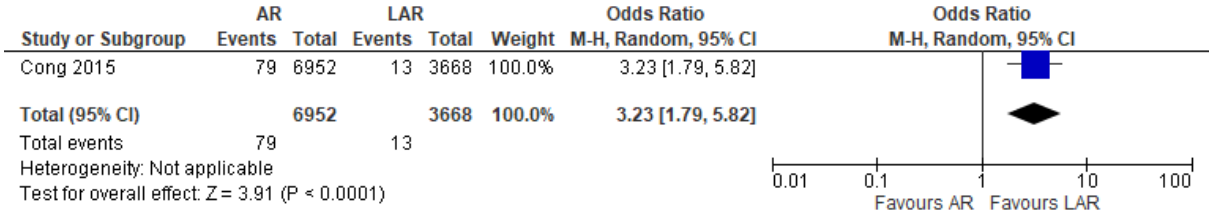




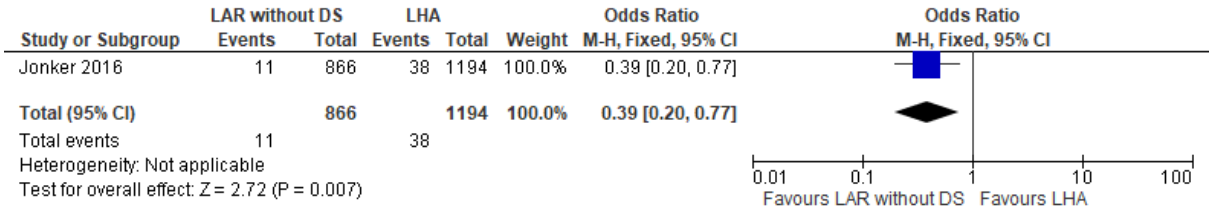


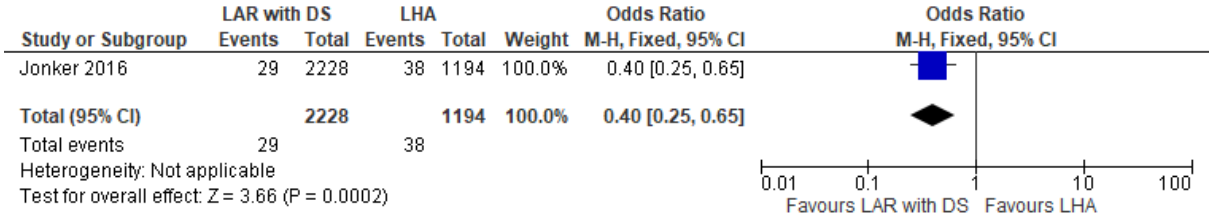
Deaths (please also refer to Table 7)

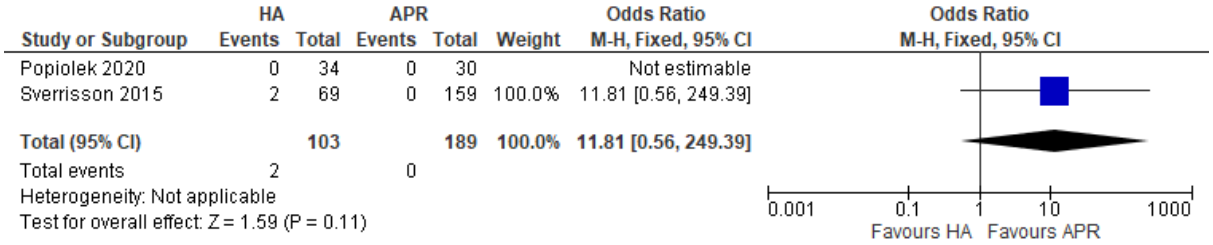




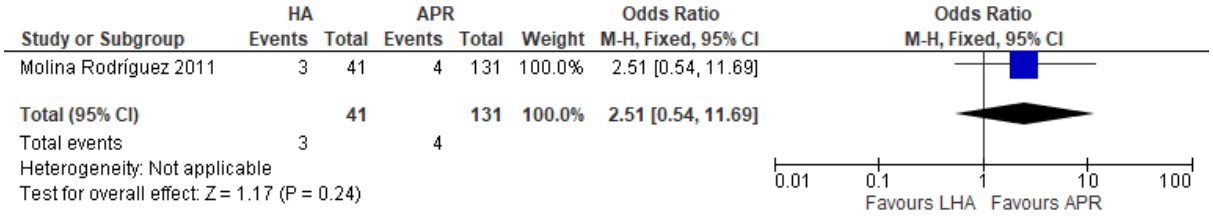
30-days mortality (please also refer to Table 7)



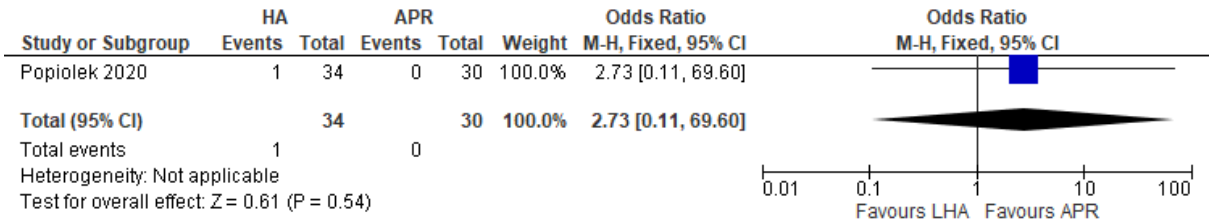




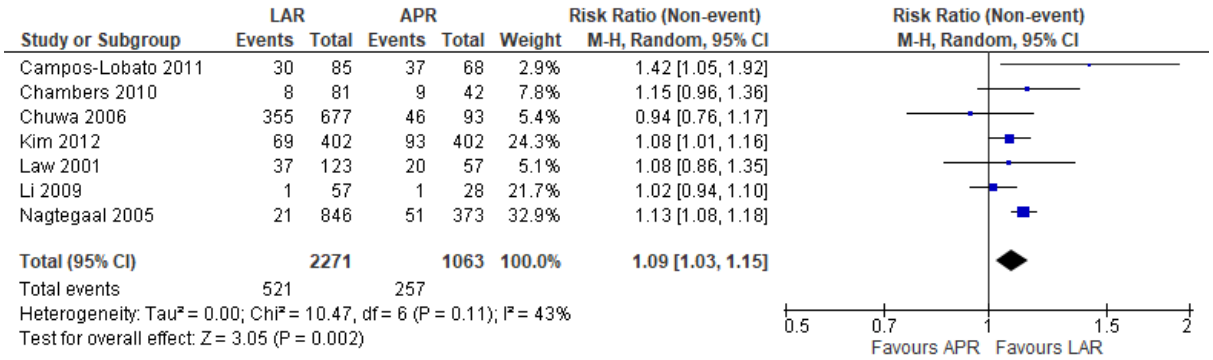
60-days mortality (please also refer to Table 7)

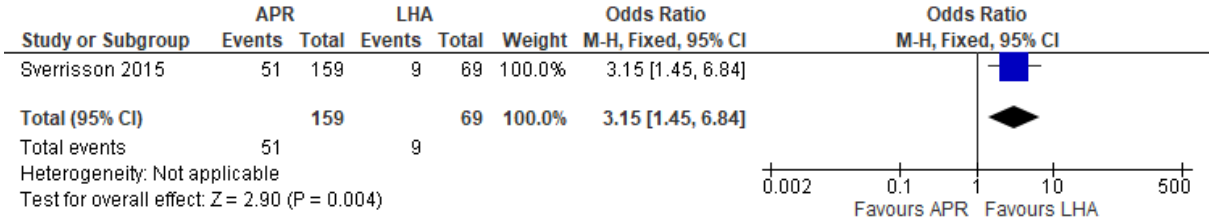


90-days mortality (please also refer to Table 7)

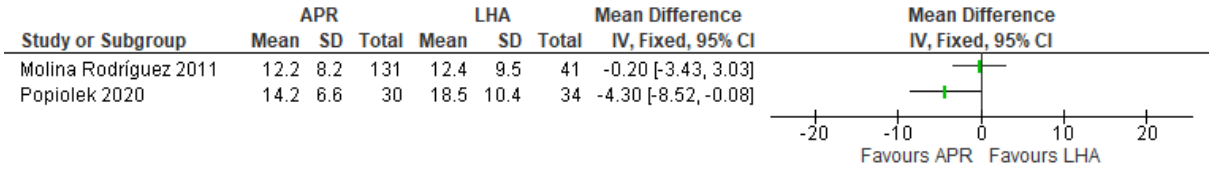


Surgical complications (please also refer to Table 7)

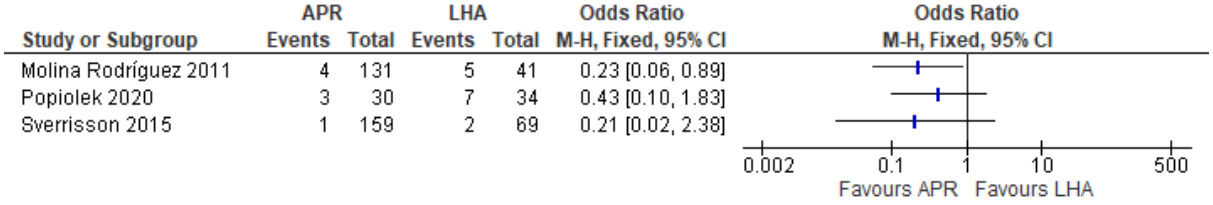




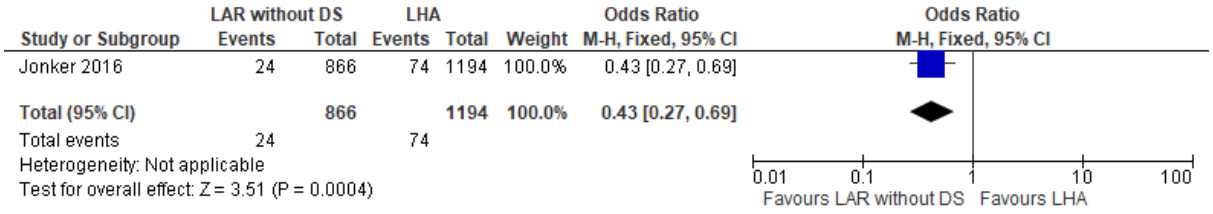
Length of hospital stay (please also refer to Table 7)

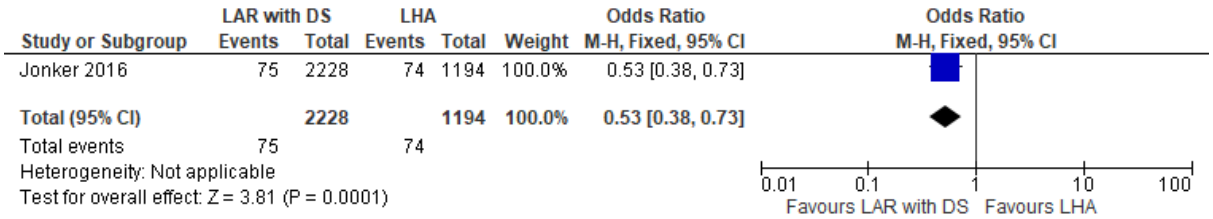


Pelvic abscess (please also refer to Table 7)

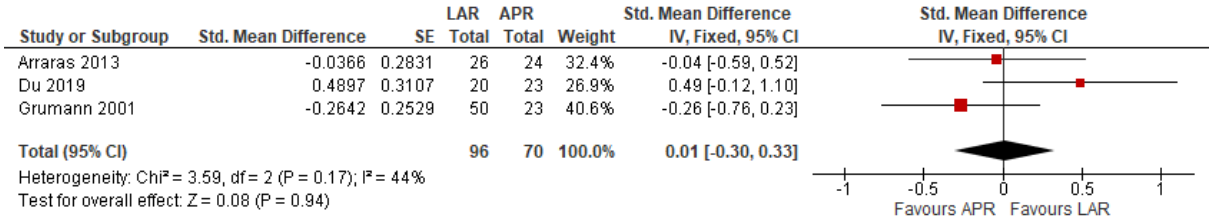


Intra-abdominal abscess (please also refer to Table 7)

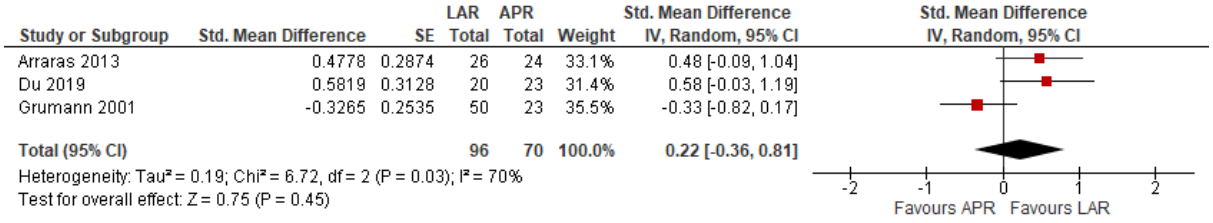




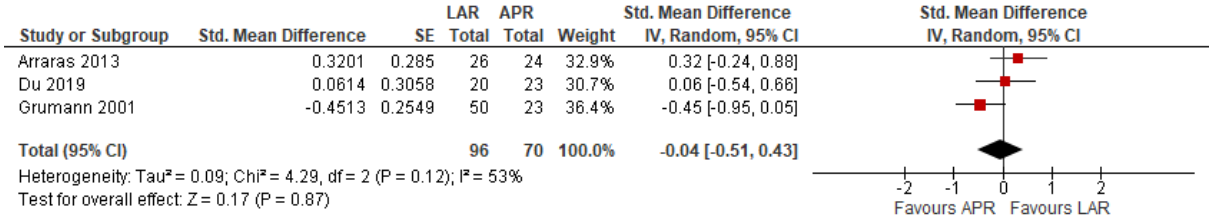
Quality of life (please also refer to Table 8)



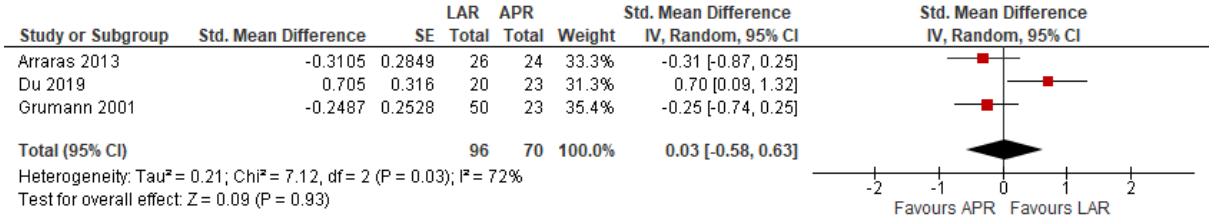
Quality of life (physical functioning) (please also refer to Table 8)



Quality of life (role functioning) (please also refer to Table 8)



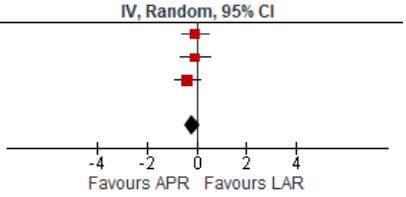
Quality of life (emotional functioning) (please also refer to Table 8)



Quality of life (cognitive functioning) (please also refer to Table 8)

Study or Subgroup	Std. Mean Difference	SE	LAR Total	APR Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arraras 2013	-0.0543	0.2831	26	24	32.3%	-0.05 [-0.61, 0.50]
Du 2019	-0.08	0.3059	20	23	27.6%	-0.08 [-0.68, 0.52]
Grumann 2001	-0.3797	0.254	50	23	40.1%	-0.38 [-0.88, 0.12]
Total (95% CI)			**96**	**70**	**100.0%**	**-0.19 [-0.51, 0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)



Quality of life (social functioning) (please also refer to Table 8)

Study or Subgroup	Std. Mean Difference	SE	LAR Total	APR Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arraras 2013	0.0853	0.2832	26	24	33.3%	0.09 [-0.47, 0.64]
Du 2019	0.698	0.3158	20	23	30.0%	0.70 [0.08, 1.32]
Grumann 2001	-0.1485	0.2523	50	23	36.7%	-0.15 [-0.64, 0.35]
Total (95% CI)			**96**	**70**	**100.0%**	**0.18 [-0.29, 0.66]**

Heterogeneity: Tau² = 0.10; Chi² = 4.46, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 0.75 (P = 0.45)