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Selective defunctioning stoma approach in low anterior resection for rectal cancer (SELSA): a prospective study and a nested randomised clinical trial

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Abstract

Introduction

Systematic use of defunctioning stoma after low anterior resection for rectal cancer has been shown to reduce symptomatic anastomotic leakage and associated interventions. However, accumulating data suggest that this comes at the price of worse bowel dysfunction, a higher rate of permanent stomas and kidney injury. We aim to study whether a selective strategy of defunctioning stoma use might lead to fewer adverse consequences, while still being safe for patients.

Methods and analysis

This is a multicentre international prospective trial including a non-blinded randomised clinical trial. All patients with a primary rectal cancer planned for low anterior resection with colorectal or coloanal anastomosis are eligible. Patients enter a prospective observational study, in which a randomised clinical trial is nested. Patients eligible for randomisation are aged below 80 years, have an American Society of Anesthesiologists' fitness grade I or II, have no unresected distant disease, and have a predicted lower risk of anastomotic leakage. Patients will be randomised 1:1 to either an experimental arm with no defunctioning stoma or to a control arm with a defunctioning stoma. The randomisation is computer-generated with a concealed sequence and stratified by participating hospital and radiotherapy use. The main outcome is the composite measure of 2-year stoma-free survival without major low anterior resection syndrome (LARS). Secondary outcomes include anastomotic leakage, postoperative mortality, reinterventions, stoma-related complications, quality of life measures, LARS, and permanent stoma rate up to two years after index surgery. To be able to state superiority of any study arm regarding the main outcome, with 90% statistical power and assuming 25% attrition, we aim to enrol 212 patients.

Ethics and dissemination

This study seeks approval by the Swedish Ethical Review Authority. The results will be disseminated through patient associations, popular science, the broader medical community, and conventional scientific channels.

Trial registration number

This study will be registered at clinicaltrials.gov pending ethical approval.

Introduction

Background and rationale

Low anterior resection with a defunctioning stoma is still considered the standard procedure for curative resection of rectal cancer where a total mesorectal excision (TME) is necessary for oncological reasons. Anastomotic leakage (AL) after anterior resection is common, amounting to 10% within 30 days and 20% within the first postoperative years in population-based studies (Borstlap, Westerduin et al. 2017). AL causes morbidity and mortality (Bostrom, Haapamaki et al. 2019), as well as impaired bowel function (Jutesten, Buchwald et al. 2022) and stoma permanence (Holmgren, Kverneng Hultberg et al. 2017, Jutesten, Draus et al. 2019). AL prevention is therefore of utmost importance. The most straightforward method to abstain from an AL is a non-restorative procedure; however, many patients strongly wish to preserve bowel continuity. In fact, patients rank avoidance of a stoma as high as survival in some studies (Wrenn, Cepeda-Benito et al. 2018). Moreover, permanent stomas are certainly not complication-free, with short- and long-term morbidity such as parastomal hernias, retraction, bowel obstruction, altered self-image as well as associated healthcare costs.

There are some well-established risk factors for AL in anterior resection whereas others remain debatable. Risk factors with strong support in the literature are male sex (Kang, Halabi et al. 2013), a distal anastomosis (Park, Choi et al. 2013), smoking (Sorensen, Jorgensen et al. 1999, Richards, Campbell et al. 2012), excessive alcohol consumption (Sorensen, Jorgensen et al. 1999), high BMI (Hu, Huang et al. 2017) and a high American Society of Anesthesiologists' fitness grade (Jestin, Pahlman et al. 2008). Poor nutritional status and electrolyte disturbances are identified AL risk factors for colorectal surgery in general (McDermott, Heeney et al. 2015). In laparoscopic anterior resection, AL is commonly reported as related to the use of multiple firings for rectal transection (Kawada, Hasegawa et al. 2014, Qu, Liu et al. 2015). Corticosteroid seems related to AL whereas no clear relationship to nonsteroidal anti-inflammatory drugs has been shown (Klein, Gogenur et al. 2012, Burton, Mittal et al. 2013, Kverneng Hultberg, Angenete et al. 2017). Furthermore, operation time, intraoperative bleeding and blood transfusion are related to AL but possibly serve as surrogate for poor technique or demanding surgery (Park, Choi et al. 2013, Katsuno, Shiomi et al. 2016, Kim, Baek et al. 2016). Whether neoadjuvant oncological treatment is a risk factor for AL is controversial, as an association of AL with neoadjuvant radiotherapy and chemoradiotherapy has been reported (Matthiessen, Hallbook et al. 2004, Park, Choi et al. 2013, Qu, Liu et al. 2015, Sparreboom, Wu et al. 2018), but also challenged in a meta-analysis (Hu, Huang et al. 2017).

Selection of patients to restorative procedures hinges on patient fitness, i.e. ability to withstand an AL and predicted postoperative bowel function. The main proven alternative to reduce symptomatic AL and early reoperations in low anterior resection in recent decades, is usage of a loop defunctioning stoma (Matthiessen, Hallbook et al. 2007, Gu and Wu 2015). In the recent RectoLeak TENTACLE study, 24.2% of patients undergoing TME for rectal cancer sustained an AL within 12 months, 93.5% of whom were defunctioned at index

operation, the vast majority with a loop ileostomy (van Workum, Talboom et al. 2021). Although defunctioning stoma is intended to be reversed within 3-4 months, in practice these temporary stomas are not reversed or have been converted to permanent colostomies in 18-21% of patients at two years follow-up (Gadan, Lindgren et al. 2019, Holmgren, Haggstrom et al. 2021). For patients having their stomas reversed, delays to such surgery is associated with more complications (Turner, Clifford et al. 2022), and up to 9% of patients return to theatre (Holmgren, Kverneng Hultberg et al. 2017). Loop ileostomies can cause high stoma output with a high risk of dehydration (Akesson, Syk et al. 2012, Gavriilidis, Azoulay et al. 2019) and subsequent acute kidney injury or even renal failure (Munshi, Bengtsson et al. 2020, Rutegard, Haggstrom et al. 2023), especially when not reversed in a timely fashion (Rutegard, Haggstrom et al. 2023). There are also accumulating data that defunctioning stomas may induce (Vogel, Reeves et al. 2021) low anterior resection syndrome (LARS), a cluster of symptoms that seem to stabilise only after 18 months (Varghese, Wells et al. 2022).

The increased awareness of the inherent drawbacks with a defunctioning loop-ileostomy has questioned routine diversion after low anterior resection. Early reversal within 14 days has been one suggested approach to overcome this (Danielsen, Park et al. 2017). Recent data has suggested that stomas rather delay than prevent AL (Borstlap, Westerduin et al. 2017, Jutesten, Draus et al. 2019). The main advantage of faecal diversion is prevention of life-threatening sepsis and mortality, as well as return to theatre. The issue is whether these short-term advantages outweigh the long-term stoma related morbidity and mortality. Attempts to risk-stratify patients and tailor stoma use have not been widely successful, but some centres have reported a selective use of stomas without obvious adverse consequences (Talboom, Vogel et al. 2021). There is an ongoing French prospective clinical trial, GRECCAR-17, where patients are randomised to routine loop-ileostomy (control arm) vs tailored loop-ileostomy (intervention arm) according to a risk prediction score based on sex, body mass index, smoking, diabetes, and tumour size after neoadjuvant treatment (Denost, Sylla et al. 2023). Dutch nationwide data suggest that usage of defunctioning stomas has decreased in later years down to 30% in 2020 (Ingwersen, van der Beek et al. 2023), with a concurrent increase of AL rates and reinterventions with simultaneous reduction in postoperative mortality (Arron, Greijdanus et al. 2021). This may negate the fear of AL translating into fatalities.

The current knowledge gap entails whether a selective approach to defunctioning stomas may be advantageous in a trial setting, and which of many approaches to use. As patients need to be selected, criteria need to be developed and agreed upon by the wider surgical community. Interestingly, surgeons and patients might have different thresholds for a defunctioning stoma in relation to anticipated AL rates, where 15 and 25%, respectively, would justify faecal diversion (Mackay, Clark et al. 2022). A selective approach is expected to increase at least early AL and reoperation rates; consequently, a corresponding readiness for early diagnosis and reintervention is necessary to avoid harm. The inclusion criteria and selection process in this study have been chosen to allow patients to tolerate an AL without excess mortality and also to reflect predicted AL rates below unselected usage.

Objectives

We hypothesise that the long-term effects will favour the selective approach, as many patients are likely to avoid having a stoma at all and thus without impairment of bowel function. The primary aim is to evaluate which of the approaches is superior when considering stoma-free survival at two years, without major LARS. The secondary objectives include anastomotic leakage, reinterventions, stoma-related complications, quality of life measures, major LARS, bowel continuity, patient reported recovery and permanent stoma, up to two years after surgery.

Trial design

This is a multicentre international prospective observational study including a nested non-blinded randomised clinical trial. The SELlective defunctioning Stoma Approach in low anterior resection for rectal cancer (SELSA) trial is designed as a pragmatic randomised, controlled, open label, non-blinded, multicentre superiority trial with two parallel groups and a primary outcome of stoma-free survival without major LARS at 2 years after surgery. Patients are block-randomised intraoperatively with a 1:1 allocation, stratified for centre and radiotherapy. The protocol was drafted in accordance with the SPIRIT 2013 statement (Standard Protocol Items: Recommendations for Interventional Trials) (Chan, Tetzlaff et al. 2013).

Methods and analysis

Participations, interventions, outcomes

Study setting

This is a multicentre prospective study conducted in Nordic hospitals that perform low anterior resection for rectal cancer.

Eligibility criteria

Inclusion criteria

- Adult patients with rectal cancer planned for a low anterior resection with anastomosis by TME with any surgical approach

Exclusion criteria

- Insufficient command of Swedish, Norwegian, Danish or English to understand questionnaires or consent
- Emergency rectal resection (tumour resection due to large bowel obstruction, perforation, etc)
- Pregnancy or breastfeeding

Additional inclusion criteria for randomised part of the study

- Patients aged less than 80 years
- Patients with American Society of Anesthetists' (ASA) fitness grade I or II as determined by the anaesthesiologist or the surgeon
- Patients without clear radiological signs of distant disease before rectal cancer surgery (previous metastatic surgery is no exclusion criterion)

- Anastomotic leak risk score of 0-1
- Willingness to be randomised

Additional exclusion criteria for randomised part of the study

- Previous pelvic irradiation (due to e.g. gynaecological or urological cancer)
- Preoperative tumour perforation or pelvic sepsis
- Beyond TME surgery and/or concurrent resection of other organ
- Concurrent corticosteroid treatment (prednisone-equivalent dosage ≥10 mg daily)
- Planned postoperative chemotherapy

Intraoperative exclusion criteria for randomised part of the study

- >2 staple firings for rectal transection
- Intraoperative blood loss ≥700 ml
- More than one intraabdominal anastomosis performed
- Incomplete doughnuts
- Air-leak test positive
- Any significant intraoperative adverse event at the discretion of the operating surgeon (e.g. ureterotomy, bowel or tumour perforation, major medical event – pulmonary embolism, cardiac arrhythmia) (Gawria, 2022)
- TME with anastomosis ultimately not done

Trial centre requirements

Centres can participate provided that the centre:

- Performs low anterior resection, regardless of approach
- Has resources to perform necessary trial measurements
- Has resources to provide timely reintervention for suspected anastomotic leak
- Has at least one local investigator in charge

Interventions

Preoperative measures

Stoma site is marked preoperatively by a specialised nurse. Mechanical bowel preparation is employed at all centres, where formulations vary according to local routines. Preoperative antimicrobial prophylaxis is administered according to local guidelines. Patients will be managed according to the principles outlined in the Enhanced Recovery After Surgery guidelines for rectal surgery (Gustafsson, 2019).

Low anterior resection

Any surgical approach, whether open, robotic-assisted or with conventional laparoscopy, is allowed. Splenic flexure mobilisation, left colic artery preservation, use of descending or sigmoid colon as conduit, or anastomotic configuration is at the discretion of the operating surgeon. TME should be conducted according to the principles of dissection in embryological planes as proposed by Heald (Heald, 1982) down to the pelvic floor. Adjuncts such as near-infrared indocyanine green assessment are allowed, but only to influence decision-making prior to construction of the anastomosis. After construction of anastomosis by any method, the integrity of the doughnuts should be evaluated, and an air-leak test should be performed. Agreement with the anaesthetics team should be sought to determine intraoperative blood loss; if this is 700 ml or more, more than two stapler firings have been

used, the doughnuts are incomplete, or a major intraoperative adverse event has taken place as judged by the operating surgeon, the patient will be excluded from the randomised part of the study and will be provided with either a defunctioning stoma or no anastomosis at all. Drains will be used at the discretion of the operating surgeon, but are generally discouraged. Anastomotic height is measured by digital rectal exam/rigid sigmoidoscopy and noted.

Experimental arm: selective approach to defunctioning stoma

With randomisation to this experimental arm (selective approach), no defunctioning stoma is constructed.

Control arm: systematic approach to defunctioning stoma

With randomisation to this control arm (systematic approach), a defunctioning stoma is constructed using the marked stoma site. A loop ileostomy is fashioned using an ileal loop close to the ileocecal valve, while a loop colostomy can be derived from either the transverse or a redundant left colon.

Postoperative surveillance

Patients will be surveyed according to the national guidelines concerning their oncological follow-up. In Sweden, this typically involves computerised tomography (CT) of the chest, abdomen, and pelvis at 1 and 3 years. Carcinoembryonic antigen (CEA) will be analysed at these time points as well, while a colonoscopy is provided at 3 years and subsequently at every 5 years. Any recurrences will be managed according to the local multidisciplinary team (MDT) and will be registered and ascertained via the Swedish Colorectal Cancer Registry (SCRCR) as well as to an eCRF. Other participating countries will have similar but slightly different follow-up, where participating centres will report to an eCRF.

Defunctioning stoma reversal will be performed according to local and national routines and guidelines regarding timing and operative procedure and will not be mandated by the trial itself. The integrity of the anastomosis is often determined by endoscopy and/or CT with water soluble contrast enema, prior to closure. Typically, stoma reversal is planned 3-6 months after index surgery as long as no anastomotic leak or other complications have taken place; in cases with adjuvant chemotherapy, stoma reversal is planned after completion of treatment and will therefore usually take place 9-12 months after the index surgery.

Adherence assessment

As this is a pragmatic trial of already established surgical techniques, no adherence assessment is planned.

Concomitant therapy

Preoperative as well as postoperative radiotherapy and chemotherapy, as well as other oncological agents, can be used according to the MDT.

Outcomes

The primary outcome is a hybrid so-called textbook outcome; stoma-free survival at two years without major LARS, reflecting a functionally appropriate outcome after low anterior resection for rectal cancer. The summary measure is the proportion of patients fulfilling this composite outcome: no extant stoma, alive, and a LARS score at 30 or less at the time point

two years after the anterior resection. This time point is chosen as most stomas are considered permanent two years after surgery, whereas bowel function has stabilised as well for those without a stoma in situ.

The secondary outcomes along with measurement variables, analysis metrics, aggregation methods and measurement time points, are presented in Table 1.

Table 1. Secondary outcomes in the SELSA trial

Secondary outcome	Measurement variable	Analysis metric	Summary measure	Time point (months)
Anastomotic leakage	ISREC grading	Final value	Proportion	1, 3, 12, and 24
Complications	Clavien-Dindo grade	Final value	Proportion	1, 3, 12 and 24
Length of hospital stay	Total days in-hospital	Final value	Median	At discharge
Postoperative mortality	Clinical assessment categorisation	Final value	Proportion	3
Major LARS	LARS domain score	Change from baseline *and* spot measure	Proportion	12 and 24
Quality of life	EORTC-C30 domain scores	Change from baseline *and* spot measure	Median	12 and 24
Quality of life	EORTC-CR29 domain scores	Change from baseline *and* spot measure	Median	12 and 24
QoR15swe	Total QoR15 score	Change from baseline	Median	1
Adjuvant chemotherapy for high-risk patients	Clinical assessment categorisation	Final value	Proportion	12
Renal function	Creatinine (mg/L)	Change from baseline *and* spot measure	Median	12 and 24

Stay out of hospital	Total days out of hospital and alive	Final value	Median	24
Stoma in situ	Clinical assessment categorisation	Final value	Proportion	24
Recurrence (local and distant)	Clinical assessment categorisation	Final value	Proportion	36 and 60
Overall survival	Clinical assessment categorisation	Final value	Proportion	36 and 60

Measures of complications

Anastomotic leakage

Anastomotic leakage is defined according to the INternational Study Group of REctal Cancer (ISREC) consensus definition (Rahbari, 2010), which states that any communication between intra- and extraluminal compartments is considered a leakage. This includes fistulae as well as isolated pelvic abscesses, without evidence of direct communication. Leakage will be categorised into three levels: grade A denotes a leak without need for reintervention, typically asymptomatic and detected radiologically at follow-up; grade B means a leak requiring reintervention without a formal reoperation, ranging from antibiotics to percutaneous or transanal drains or vacuum-treatment or similar procedures; grade C denotes a leak necessitating formal laparotomy or laparoscopy under general anaesthesia.

Leakage will be characterised by day of diagnosis, leak grade, type of leak, modalities used to make the diagnosis, and management of the leak itself, including subsequent reoperations and other measures. This will be included in an eCRF attached to the conventional SCRCR registration and will be registered at several time points. In particular, a postoperative examination using flexible sigmoidoscopy or contrast enema is required in order to detect even asymptomatic leaks.

Complications

Measures of complications will be registered and ascertained using an eCRF at all time points. Study-specific variables include stoma-related complications (high-output stoma, admission for dehydration, kidney injury, stoma retraction, stoma prolapse, symptomatic parastomal hernia, peristomal skin irritation, stoma leaks, stoma reversal complications).

Safety measures, early postoperative complications, and other clinical adverse events

A safety analysis will be carried out after recruitment and 90-day follow-up of 40 patients (see paragraph monitoring and quality control). Serious adverse events, e.g. admission to the intensive care unit or mortality will be reported to PIs.

Participant timeline

Patients in the SELSA trial will be screened for inclusion at each participating centre's local MDT. At the preoperative visit, after completion of potential neoadjuvant treatment, patients will be assessed for eligibility, informed of the study and informed consent will be provided. Baseline measurements include biochemical tests, quality of life and functional measures; these measures will be repeated at postoperative month one, at one year, and at two years. At these time points, an eCRF detailing postoperative complications will be filled in. Of importance, an examination at 1–3 months after surgery is scheduled, using flexible sigmoidoscopy or contrast enema. A schedule of study events is displayed in Table 2.

Table 2. Schedule of study events in the SELSA trial.

Study events	**Inclusion**	**Surgery (day 0)**	**Follow-up (month 1)**	**3 months**	**Year 1**	**Year 2**
Patient information	x					
Signed consent	x					
Confirmation of eligibility	x					
Clinical examination	x		x			
eCRF	x	x	x	x	x	x
Biochemical tests	x			x	x	x
Contrast enema and/or flexible sigmoidoscopy			x	x (if not done)	x	
QLQ-C30 & QLQ-CR29	x		x		x	x
QoR-15	x		x			
LARS	x		x		x	x
Clavien-Dindo			x		x	x
Serious adverse event	x	x	x	x	x	x
Blood sample (translational study)	x					

Clinical examination: preop – digital rectal exam, review ASA grade, body mass index; postop – chart review (eCRF) Biochemical tests: C-reactive protein, albumin, hemoglobin, creatinine and electrolytes.

Some patients will be eligible for the randomised part. The study variables are the same for the prospective and the nested randomised trial. All data will be used up to the point of discontinuation unless the reason for discontinuation is withdrawal of consent (Figure 1).

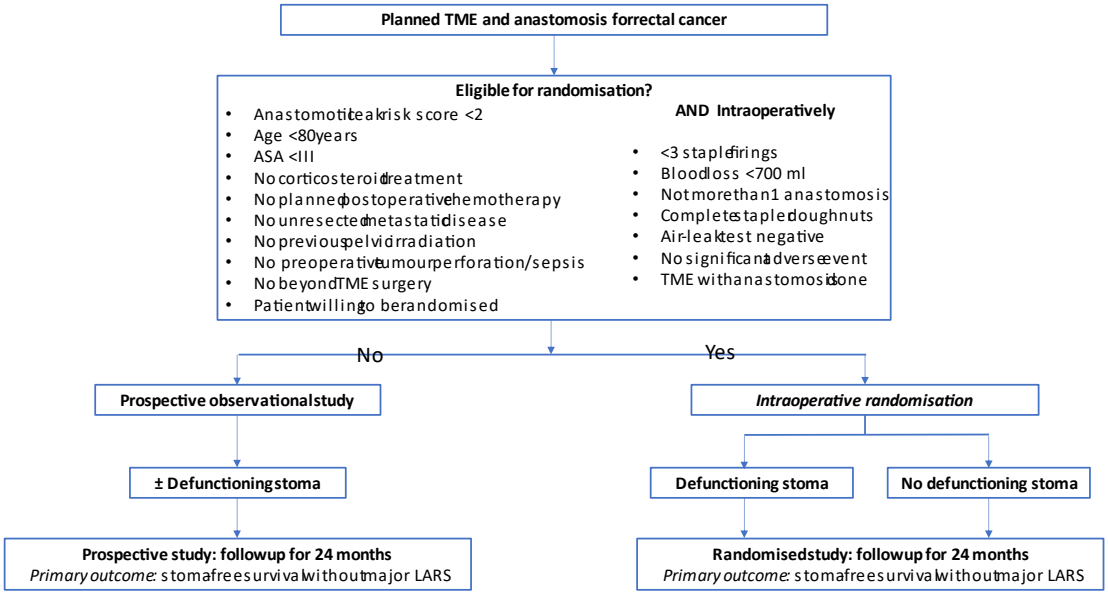

Figure 1. Study flowchart. ASA = American Society of Anaesthesiologists' fitness grade; LARS = Low anterior resection syndrome.

The anastomotic leak risk score is derived from SCRCR data on low anterior resections during 2007–2020. Using established risk factors for anastomotic leakage such as male sex, elevated body mass index (BMI), and receipt of radiotherapy, a risk prediction model was constructed and tested in an independent multicentric cohort with chart-reviewed leakage data (RectoLeak cohort: 2014–2018). This risk score model, or a similar but improved one, will be used to stratify risk of anastomotic leakage and is presented below in Table 3.

Table 3. Risk prediction modelling including male sex +1, BMI >30 +1, and radiotherapy +1 in patients with AL within ≤30 days in SCRCR 2007-2020 and ≤30 days RectoLeak cohort 2014-2018. All patients undergoing TME, <ASA 3, age ≤80 years and perioperative bleeding ≤700 ml. In the SCRCR cohort tumour height is 5-10 cm instead of TME.

Risk Score	SCRCR AL (%)	RectoLeak Early AL (%)	RectoLeak – study criteria applied early AL (%)
0	4.3	5.2	5.3
1	7.2	17.0	13.2
2+	12.0	20.8	17.2

Sample size

The sample size is considered in relation to proving superiority of the experimental no stoma arm to the control stoma arm in terms of the primary outcome stoma-free survival without major LARS at two years. The sample size is calculated with the following assumptions:

- Mortality at two years is estimated to be 4% in both groups
- Proportion of patients with stoma-free survival without major LARS is estimated at 65% in the experimental no stoma group
- Proportion of patients with stoma-free survival without major LARS is estimated at 40% in the control stoma group
- The loss of data due to for example, non-adherence to study protocol, is anticipated to be 25%

With the above assumptions, a total of 158 randomised patients (79 in each arm) are needed for 90% statistical power and a significance level of 5%. Considering attrition and missing data, this means 212 patients.

The first 100 included patients will be regarded feasibility, and after inclusion of 100 patients assumptions will be checked descriptively and sample size may be adjusted accordingly.

The prospective part will approximately contain 500 patients.

Recruitment considerations

We anticipate that study recruitment can take place within 3 years, assuming that at least 12 Nordic centres with different caseloads include on average 6 patients per year eligible for randomisation. Given successful grant applications, reimbursement for recruitment may be considered.

Assignment of interventions

Allocation

After written consent has been provided, eligibility for the prospective or the randomised part of the study is confirmed. The actual randomisation occurs intraoperatively after construction of the anastomosis and air leak test, making sure that no intraoperative exclusion criteria have been fulfilled for patients eligible for randomisation.

The randomisation will be done online via a web application (https://www.randomizer.at/) or within RedCAP. Participants will be randomly assigned to either the control or the experimental arm with a 1:1 allocation. Permuted blocks are used and the computerised randomisation is stratified by centre and radiotherapy use. The size of the randomisation blocks will vary by chance within predefined concealed limits.

Concealment mechanism

The randomisation will be centralised to prevent influence on the randomisation process.

Blinding

Blinding in surgical studies is difficult to accomplish. This study is performed without attempts for blinding and thus the healthcare workers and the patient do not have to be blinded. This may cause detection bias by the assessors, a bias which is partly reduced by the use of validated outcome scales and questionnaires.

Data collection, management and analysis

Data collection methods

The trial data will be collected as part of the routine registration in the SCRCR, but also by using study-specific eCRFs and questionnaires. Surgeons, and nurses participating in this trial are asked to provide baseline data, intraoperative data, and postoperative visit data including surveillance (as specified in Table 2 above). Patients will provide patient-reported outcomes using questionnaires, which will be administered in paper form and collected by study nurses.

Compliance and retention

To improve compliance, there will be an option to allow the central administration of the study to administer 1-year and 2-year questionnaires, including reminders. Periodical reminders to participating centres will be issued to fill in eCRFs. Prestudy meetings to explain study logistics will be held.

Statistical methods: outcomes, additional analyses, analysis population and missing data

Analysis principles

All primary analyses in this study will be performed according to the intention-to-treat (ITT) principle, that is, patients will be allocated to treatment groups corresponding to their assigned treatment, even if the patient does not receive the correct treatment.
The ITT population will consist of all patients who are operated with low anterior resection and eligible for study inclusion, subsequent randomisation and with complete data for the primary outcome.

Patient discontinuations

Reasons for discontinuations in the study will be compared between the two treatment groups. Tables or a CONSORT diagram (Moher, 2012) will reveal the number and proportion of patients who have completed the study as well as patients that have discontinued, grouped by reason for discontinuation.

Primary outcome analysis

The main analysis in this trial consists of a comparison of the proportion of patients that are stoma-free, alive and without major LARS at 2 years after surgery; the $\chi 2$ test will be used in an ITT analysis. A sensitivity analysis will be conducted, with adjustment for centre as well as preoperative variables indicating a high risk of anastomotic leakage and permanent stoma, such as sex, age, ASA fitness grade, radiotherapy, and clinical tumour stage. These adjustments, using binomial regression, are done in order to alleviate the impact of chance confounding, as this is a relatively small trial; estimates of relative risk ratios and absolute risk differences with 95% confidence intervals will be produced.

Missing data

Every effort will be made to ensure that missing data is kept at a minimum. As the primary outcome is dependent on several parameters, one of which is derived from the LARS questionnaire, multiple imputation by chained equations is planned to impute missing data for the 24-month assessment, using available data on perioperative and functional information from other time points.

Secondary analyses

Comparison between proportions in study arms will be made with the $\chi 2$ test or the Fisher's exact test, while comparisons of continuous variables will be made with the Student's t-test or Mann-Whitney U test, post hoc Bayesian analysis as appropriate. The pertinent outcomes and time points are outlined in Table 1. The following comparisons between study arms will be conducted:

- Anastomotic leakage
- Leakage grading
- Stoma-related complications
- Length of hospital stay
- Postoperative mortality
- Incidence of major LARS
- Quality of life measured with QLQ-C30 and QLQ-CR29
- Postoperative recovery measured with QoR15Swe
- Adjuvant chemotherapy receipt in patients deemed high-risk for recurrence
- Renal function
- Days out of hospital during study period
- Stoma in situ

These secondary outcome analyses are deemed exploratory.

Registry-based comparison

The trial participants can be seen as nested in a larger, population-based study based on the prospectively collected SCRCR data. This data collection can be used to provide external validation of effectiveness, where defunctioning stoma use or no use is treated as exposure and anastomotic leak as well as stoma-free survival can be seen as outcome. The relevant data can be derived from the SCRCR, where patients not included in the trial, but who could have been, are evaluated, using the same inclusion and exclusion criteria as far as possible.

Translational sub study

Participating centres may collect preoperative blood samples from all patients for later molecular analysis of predictors for anastomotic leakage. Previous research has indicated that chemokines CXCL6 and CLL11 might be strong predictors of anastomotic leakage in rectal cancer patients, but these findings require external validation (Holmgren, 2022).

Blood samples are collected the day before or on the day of surgery. The blood sampling includes EDTA plasma and serum. The aim is to have a time of less than 4 h between blood sampling and obtaining frozen aliquots. Fractions are stored in 0.5-ml microvials (Micronic, Lelystad, The Netherlands) and preserved at -–80°C. Local biobanks need to be employed.

The frozen samples will be transported to the analysis company Olink (Uppsala, Sweden), where the bespoke protein panel Olink Insight will be used. In this panel, proteins have been selected reflecting both the aforementioned chemokines CXCL6 and CLL11 as well as other proteins with high significance clinically and statistically with regards to leakage development. The panel proteins are summarised below in Table 4.

Table 4. Selected proteins of interest in the translational substudy on prediction of anastomotic leakage.

Assay name	UniProt ID	Gene
Eotaxin	P51671	CCL11 (SCYA11)
Eukaryotic translation initiation factor 4E	P06730	EIF4E (EIF4EL1 EIF4F)
C-C motif chemokine 8	P80075	CCL8 (MCP2 SCYA10
C-X-C motif chemokine 11	O14625	CXCL11 (ITAC SCYB11
Tumor necrosis factor ligand superfamily member 14	O43557	TNFSF14 (HVEML LIGHT)
Tumor necrosis factor receptor superfamily member 9	Q07011	TNFRSF9 (CD137 ILA)
Adenosine deaminase	P00813	ADA (ADA1)
C-C motif chemokine 25	O15444	CCL25 (SCYA25 TECK)
STAM-binding protein	O95630	STAMBP (AMSH)
Caspase-8	Q14790	CASP8 (MCH5)
Leukemia inhibitory factor receptor	P42702	LIFR (CD118)
Interleukin-6	P05231	IL6 (IFNB2)
C-X-C motif chemokine 6	P80162	CXCL6 (GCP2 SCYB6)
Interleukin-8	P10145	CXCL8 (IL8)
Vascular endothelial growth factor A	P15692	VEGFA (VEGF)
Matrilysin	P09237	MMP7 (MPSL1 PUMP1)
Growth-regulated alpha protein	P09341	CXCL1 (GRO GRO1
Interleukin-7	P13232	IL7
C-C motif chemokine 20	P78556	CCL20 (LARC MIP3A
Hepatocyte growth factor	P14210	HGF (HPTA)
Kit ligand	P21583	KITLG (MGF SCF)

Area under the curve with receiver operating characteristics will be derived for each protein as well as selected combinations (CXCL6 + CLL11). Thresholds to optimise subsequent diagnosis of anastomotic leakage will be calculated.

Monitoring and quality control

A safety monitoring board will be appointed with the task to contact each centre annually and ask for unforeseen adverse events and problems. If severe adverse events occur the PI and the monitoring board have the responsibility to decide whether the study can continue or should be stopped after a safety analysis – such a safety analysis will be executed after

recruitment and 90-day follow-up of 40 patients. Difference in reoperation rate, anastomotic leakage, intensive care unit admission, and mortality will be analysed.

A higher reoperation rate is anticipated in the experimental group, where earlier data suggest that this should be up to three times as likely. If a safety analysis would indicate a risk increase higher than this, early termination will be considered.

Interim analyses are planned according to the statistics paragraph. All safety analyses will be performed based on the intent-to-treat population. All statistical tests of safety will be conducted with a two-sided test, using an alpha level of 0.05.

Quality assurance

To ensure accurate and reliable data the study administration will do the following:

- Instigate start-up training and meetings with investigators
- Be available for consultation
- Regular communication to investigators with data on recruitment
- Conduct quality review of the database (a monitor may be sent to participating centres)

Monitoring of the study interventions while the trial is underway is planned, conditioned on funding, where monitors will conduct regular site visits. Individual surgical teams and centres are responsible to adhere to the protocol, nevertheless.

Ethics and dissemination

Ethical review

This study will be conducted in accordance with the ethical principles stated in the most recent version of the declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual. National ethical approval will be sought from the relevant authorities.

Informed consent

The informed consent document (supp file: informed consent) with study information will be used to explain in simple terms to patients what participation in the study means for the patient. The patient will receive information of the risks, benefits, and potential alternatives.

It is the investigators' responsibility to ensure that informed consent is obtained from each patient study inclusion. The informed consent document must be signed, dated and subsequently stored in an archive at each participating centre. The signed document may also be photo-scanned to an electronic document and included in the hospital electronic patient file.

Patient and public involvement

The protocol has been developed in conjunction with national and international patient representatives. Lay men will be involved in the approval by the Swedish Ethical Review Authority.

Confidentiality

The study participants' data are entered into eCRF in RedCap or attached to the patient's SCRCR record. Each participant is deidentified, using a linking code, which is separate from the database server; the code is encrypted, stored on a universal serial bus device and kept in a locked office space. Code access is limited to the PI and the independent observer, if need be. Only deidentified data is shared with co-investigators.

Access to data

The full dataset will only be accessible by the PI and the co-investigators who are involved in the analysis part of the drafted manuscripts.

Compensation for damage incurred

Every participant in the study may be compensated for damage incurred, by the regular insurance policy for patients as provided by the appropriate legal bodies in Sweden.

Publication policy

Every attempt will be made to reduce to a minimum the time interval between data collection completion and the release of study results. After data collection is finalised, we expect that a time period of at least 6 months is needed to compile the results and submit the findings to an appropriate journal. All results will be disseminated to the site investigators, patients and the general medical community.

At least two publications including study protocol and main finding will be submitted. The translational part will be published separately. Most likely several spinoff papers including sub-group outcomes and long-term outcomes will be published.

Authorship rules

We aim to recruit co-authors for the reports of this study among the investigators in participating centres. One site investigator from each centre will be offered co-authorship as long as patients are eventually recruited, while other participants with a substantial contribution will be denoted collaborators.

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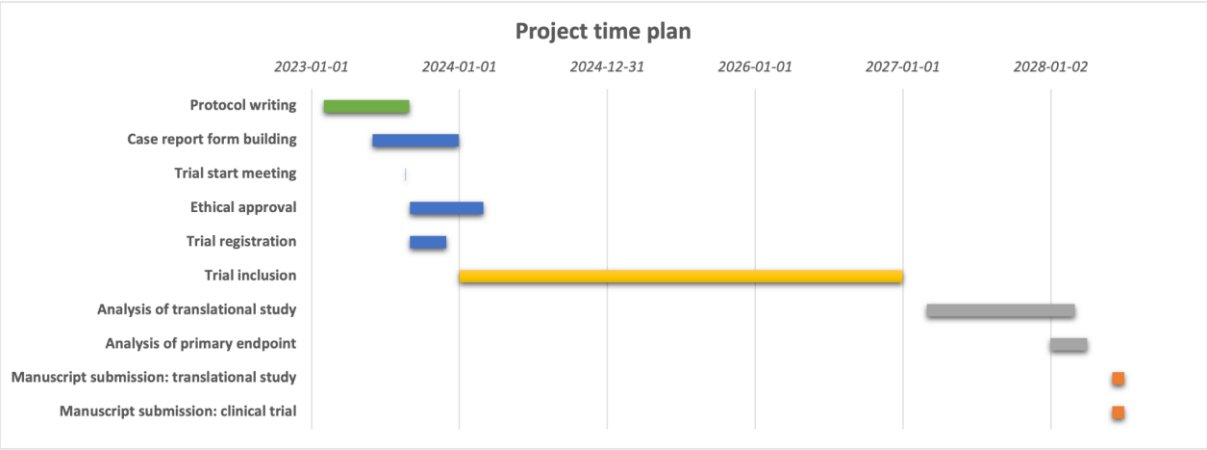
Appendix

SELSA estimated time plan.


Project time plan
2023-01-01
2024-01-01
2024-12-31
2026-01-01
2027-01-01
2028-01-02
Protocol writing
Case report form building
Trial start meeting
Ethical approval
Trial registration
Trial inclusion
Analysis of translational study
Analysis of primary endpoint
Manuscript submission: translational study
Manuscript submission: clinical trial

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