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PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled studY (PROSPERITY)

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Key words: colorectal cancer, ostomy, stoma, ileostomy, colostomy

Abstract

Introduction

Loop ileostomy and loop colostomy are both used as protective stomas after anterior resection. Evidence is lacking regarding on the superiority of these two. Additionally, no studies exist comparing the changes in microbiome after loop ileostomy or loop colostomy.

Methods and analysis

This is a multicenter, open-label, superiority, individually randomized controlled trial including patients undergoing anterior rectal resection with primary anastomosis and a protective stoma. The exclusion criteria are patient already having a stoma, technical inability to create either type of stoma, age <18 years and inadequate cooperation. Patients scheduled for anterior rectal resection are randomized intraoperatively in a 1:1 ratio to receive either a loop ileostomy or a loop colostomy. The primary outcome is cumulative stoma-related adverse events within 60 days post-primary surgery measured by the Comprehensive Complication Index (CCI). Secondary outcomes are all postoperative complications (using CCI), hospital-free days within 30 days after primary surgery, quality of life at 2 months (measured by EORTC Quality of life questionnaires Core 30 and Colorectal 29), complications within 30 days after stoma closure (using CCI), and kidney function (estimated glomerular filtration rate) at 1 year. Tertiary outcomes are survival, kidney function, and number of stoma site hernias at 5 years. The sample size was calculated to detect mean difference of 5 CCI points between the groups, resulting to a final sample size of 350 patients. Additionally, microbiome samples will be collected from the faeces and mucous membrane.

Ethics and dissemination

The Helsinki University Hospital ethics committee approved the study (4579/2024). The findings will be disseminated in peer-reviewed academic journals.

Trial registration number: NCT06650085

Strengths and limitations of this study

- The prospective study design and randomization together with meticulously calculated power analysis will provide level 1 evidence on the differences between the two treatment methods, which previous small RCTs did not provide.
- The multicenter trial setting will provide a more generalizable and reliable study cohort.
- The definition of a stoma related adverse events is rigorously defined before the study initiation. In cases of uncertainty, these events are reviewed by an outcome board (consisting of three persons not involved in patient recruitment, surgery, treatment, or data collection). The board members will be blinded to the allocation group.

Introduction

Anterior resection or abdominoperineal resection with total mesorectal excision are the two standard methods of treating middle and low rectal cancer (1). The sphincter saving anterior resection is generally preferred when tumor margins and patient fitness allow, as it is associated with better quality of life after surgery compared to abdominoperineal resection, which results in a permanent stoma (2). However, anterior resection carries the risk of anastomotic leakage, a complication associated with costly postoperative morbidities and a negative impact on long-term outcomes, including reduced overall survival (3).

Several preventive methods have been introduced to mitigate the risk of anastomotic leakage following anterior resection for rectal cancer. These include preoperative mechanical bowel preparation, oral antibiotics, intraoperative testing of anastomotic integrity and perfusion, anastomotic buttressing, anastomotic reinforcement, and use of a protective stoma among other techniques (4).

The use of protective stoma has been a common practice in low anterior resection for decades (5). The diversion of feces is thought to reduce intraluminal pressure and decrease the bacterial load at the distal anastomosis (6). While protective stoma does not reduce the incidence of anastomotic leakage (7-8), it does limit morbidity by lowering the risk of faecal peritonitis and septicemia in the event of leak (9).

Loop ileostomy and loop colostomy are the two methods for creating a temporary protective stoma (4). Despite their long-standing use, no clear superiority of one over another has been established, resulting in large variation in the use of stoma type between surgeons, centers, and countries.

We are aware of five randomized controlled trials (RCT) comparing loop ileostomy and loop colostomy during anterior resection for rectal cancer (**Table 1).** These trials are over two decades old, have small sample size, and have various endpoints. In addition, several retrospective series have compared the two stoma types, but they are limited and biased by various confounding factors. Meta-analyses including also retrospective series indicate differing risk-benefit profile for the two stoma types. While loop ileostomy may result in fever parastomal hernia, prolapses, and stoma retractions, loop colostomy seem to have fever issues with dehydration (10-11). Regarding stoma closure, loop ileostomy may be associated with fever surgical site infections but a higher incidence of postoperative bowel obstruction (10-11). Adding to this debate, a nationwide study reported an alarming rate of renal failure

in patients with loop ileostomy (12), and another recent study linked loop ileostomy with a higher incidence of low anterior resection syndrome (13).

Table 1. RCTs comparing loop ileostomy (LI) and loop colostomy (LC) in patients undergoing anterior resection

Author, Publication year	n	Primary endpoint	Main findings	Conclusions
Williams et al, 1986 (14)	47 (23 LI vs. 24 LC)	Stoma-related morbidity	LI: 3(18%) LC: 11 (58%)	In favor of LI
Khoury et al, 1987 (15)	61 (32 LI vs 29 LC)	Anastomotic leakage after primary operation	LI: 2 (6%) LC: 6 (21%)	In favor of LI
Gooszen et al, 1998 (16)	76 (37 LI vs 39 LC)	Stoma-related morbidity	LI : 9 (24%), LC: 1 (3%)	In favor of LC
Edwards et al, 2001 (17)	70, (34 LI vs 36 LC)	Clinically relevant anastomotic leakage	LI: 2 (6%) LC: 1 (3%), more other stoma-related complications in the LC group	In favor of LI
Law et al, 2002 (18)	80 (42 LI vs 36 LC)	Ileus after primary operation	5 postoperative ileus, 2 intestinal obstruction before stoma closure [6 (14%) LI, 1 (3%) LC]	In favor of LC

In the past few years, the relationship between pathological imbalance in the colonic microbiome and colorectal cancer has been distinguished (19). The colonic microbiome is known to play a role in carcinogenesis (19-20), progression (21-22) and treatment of colorectal cancer (22-23). The only study that we are aware of comparing microbiome of colorectal cancer patients with or without loop ileostomy or colostomy is a recent observational cohort study from Japan involving 165 patients (24). In that study, patients with stoma had a reduced number of microbes favorable for cancer immunotherapy compared to patients without a stoma. There are no studies comparing the differences of microbiome between loop ileostomy and loop colostomy. Given that the colonic microbiome is recognized to play a significant role in the treatment of colorectal cancer, there might be important differences in the colonic microbiome in patients with loop ileostomy and loop colostomy (19-23).

To provide Level 1 evidence for clinical practice, we designed PROSPERITY trial (PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a

multicenter, open-label, randomized conTrolled studY) which primarily aims to compare loop ileostomy to loop colostomy in terms of stoma-related adverse events. The study includes also microbiological analyses to assess the changes in and the role of the microbiome in patients undergoing either of the stomas. The hypothesis of the study is that protective loop colostomy will result in fever and/or less severe stoma-related adverse events than a loop ileostomy within 60 days.

Methods and analysis

Study design

PROSPERITY (PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled study) is a multicentre, open-label, superiority, individually randomized study. Participating hospitals are Helsinki University Hospital, Turku University Hospital and Tampere University Hospital. More hospitals may join after the commencement of the trial. The study has been registered on ClinicalTrials.gov (NCT06650085) prior to commencement. The Ethical Committee of Helsinki University Hospital has approved the study plan (4579/2024). This protocol is constructed according to the guidance in SPIRIT statement, and the checklist is available in the Supplementary Material.

Inclusion criteria

Patients undergoing anterior resection (resection of the rectum with colorectal or coloanal anastomosis) due to rectal neoplasia, and a protective stoma is planned are assessed for eligibility.

Exclusion criteria

The exclusion criteria are: (1) patient already having a stoma (or an additional stoma made during surgery), (2) technical inability to create ileostomy or colostomy (e.g. previous bowel resection, anatomical factors), (3) age <18 years, (4) inability to adequately co-operate.

Trial intervention

Intervention groups are: (1) loop colostomy, (2) loop ileostomy. Both protective stomas will be created using standard surgical techniques: Stoma sites, both for ileostomy (typically lower right quadrant) and for colostomy (typically upper right quadrant, right transversostomy) are

marked preoperatively when patient is in sitting position. A circular or transverse incision is made into the skin at the marked place. The subcutaneous tissue is dissected in a cylinder shape. A cross shaped or horizontal incision is made in the external rectus sheet fascia. Rectus muscle is pulled apart (not transected) to reach the internal rectus sheet fascia, where a cross shaped or horizontal incision of approximately two fingers wide is made. A loop of the transverse colon/ileum is brought to the skin with two lumens draining into a stoma bag. Transverse colon/ileum is attached to skin with absorbable sutures, preferably with three point sutures. A stoma bridge can be used if warranted. Stoma incision should not be made outside rectal sheet and distance from costal margin should be long enough to allow proper fixation of the stoma bag.

Randomization

Recruitment will take place before surgery, preferably at the preoperative clinical visit, and the patient will need to provide written informed consent before enrolment to the trial. The final inclusion and randomization will occur during surgery after the anterior resection and colorectal or coloanal anastomosis have been completed, and the surgeon has confirmed that a protective stoma is required and that both ileostomy and colostomy are technically feasible.

Patients are individually randomized in a 1:1 ratio to either to formation of loop ileostomy or loop colostomy. The randomization sequence is generated by computer using variable block size of 4-6. The randomization sequence is stratified according to: (1) center, (2) body mass index (<30 kg/m^2 and >30 kg/m^2), and (3) any neoadjuvant treatment given (yes/no) (radiotherapy, chemotherapy or combination of these two). The allocation will be done using REDCap randomization service.

Blinding

The study will be conducted as open label trial, as blinding of neither patients, treating personnel nor data collectors is considered feasible. However, to minimize bias in open label design, the primary outcome has been carefully designed to be as objective as possible. Additionally, outcomes that are not predefined will be assessed by blinded outcome board (see details in Primary outcome justification).

Study outcomes

The primary outcome is the occurrence of prespecified stoma-related adverse events within 60 days from primary surgery, reported using Comprehensive Complication Index (CCI). As what

constitutes a stoma-related adverse event can be subjective, these events have been pre-defined and listed in **Table 2**. Similarly, adverse events that are not considered stoma-related are also detailed in **Table 3**. The list of stoma-related adverse events was complified based on a comprehensive literature search conducted using the words "ileostomy and colostomy and complications" from 2022 to 2023. A total of 99 publications were assessed, and all relevant complications were included in the list. From this list, a panel of 10 consultant surgeons assessed if an adverse event was stoma-related or not. A second round of assessment was performed for those adverse events that did not meet 90% agreement. Any other adverse event occurring during the period (within 60 days from primary operation) and is not included in the list, will be reviewed by outcome board (consisting of three persons not involved in patient recruitment, surgery, treatment, or data collection). The board members will be blinded to the allocation group. The time frame of 60 days was chosen bearing in mind that protective stomas are recommended to be closed within 2 – 3 months from primary operation. The CCI is based on Clavien-Dindo classification and takes into account cumulative burden of adverse event (25). Comprehensive Complication Index has values from 0 to 100. Value 0 indicates no events and 100 indicates death due to an adverse event. Details of adverse event types will be reported, but not statistically analysed.

Secondary outcomes are: (1) all complications within 30 days from primary operation reported using CCI in order to capture all (not just stoma-related) postoperative complications, (2) all complications within 30 days from stoma closure operation, reported using CCI (including only patients who have undergone stoma closure within 1 year from primary surgery), (3) hospital-free days within 30 days from primary operation, (4) quality of life at 2 months measured using EORTC Quality of life questionnaires core 30 and colorectal 29 (QLQ-C30+QLQ-CR29), 2 months was chosen as the time-point to reflect quality of life while the stoma is still in place, but still enough time to recover from the primary operation, (5) kidney function change at 1-year compared with initial kidney function (measured by the difference in eGFR before and 1 year after primary operation). Tertiary outcomes are: (1) 5-year overall survival, (2) 5-year disease-free survival (including only patients with M0 at primary operation undergoing radical R0/1 surgery), (3) kidney function change at 5 years compared with initial kidney function (difference in eGFR before and 5 years after primary operation), (4) number of incision hernias of ostomy site within 5 years from primary surgery (only patients who have undergone successful stoma closure and are alive at 5 years will be included in this analysis), (5) cumulative death-censored successful stoma closure, within 5 years from primary surgery (if a

stoma closure is attempted, but, for example, an anastomotic dehiscence occurs and stoma is refashioned, it is not considered a successful stoma closure), and (6) quality of life at 5 years EQ-5D-5L, QLQ-C30, QLQ-CR29, low anterior resection syndrome score (LARS scores, only for patients without stoma). The exploratory outcomes/variables are: (1) quality of life within 1 year (EQ-5D-5L at 2 months, 6 months and 1 year after primary operation, LARS score at 6 months and 1 year after primary operation (only for patients without stoma), and QLQ-C30, QLQ-CR29 at 6 months and 1 year after primary operation), (2) total number of anastomotic leakages reported also with grading (26) within 60 days from primary operation, and (3) intestinal microbiome (only patients of the Helsinki University Hospital) composition and functional potential during the stoma in place and stabilization of microbiome after stoma closure. We will correlate bacterial taxa with the clinical outcomes to study whether microbiome characteristics are linked to the clinical outcomes in short (1-year) or long (5-year) term.

Table 2. Stoma-related adverse events

Complication
Stoma necrosis *) **)
Stoma prolapse*) **)
Parastomal hernia*) **)
Bleeding from stoma site*) **)
Stoma retraction or stoma lift off from the skin*) **)
Peristomal skin irritation requiring change in treatment (extra stoma bag change, topical creams, etc) *) **)
Stoma stenosis or obstruction*) **)
Peristomal fistula or abscess*) **)
Stoma mucosal hypertrophy requiring change in treatment
Ileus, including stoma site related occlusion, but excluding if a specific other reason for ileus is found (for example internal hernia not related to stoma or mechanical bowel obstruction not at the site of stoma)
Pneumonia if caused by aspiration due to ileus (ileus as described above)
Surgical site infection at stoma site or other incision site
Fascial dehiscence if occurring with SSI or ileus (ileus as described above)
Electrolyte imbalance or acute kidney failure (KDIGO stage 1 [serum creatinine rise >1.5x baseline or >26.5mikromol/L) or higher) or need for iv fluids due to high stoma output (>1500ml/d) (each day of needing iv fluids is counted as one complication)
Cerebro/cardiovascular or thromboembolic event if occurring at a time of dehydration and high-output stoma (>1500ml/d)
Atrial fibrillation or other arrhythmia if occurring with dehydration or electrolyte imbalance and high-output stoma (>1500ml/d)

*) Clavien-Dindo class 1 if does no intervention is required, otherwise according to intervention as according to Clavien- Dindo classification.

**) Counted once for first occurrence, and subsequently only extra visit(s) to medical unit (stoma nurse, emergency deparment, or other) due to this particular reason is counted as another cumulative adverse event.

Table 3. Adverse events that are not considered stoma-related

Complication
Pneumonia if not caused by aspiration due to ileus
Urinary tract infection
Cerebro/cardiovascular or thromboembolic event if occurring without dehydration.
Bleeding, other site than stoma
Delirium if occurring without dehydration or electrolyte imbalance
Urinary retention
Peripheral nerve paresthesia / paralysis
Fever, unknown origin
Clostridium difficile infection
Respiratory distress
Cholecystitis
Atrial fibrillation or other arrhythmia if occurring without dehydration or electrolyte imbalance
Ascites
Epidural complications (headache, hematoma, etc)
Fascial dehiscence if occurring without SSI and without ileus
Intestinal perforation if not anastomotic leakage and not at the stoma site
Haematuria
Allergic reactions
Abnormal pain
Anastomosis stricture
Pleural effusion
Ureteral complications (stone, stricture, lesion, etc)
Bowel obstruction if a mechanical obstruction not caused by stoma site
Bowel necrosis not at the stoma site
Anastomotic leakage
Intra-abdominal abscess not located at the stoma site
Acute kidney injury without concomitant high-output stoma (>1500ml/d)

Follow-up

Patients will be monitored via telephone by the study nurse every two weeks to identify any potential postoperative or stoma-related adverse events for up to 60 days after primary operation. Additionally, a follow up call will be made at 30 days after stoma closure operation. Colorectal/coloanal anastomosis will be assessed by computed tomography imaging using per

rectal contrast medium, colonography, or by endoscopy at approximately 6 weeks after primary operation. Patients will be contacted by letter or telephone at 1 year and 5 years after primary operation. Creatinine tests will be taken at 1 year and 5 years after primary operation to calculate eGFR. Outcomes will also be assessed from patient records, and if necessary, by requesting patient records from other hospitals. Patients will be asked to complete quality of life questionnaires EQ-5D-5L (27), QLQ-C30 (28), QLQ-CR29 (29), and LARS score (30) before surgery, at 2 months, at 1 year, and at 5 years after primary operation. The patient can be contacted by letter or telephone, if necessary, at any time point.

Costs and funding

There will be no additional cost for the hospitals involved in this study concerning the operative treatment of the patients, since both studied interventions are standard procedures in daily use when treating patients with rectal tumours. Patients will not require extra visits or examinations due to participating in the study. Follow-up is done via telephone call by a study nurse. Routine follow-up according to normal clinical practice after rectal surgery is up to 5 years and includes needed laboratory tests. The cost of handling and analysing microbiome samples, and researcher and study nurse salaries are paid from research grants. This is an investigator-initiated study without any commercial funders.

Intestinal microbiome analysis

Samples will be taken from the faeces stored in the colon as well as the mucous membrane biopsies of all patients who undergo preoperative endoscopy at Helsinki University Hospital. Mucous membrane biopsies will be taken at the planning visit, in the primary operation, at the stoma closure operation and at the 1-year follow up visit. Stool samples will be collected preoperatively, at the primary operation, at the stoma closure operation (from the stoma pouch) (**Table 4**). Additional samples will be taken 3, 6 and 12 months after the stoma closure operation. Microbial swab sample will be taken from the rectum at the stoma closure operation. Samples will be used for microbiome analysis and mucosal gene expression. The mucosal samples will be stored directly in RNAlater solution for analysis and feacal samples will be frozen and stored in – 80C within one day of the defecation.

The primary analysis for mucosal samples method will be high-throughput sequencing of the 16S rRNA genes of the bacteria. Profiling of 16S rRNA genes reveals the composition of the bacterial population. The primary method for faecal samples is shotgun metagenomic sequencing, in which the genetic material of the microbes is extensively sequenced and allows

to study also the functional potential of microbiome in addition to its composition. The analyses will be performed using methods and bioinformatic pipelines that are used routinely and updated frequently in the research group. The research group has extensive experience on intestinal microbiome composition studies, therapeutic use of intestinal bacteria (faecal transplants), and studying host–microbe interactions (31-34).

Sample size

For power calculation purposes, a sample of 95 consecutive patients who underwent anterior resection with loop colostomy for rectal cancer in Helsinki University Hospital in MOBILE2 trial (35) were assessed. The stoma-related CCI in this group was mean 2.5, SD 6.2. The sample size calculation was based on detecting a 5-point difference in CCI between the groups (hypothesis: 2.5 points in the loop colostomy group and 7.5 points in the loop ileostomy group, with an SD of 14). With a power of 90% and significance level set at 5%, 330 patients are required (36). Accounting for up to 5% lost to follow-up, the final sample size of 350 patients.

Statistical analysis plan

The primary analyses will be conducted on an intention-to-treat basis. The primary outcome will be analysed using either the Mann-Whitney U-test or the t-test, bootstrapped or log-transformed if necessary. Secondary outcomes will be analysed using either the t-test or the Mann-Whitney U-test for continuous variables, depending on the distribution, and using Chi-square or Fisher's exact test for categorical variables. If necessary, log-transformation can be performed on non-normally distributed continuous variables, or a bootstrapped t-test can be used. Tertiary outcomes will be analysed separately when at least 5-year follow-up is available for all patients. Kaplan-Meier and the log-rank test will be used for survival analysis and eGFR will be analysed using t-test or Mann-Whitney U test. Kaplan-Meier method and log-rank test will be used estimate the cumulative incidence of incisional site hernias. Statistical significance is set at two-tailed p value <0.05. Effect sizes will be reported using relative risk (RR) corrected from odds ratio (OR) with 95% confidence intervals, or as Wilcoxon effect size ($r=z\ \sqrt{n}$).

Prespecified subgroup analyses according to 1) body mass index (<30 kg/m^2 and >30 kg/m^2), 2) surgical approach (minimally invasive vs open surgery), 3) neoadjuvant treatment (yes / no), 4) adjuvant treatment (yes / no) and 4) cancer stage (stage 1-3 vs 4) will be done.

Data collection, management and post-trial care

Data will be gathered to Case Report Forms (CRF) 1-8 into REDCap web application (Table

4). Data or safety monitoring is not deemed necessary, as the study involves standard care treatments without novel interventions. Access to data will be restricted to investigators and study nurses. Post-trial care is not warranted since the interventions used in this trial are standard, widely accepted treatments for rectal cancer, and patients will receive standard clinical care outside the trial.

Table 4. Participant timeline

	Enrollment	Primary operation	Hospital stay	Anastomosis assessment, imaging or endoscopy, 6 weeks from operation	Follow-up 60 days after primary operation, phone call	Follow-up 6 months after primary operation, phone call and/or letter	Follow-up 1 year after primary operation, phone call and/or letter	Stoma seclusion	Follow-up 30 days after stoma seclusion, phone call	Follow-up 5 years after primary operation, phone call and/or letter
CRF	CRF1	CRF2-3			CRF4	CRF5	CRF6	CRF8	CRF9	CRF7
Written informed consent	x									
Inclusion / exclusion evaluation	x	x								
Randomization		x								
QOL	x				x	x	x			x
Medical history	x							x		
eGFR and creatinine	x	x			x		x	x		x
Operative details	x	x						x		
Assessment for adverse		x	x	x	x				x	

events / complications										
Assessment for stoma site hernia										x
Assessment for recurrence							x			x
Assessment for survival							x			x
Microbiome samples	MMB, SS	MMB, SS					MMB, SS	MMB, SS, S		

Abbreviations: CRF – case report form, QOL – quality of life, eGFR – estimated glomerular filtration rate, MMB – mucous membrane biopsies, SS – stool samples, S – swap sample from rectum

Schedule

The research project is scheduled to begin during 2024 or once the study protocol has been peer reviewed, and potentially updated. It is estimated that patient recruitment will take approximately 2-3 years to reach the required sample size as determined by the power calculation. The follow-up phase is estimated to continue until the end of 2032 (5 years from last patient undergoing primary surgery).

Ethics and dissemination

The study plan has been approved by the ethics committee of Helsinki University Hospital. Permit to conduct the study will be sought from each participating centers' institutional review board. All patients fulfilling the inclusion / exclusion criteria are eligible to participate in the trial regardless of their gender, sex, or race. All patients in the study are adults and need to have a sufficient comprehension regarding language (Finnish, Swedish, or English) and information in the written informed consent form. The patient is informed by the recruiting surgeon in verbal and written form. It is voluntary to participate in the study and it will not affect the patient's other treatment. The informed consent form must be signed by the patient and the recruiting surgeon before participation to study. Patient may withdraw their consent any time

without losing any of their rights as a patient.

Both intervention arms (loop ileostomy and loop colostomy) are standard treatment and the choice between them is based on surgeon or center preference outside the trial. Thus, it is considered ethical to randomize patients to either intervention.

During the study, patient identification data will be collected in a study folder. The data collected in the study is stored and analysed without patient identification data. At randomization, each study patient will receive a study number, which will be linked to their identification information in the study folder. Data will be stored in a locked room, and electronic data will be stored on hospital computers, on password-protected drives. Data will be processed in accordance with the General Data Protection Regulation (GDPR) and the basis for processing the data will be Article 6 (e) in conjunction with Article 9 (i).

Two patients who had undergone anterior resection with a protective colostomy as well as a stoma nurse contributed to the study plan and consent forms. The patients wished to remain anonymous.

Study protocol has been sent to an international peer-reviewed journal before the study is commenced. The results will be reported in a scientific manuscript submitted to an international peer-reviewed journal. First report will cover primary, secondary and exploratory outcomes up to 1-year follow-up. Second report will address outcomes up to 5-years. Microbiological analyses will be reported separately once 1- and 5-year outcomes are available. All reports will be published open access provided that the journal has an open access option and funding for article processing charges is obtained. No usage of professional writers is intended.

Data availability statement: Data may be shared if appropriate permissions are first sought and obtained, if obtained study permissions allow it, and sharing is compliant with the Finnish law.

Authors contributions: LK, VS, PP, PM, RM, AL, TS, MCH, CH, AC and KL have contributed to the design of this protocol. VS is the principal investigator. The protocol was drafted by LK, PP and VS, which was further refined by other authors. All authors have read and approved the final manuscript.

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Competing interests statement

All authors declare no conflict of interest.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	11, 15, 16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	-
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6-7

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6-7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	13-14

		(see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	12-13

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	-
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	8-11

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of	#28	Financial and other competing interests for principal	15

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12-13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12-13
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14-15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

BMJ Open

PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled studY (PROSPERITY)

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PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled studY (PROSPERITY) - study protocol

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Key words: colorectal cancer, ostomy, stoma, ileostomy, colostomy

ABSTRACT

Introduction

Loop ileostomy and loop colostomy are both used to form a protective stoma after anterior resection. Evidence regarding which of these two procedures is superior is lacking. Furthermore, no studies comparing changes in the microbiome after loop ileostomy or loop colostomy exist.

Methods and analysis

This multicenter, open-label, superiority, individually randomized controlled trial will include patients who undergo anterior rectal resection with primary anastomosis with a protective stoma. The exclusion criteria are patients who already have a stoma, technical inability to create either type of stoma, aged <18 years, and inadequate cooperation. Patients scheduled for anterior rectal resection will be randomized intraoperatively in a 1 to 1 ratio to undergo either loop ileostomy or loop colostomy. The primary outcome is cumulative stoma-related adverse events within 60 days after primary surgery, measured using the Comprehensive Complication Index (CCI). Secondary outcomes include all postoperative complications (measured using the CCI), number of hospital-free days within 30 days after primary surgery, quality of life at 2 months (measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires Core 30 and Colorectal 29), complications within 30 days after stoma closure (measured using the CCI), and kidney function (measured using estimated glomerular filtration rate) at 1 year. Tertiary outcomes are survival, kidney function, and number of stoma site hernias at 5 years. The sample size was calculated to detect a mean difference of five CCI points between groups, resulting in a final sample size of 350 patients. Microbiome samples will be collected from the feces and mucous membrane from patients in Helsinki University Hospital.

Ethics and dissemination

The Ethics Committee of Helsinki University Hospital approved the study (approval number 4579/2024). The findings will be disseminated in peer-reviewed academic journals.

Trial registration number: ClinicalTrials.gov: National Clinical Trial number: 06650085, registered on 20th August 2024.

Strengths and limitations of this study

- The prospective study design and randomization, together with meticulously calculated power analysis, will provide level 1 evidence on the differences between the two treatment methods, which previously conducted small randomized controlled trials have not provided.
- The multicenter trial setting will provide a more generalizable and reliable study cohort.
- A stoma-related adverse event was rigorously defined before study initiation. In cases of uncertainty, these events will be reviewed by an Outcome Adjudication Committee consisting of three individuals not involved in patient recruitment, surgery, treatment, or data collection. The committee members will be blinded to the allocation group.

INTRODUCTION

Anterior resection or abdominoperineal resection with total mesorectal excision are the two standard methods used to treat middle and low rectal cancer [1]. The sphincter saving anterior resection is generally preferred when tumor margins and patient fitness allow because it is associated with better quality of life after surgery than abdominoperineal resection, which results in a permanent stoma [2]. However, anterior resection carries the risk of anastomotic leakage, a complication associated with costly postoperative morbidities and a negative impact on long-term outcomes, including reduced overall survival [3].

Several preventive methods have been introduced to mitigate the risk of anastomotic leakage following anterior resection for rectal cancer. Among others, these techniques include preoperative mechanical bowel preparation, oral antibiotics, intraoperative testing of anastomotic integrity and perfusion, anastomotic buttressing, anastomotic reinforcement, and creation of a protective stoma [4].

Use of a protective stoma has been common practice in low anterior resection for decades [5]. Diverting feces is thought to reduce intraluminal pressure and decrease the bacterial load at the distal anastomosis [6]. Although a protective stoma does not reduce the incidence of anastomotic leakage [7, 8], it does limit morbidity by lowering the risk of fecal peritonitis and septicemia in the event of leak [9].

Loop ileostomy and loop colostomy are the two methods used to create a temporary protective stoma [4]. Despite their long-standing use, no clear superiority of one over the other has been established, resulting in a large variation in the stoma type used between surgeons, centers, and countries.

We are aware of five randomized controlled trials in which the use of loop ileostomy and loop colostomy during anterior resection for rectal cancer have been compared (**Table 1).** These trials took place more than 2 decades ago, used small sample sizes, and had various outcomes. Several retrospective series have also compared the two stoma types, but these studies were limited and biased by diverse confounding factors. Meta-analyses, including also retrospective series, indicate differing risk–benefit profiles for the two types of stomata: Loop ileostomy may result in fewer parastomal hernias, prolapses, and stoma retractions, whereas loop colostomy appears to result in fewer problems related to dehydration [10, 11]. Regarding stoma closure, loop ileostomy may be associated with a lower incidence of infection at the surgical site but a higher incidence of postoperative bowel obstruction [10,

11]. Adding to this debate, one nationwide study reported an alarming rate of renal failure in patients with loop ileostomy [12] and another, recent, study linked loop ileostomy with a high incidence of low anterior resection syndrome [13].

Table 1. Randomized controlled trials in which loop ileostomy and loop colostomy in patients undergoing anterior resection were compared

Author, Publication year	Number	Primary outcome	Main findings	Conclusions
Williams et al., 1986 [14]	47 (23 LI vs. 24 LC)	Stoma-related morbidity	LI: 3 (18%) LC: 11 (58%)	Favored: LI
Khoury et al., 1987 [15]	61 (32 LI vs. 29 LC)	Anastomotic leakage after primary surgery	LI: 2 (6%) LC: 6 (21%)	Favored: LI
Gooszen et al., 1998 [16]	76 (37 LI vs. 39 LC)	Stoma-related morbidity	LI: 9 (24%) LC: 1 (3%)	Favored: LC
Edwards et al., 2001 [17]	70, (34 LI vs. 36 LC)	Clinically relevant anastomotic leakage	LI: 2 (6%) LC: 1 (3%) More other stoma-related complications in the LC group	Favored: LI
Law et al., 2002 [18]	80 (42 LI vs. 38 LC)	Ileus after primary surgery	LI: 6 (14%) LC: 1 (3%) 5 cases of postoperative ileus, 2 of intestinal obstruction before stoma closure	Favored: LC

Abbreviations: LC, loop colostomy; LI, loop ileostomy.

In recent years, a relationship between pathological imbalance in the colonic microbiome and colorectal cancer has been discerned [19]. The colonic microbiome is known to play a role in carcinogenesis [19, 20], as well as progression [21, 22] and treatment of colorectal cancer [22, 23]. We are aware of only one study that compared the microbiomes of patients with colorectal cancer with or without loop ileostomy or colostomy; this recent observational cohort study conducted in Japan involved 165 patients [24]. In that study, patients with stoma had fewer microbes favorable for cancer immunotherapy than patients without. No studies comparing the differences in microbiomes between loop ileostomy and loop colostomy are available. Given that the colonic microbiome is recognized to play a significant role in treating colorectal cancer, important differences in the colonic microbiomes of patients undergoing loop ileostomy and loop colostomy may exist [19-23].

To provide Level 1 evidence for clinical practice, we designed the PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled studY (PROSPERITY) trial. This trial primarily aims to compare loop ileostomy to loop colostomy in terms of stoma-related adverse events. The study also includes microbiological analyses to assess the changes in, and role of, the microbiome in patients undergoing either of the stomata. In this study, we hypothesized that protective loop colostomy will result in fewer and or less severe stoma-related adverse events than a loop ileostomy within 60 days.

METHODS AND ANALYSIS

Study design

The PROSPERITY trial is a multicenter, open-label, superiority, individually randomized study. The trial will be coordinated by the Helsinki University Hospital, which will oversee study implementation and ensure adherence to the protocol. The Steering Committee, composed of adjunct professors from Helsinki University Hospital, will provide scientific guidance and strategic oversight throughout the trial. An Outcome Adjudication Committee consisting of three consultant gastroenterological surgeons will be responsible for assessing trial outcomes to ensure consistency and unbiased evaluation. The Data Management Team will be responsible for collecting, processing, and validating data to maintain the integrity and accuracy of the study findings. The participating hospitals include all the university hospitals in Finland, namely, Helsinki University Hospital, Turku University Hospital, Tampere University Hospital, Oulu University Hospital, and Kuopio University Hospital. More hospitals may join the trial after its commencement. The study was registered with ClinicalTrials.gov (registration number NCT06650085) prior to commencement and the Ethical Committee of Helsinki University Hospital approved the study design (approval number 4579/2024). This protocol was designed according to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement and the SPIRIT checklist is available in the Supplementary Material.

Inclusion criteria

Patients undergoing elective anterior resection—resection of the rectum with colorectal or coloanal anastomosis—due to rectal neoplasia, with a protective stoma planned, will be assessed for eligibility.

Exclusion criteria

The exclusion criteria are: (1) the patient already has a stoma or an additional stoma is created during surgery; (2) technical inability to perform ileostomy or colostomy, e.g., previous bowel resection or anatomical factors; (3) aged <18 years; and (4) inability of the patient to adequately cooperate.

Trial intervention

The intervention groups will be the (1) loop colostomy and (2) loop ileostomy groups. Both types of protective stomata will be created using standard surgical techniques: Stoma sites, both for ileostomy (typically lower right quadrant) and colostomy (typically upper right quadrant, right transversostomy) are marked preoperatively, with the patient in a sitting position. A circular or transverse incision is made into the surface of the skin at the place thus marked. The subcutaneous tissue is dissected in a cylindrical shape. A cross shaped or horizontal incision is made in the external fascia of the rectus sheath. The rectus muscle is separated, not transected, to reach the internal fascia of the rectus sheath; a cross-shaped or horizontal incision, the approximate length of two finger widths, is made in the sheath. A loop of the transverse colon and or ileum is brought to the surface of the skin with two lumens draining into a stoma pouch. The transverse colon and or ileum is attached to the skin using absorbable sutures, preferably with three-point sutures. A stoma bridge can be used if warranted. The stoma incision should not be made outside the rectal sheath and the distance from the costal margin should be sufficient to allow for proper fixation of the stoma pouch. All surgeries should be performed by a consultant colorectal surgeon, or by a surgeon under the direct supervision of a consultant colorectal surgeon, who has experience in performing both types of stoma surgeries.

Randomization

Recruitment will take place before surgery, preferably at the preoperative clinical visit. The patient will need to provide written informed consent before enrolment to the trial. The final inclusion and randomization will occur during surgery, after the anterior resection and colorectal or coloanal anastomosis have been completed and the surgeon has confirmed that a protective stoma is required and that both ileostomy and colostomy are technically feasible.

Patients will be individually randomized in a 1 to 1 ratio to undergo either loop ileostomy or loop colostomy. The randomization sequence will be generated by computer using a variable

block size of 4 to 6. The randomization sequence will be stratified according to: (1) center, (2) body mass index (<30 kg/m^2 and ≥30 kg/m^2), and (3) any neoadjuvant treatment administered (yes/no; radiotherapy, chemotherapy, or a combination of the two). Allocation will be performed using the Research Electronic Data Capture (REDCap) software.

Blinding

The study will be conducted as an open-label trial because blinding of patients, treating personnel, or data collectors is not considered feasible. However, to minimize bias in the open-label design, the primary outcome has been carefully designed to be as objective as possible. Furthermore, outcomes that are not predefined will be assessed by committee blinded to the study group.

Study outcomes

The primary outcome is the occurrence of prespecified stoma-related adverse events within 60 days from primary surgery, reported using the Comprehensive Complication Index (CCI). What constitutes a stoma-related adverse event can be subjective; therefore, these events have been predefined and are listed in **Table 2**. Similarly, adverse events that are not considered stoma-related are detailed in **Table 3**. The list of stoma-related adverse events was compiled based on a comprehensive literature search conducted using the term *ileostomy and colostomy and complications* from 2022 to 2023. In total, 99 publications were assessed, and all relevant complications were included in the list. From this list, a panel of 10 consultant surgeons assessed if an adverse event was stoma-related or not. A second round of assessment was performed for those adverse events that did not achieve 90% agreement. Any other adverse event that occurs within 60 days from primary surgery and is not included in the list will be reviewed by the Outcome Adjudication Committee. The committee members will be blinded to the allocation group. The time frame of 60 days was chosen in consideration of the recommendation that protective stomata be closed within 2 to 3 months of the primary surgery. Should a stoma be reversed within 60 days, data regarding the adverse events will be collected up to the point of reversal surgery. The CCI is based on Clavien–Dindo classification and takes into account the cumulative burden of adverse events [25]. Index values can range from 0 to 100, with a value of 0 indicating no events and one of 100 indicating death due to an adverse event. Details of types of adverse events will be reported, but not statistically analyzed.

Table 2. Stoma-related adverse events

Complication
Stoma necrosis*, **
Stoma prolapse*, **
Parastomal hernia*, **
Bleeding from stoma site*, **
Stoma retraction or lift of the stoma from the surface of the skin*, **
Peristomal skin irritation requiring a change in treatment (additional changes of the stoma bag, use of topical creams, etc.)*, **
Stoma stenosis or obstruction*, **
Peristomal fistula or abscess*, **
Mucosal hypertrophy of the stoma requiring a change in treatment
Ileus, included if occlusion related to the stoma site is present, but excluded if a specific other reason for ileus is identified (e.g., internal hernia unrelated to stoma or mechanical bowel obstruction not at the site of stoma)
Pneumonia, if caused by aspiration due to ileus (ileus, as described above)
Surgical site infection at stoma or another incision site
Fascial dehiscence, if occurring with surgical site infection or ileus (ileus, as described above)
Electrolyte imbalance or acute kidney failure (Kidney Disease: Improving Global Outcomes stage 1 (increase in serum creatinine of >1.5 × baseline or >26.5 µmol/L or more, or requirement for intravenous fluids due to high stoma output (>1500 mL/day); each day on which intravenous fluids are required is counted as one complication
Cerebrovascular, cardiovascular, or thromboembolic event, if occurring at a time of dehydration and high-output stoma (>1500 mL/day)
Atrial fibrillation or other arrhythmia, if occurring with dehydration or electrolyte imbalance and high-output stoma (>1500 mL/day)

* Clavien–Dindo class 1 if no intervention is required, otherwise according to intervention based on Clavien–Dindo classification.

** Counted once for first occurrence; subsequently, only an additional visit(s) to the medical unit (including stoma nurse, emergency department, or other) for the same reason is counted as another cumulative adverse event.

Table 3. Adverse events that are not considered stoma-related

Complication
Pneumonia, if not caused by aspiration due to ileus
Urinary tract infection
Cerebrovascular, cardiovascular, or thromboembolic event, if occurring without dehydration
Bleeding, other than at the stoma site
Delirium, if occurring without dehydration or electrolyte imbalance
Urinary retention
Peripheral nerve paresthesia and or paralysis
Fever, unknown origin
Clostridium difficile infection
Respiratory distress

Cholecystitis
Atrial fibrillation or other arrhythmia, if occurring without dehydration or electrolyte imbalance
Ascites
Epidural complications (headache, hematoma, etc.)
Fascial dehiscence, if occurring without surgical site infection and without ileus
Intestinal perforation, if not anastomotic leakage and not at the stoma site
Hematuria
Allergic reactions
Abnormal pain
Anastomosis stricture
Pleural effusion
Ureteral complications (stone, stricture, lesion, etc.)
Bowel obstruction, if the mechanical obstruction is not caused by the stoma site
Bowel necrosis, not at the stoma site
Anastomotic leakage
Intra-abdominal abscess, not located at the stoma site
Acute kidney injury without concomitant high-output stoma (>1500 mL/day)

The secondary outcomes include: (1) all complications within 30 days from primary surgery, reported using the CCI to capture all—not only stoma-related—postoperative complications; (2) all complications within 30 days from stoma closure, reported using the CCI and including only patients who have undergone stoma closure within 1 year from primary surgery; (3) number of hospital-free days within 30 days from the primary surgery; (4) quality of life at 2 months from primary surgery, measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires Core 30 and Colorectal 29 (QLQ-C30+QLQ-CR29). Two months was chosen as the time point to reflect quality of life while the stoma is still in place, but with enough time having passed to recover from the primary surgery; and (5) change in kidney function at 1 year, compared with initial kidney function, measured using the difference in estimated glomerular filtration rate (eGFR) before and 1 year after primary surgery. Tertiary outcomes include: (1) 5-year overall survival; (2) 5-year disease-free survival, including only patients with M0 at primary surgery undergoing radical R0/1 surgery; (3) change in kidney function at 5 years, compared with initial kidney function, that is, difference in eGFR before and 5 years after primary surgery; (4) number of incision hernias at the ostomy site within 5 years from the primary surgery. Only patients who have undergone successful stoma closure and are alive at 5 years will be included in this analysis; (5) cumulative death-censored successful stoma closure, within 5 years from primary surgery. If a stoma closure is attempted but, for example, an anastomotic dehiscence occurs and the

stoma is modified, it will not be considered a successful stoma closure; and (6) quality of life at 5 years, measured using the European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L), QLQ-C30, QLQ-CR29, and—only for patients without stoma—low anterior resection syndrome scores. The exploratory outcomes/variables are: (1) quality of life within 1 year (EQ-5D-5L at 2 months, 6 months, and 1 year after primary surgery, low anterior resection syndrome score (LARS) at 6 months and 1 year after primary surgery (only for patients without a stoma), and QLQ-C30, QLQ-CR29 at 6 months and 1 year after primary surgery), (2) total number of anastomotic leakages reported with grading [26] within 60 days of primary surgery, and (3) intestinal microbiome composition and functional potential (only for patients at Helsinki University Hospital) during the stoma phase and stabilization of the microbiome after stoma closure. We will correlate bacterial taxa with the clinical outcomes to study whether microbiome characteristics are linked to clinical outcomes in short term (1 year) or long term (5 years).

Follow-up

Computed tomography imaging with per rectal contrast medium, colonography, or endoscopy will be used to assess colorectal and or coloanal anastomosis at approximately 6 weeks after primary surgery. At this time, contact will be made either through an outpatient visit or by telephone. Patients will also be telephonically monitored every 2 weeks by the study nurse to identify any potential postoperative or stoma-related adverse events for up to 60 days after primary surgery. A follow-up call will be made 30 days after the surgery to close the stoma. If, via a telephone call, suspicion of a complication is raised or the patient reports a complication, patients will be requested to undergo a physical assessment as necessary. Patients will be contacted by letter or telephone at 1 and 5 years after primary surgery. Creatinine tests will be conducted at 1 and 5 years after primary surgery to calculate eGFR. Outcomes will also be assessed from patient records and, if necessary, by requesting patient records from other hospitals. Patients will be asked to complete the EQ-5D-5L [27], QLQ-C30 [28], QLQ-CR29 [29], and low anterior resection syndrome score (LARS) [30] assessments before and at 2 months, 1 year, and 5 years after primary surgery. If necessary, the patient can be contacted by letter or telephone at any time.

Costs and funding

The hospitals involved in this study will not carry any additional costs concerning the surgical treatment administered to patients. This is because both interventions included in this study are

standard procedures used daily in clinical practice when treating patients with rectal tumors. Patients will not require additional visits or examinations due to their participation in the study. Follow-up will be conducted via telephone by a study nurse. Routine follow-up according to normal clinical practice after rectal surgery is up to 5 years and includes the necessary laboratory tests. The cost of handling and analyzing microbiome samples, and researcher and study nurse salaries will be paid from research grants. This is an investigator-initiated study without any commercial funders.

Intestinal microbiome analysis

Samples will be obtained from feces stored in the colon and the mucous membrane biopsies of all patients undergoing preoperative endoscopy at Helsinki University Hospital. Mucous membrane biopsies will be obtained at the planning visit, during the primary surgery, at the stoma closure, and at the 1-year follow-up visit. Stool samples will be collected preoperatively, during the primary surgery, and during the stoma closure, from the stoma pouch (**Table 4**). Additional samples will be taken 3, 6, and 12 months after stoma closure. Microbial swab samples will be taken from the rectum during stoma closure. Samples will be used to analyze the microbiome and mucosal gene expression. Mucosal samples will be directly stored in RNAlater solution for analysis and fecal samples will be frozen and stored at −80 °C within 1 day of defecation.

Table 4. Participant timeline

	Enrollment	Primary surgery	Follow-up 60 days after primary surgery, phone call	Follow-up 6 months after primary surgery, phone call/letter	Follow-up 1 year after primary surgery, phone call/letter	Stoma closure	Follow-up 30 days after stoma closure, phone call	Follow-up 5 years after primary surgery, phone call/letter
CRF	CRF1	CRF2–3	CRF4	CRF5	CRF6	CRF8	CRF9	CRF7
Written informed consent	x							
Inclusion/exclusion evaluation	x	x						

Randomization		x						
QOL	x		x	x	x			x
Medical history	x					x		
eGFR and creatinine	x	x	x		x	x		x
Operative details	x	x				x		
Assessment for adverse events/complications		x	x				x	
Assessment for stoma site hernia								x
Assessment for recurrence					x			x
Assessment for survival					x			x
Microbiome samples	MMB, SS	MMB, SS			MMB, SS	MMB, SS, S		

Abbreviations: CRF, case report form; eGFR, estimated glomerular filtration rate; MMB, mucous membrane biopsy; SS, stool sample; S, swab sample from rectum; QOL, quality of life.

The primary method of analysis for mucosal samples will be high-throughput sequencing of the 16S rRNA genes of bacteria. Profiling of 16S rRNA genes reveals the composition of the bacterial population. The primary method of analysis of fecal samples will be shotgun metagenomic sequencing, in which the genetic material of the microbes is extensively sequenced, enabling the functional potential of the microbiome, in addition to its composition, to be studied. The analyses will be performed using methods and bioinformatic pipelines that are routinely used and frequently updated within the research group. The research group has extensive experience studying the composition of the intestinal microbiome, therapeutic use of intestinal bacteria (fecal transplants), and host–microbe interactions [31-34].

Sample size

For power calculation purposes, a sample of 95 consecutive patients who underwent anterior resection with loop colostomy for rectal cancer at Helsinki University Hospital for the previous

trial [35] were assessed. The mean and standard deviation stoma-related CCI values in this group were 2.5 and 6.2 points, respectively. The sample size calculation was based on detecting a 5-point difference in the CCI mean values between the groups, hypothesizing 2.5 points in the loop colostomy group and 7.5 points in the loop ileostomy group, with a standard deviation of 14. A 10-point difference in the CCI mean values reflects a single grade difference in the established Clavien–Dindo classification [36] and stoma-related adverse events are usually minor; therefore, we considered a 5-point difference would indicate a clinically meaningful threshold. With a power of 90% and significance level set at 5%, 330 patients are required [37]. Taking into account a loss to follow-up of up to 5%, the final sample size required was calculated to be 350 patients.

Statistical analysis plan

Primary analyses will be conducted on an intention-to-treat basis. The primary outcome will be analyzed using either the Mann–Whitney U test or t-test, bootstrapped or log-transformed if necessary. Secondary outcomes will be analyzed using either the Mann–Whitney U test or t-test for continuous variables, depending on the distribution, and the chi-square or Fisher's exact test for categorical variables. If necessary, log transformation or a bootstrapped t-test will be performed on non-normally distributed continuous variables. Tertiary outcomes will be analyzed separately when a minimum of the 5-year follow-up data for all patients is available. Survival analysis will be conducted using the Kaplan–Meier method and log rank test; the eGFR will be analyzed using the Mann–Whitney U test or t-test. The Kaplan–Meier method and log rank test will be used to estimate the cumulative incidence of incisional site hernias. Statistical significance will be set at a two-tailed p value of <0.05. Effect sizes will be reported using relative risk, corrected from the odds ratios with 95% confidence intervals, or as Wilcoxon effect sizes ($r = z \sqrt{n}$).

Prespecified subgroup analyses according to (1) body mass index (<30 kg/m^2 and >30 kg/m^2), (2) surgical approach (minimally invasive vs. open surgery), (3) neoadjuvant treatment (yes/no), (4) adjuvant treatment (yes/no), and (4) cancer stage (stages 1–3 vs. stage 4) will be conducted.

Conducting interim analyses is not planned as both arms are currently standard care and considered safe.

Data collection and management, and post-trial care

Data will be collected using Case Report Forms 1 to 8 within the REDCap web application. Table 4). Data will be monitored by the Clinical Research Institute Helsinki University Hospital monitoring services for researcher-initiated clinical studies, or similar services for the other university hospitals. Monitoring will be performed in accordance with currently valid official rules and regulations and the Good Clinical Practice guidelines. Access to data will be restricted to monitors, investigators, and study nurses. Post-trial care is not warranted since the interventions used in this trial are standard, widely accepted treatments for rectal cancer and patients will receive standard clinical care outside of the trial.

Schedule

The research project is scheduled to begin during 2024 or once the study protocol has been peer reviewed and potentially updated. Patient recruitment is estimated to take approximately 2 to 3 years to reach the sample size determined by the power calculation. The follow-up phase is estimated to continue until the end of 2032, 5 years from the time the last patient undergoes primary surgery.

ETHICS AND DISSEMINATION

The study plan has been approved by the Ethics Committee of Helsinki University Hospital. Permission to conduct the study will be sought from each participating centers' institutional review board. All patients meeting the inclusion and or exclusion criteria are eligible to participate in the trial, regardless of their gender, sex, or race. All patients in the study will be adults and must have sufficient comprehension of the Finnish, Swedish, or English language and information provided in the written informed consent form. The recruiting surgeon will inform each patient in verbal and written form. Participation in the study will be voluntary and will not affect the patient's other treatment. The informed consent form must be signed by the patient and the recruiting surgeon before inclusion in the study. Patients may withdraw their consent at any time without losing any of their rights as a patient.

Both intervention arms (loop ileostomy and loop colostomy) are standard treatments and the choice between them is based on surgeon or center preference outside the trial. Thus, randomizing patients to either intervention is considered ethical.

During the study, patient identification data will be collected in a study folder. The data collected during the study will be stored and analyzed without the patient identification data.

At randomization, each study patient will receive a study number, which will be linked to their identification information in the study folder. Data will be stored in a locked room and electronic data will be stored on password-protected drives of hospital computers. Data will be processed in accordance with the General Data Protection Regulation and data processing will be conducted based on Article 6 (e) in conjunction with Article 9 (i) of the regulations.

The study protocol has been sent to an international peer-reviewed journal before commencing the study. The results will be reported in a scientific paper submitted to an international peer-reviewed journal. The first report will cover primary, secondary, and exploratory outcomes up to the 1-year follow-up examination. The second report will address outcomes up to 5 years. Microbiological analyses will be reported separately once 1- and 5-year outcomes are available. All reports will be published with open access, provided the journal has an open access option and funding for article processing charges is obtained. The use of professional writers is not intended.

PATIENT AND PUBLIC INVOLVEMENT

Two patients who underwent anterior resection with a protective colostomy as well as a stoma nurse contributed to developing the study design and consent forms. The patients wished to remain anonymous.

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Data availability statement: Data may be shared if appropriate permissions are first sought and obtained, if the study permissions obtained allow it, and if sharing is compliant with Finnish law.

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Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	11, 15, 16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	-
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6-7

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6-7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	13-14

		(see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	12-13

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	-
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	8-11

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of	#28	Financial and other competing interests for principal	15

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12-13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12-13
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14-15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

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PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon: study protocol for a multicenter, open-label, randomized conTrolled studY (PROSPERITY)

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PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon: study protocol for a multicenter, open-label, randomized conTrolled studY (PROSPERITY)

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Keywords: colorectal cancer, ostomy, stoma, ileostomy, colostomy

ABSTRACT

Introduction

Loop ileostomy and loop colostomy are both used to form a protective stoma after anterior resection. Evidence regarding which of these two procedures is superior is lacking. Furthermore, no studies comparing changes in the microbiome after loop ileostomy or loop colostomy exist.

Methods and analysis

This multicenter, open-label, superiority, individually randomized controlled trial will include patients who undergo anterior rectal resection with primary anastomosis with a protective stoma. The exclusion criteria are patients who already have a stoma, technical inability to

create either type of stoma, aged <18 years, and inadequate cooperation. Patients scheduled for anterior rectal resection will be randomized intraoperatively in a 1 to 1 ratio to undergo either loop ileostomy or loop colostomy. The primary outcome is cumulative stoma-related adverse events within 60 days after primary surgery, measured using the Comprehensive Complication Index (CCI). Secondary outcomes include all postoperative complications (measured using the CCI), number of hospital-free days within 30 days after primary surgery, quality of life at 2 months (measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires Core 30 and Colorectal 29), complications within 30 days after stoma closure (measured using the CCI), and kidney function (measured using estimated glomerular filtration rate) at 1 year. Tertiary outcomes are survival, kidney function, and number of stoma site hernias at 5 years. The sample size was calculated to detect a mean difference of five CCI points between groups, resulting in a final sample size of 350 patients. Microbiome samples will be collected from the feces and mucous membrane from patients in Helsinki University Hospital.

Ethics and dissemination

The Ethics Committee of Helsinki University Hospital approved the study (approval number 4579/2024). The findings will be disseminated in peer-reviewed academic journals.

Trial registration

ClinicalTrials.gov, NCT06650085, registered on 20th August 2024. Protocol version: Version 3.0, dated April 17, 2025.

Strengths and limitations of this study

- The study uses a prospective, multicenter, individually randomized controlled trial design, ensuring high methodological rigor.
- Intraoperative randomization minimizes selection bias and ensures both stoma types are technically feasible.
- Primary and secondary outcomes are assessed using the validated Comprehensive Complication Index (CCI), enhancing reliability and comparability.
- The open-label nature of the trial may introduce bias, though stoma-related adverse events were rigorously defined before study initiation outcome and adjudicators are blinded to treatment allocation.
- Microbiome analysis is limited to one participating center, which may affect the generalizability of those specific findings.

INTRODUCTION

Anterior resection or abdominoperineal resection with total mesorectal excision are the two standard methods used to treat middle and low rectal cancer [1]. The sphincter saving anterior resection is generally preferred when tumor margins and patient fitness allow because it is associated with better quality of life after surgery than abdominoperineal resection, which results in a permanent stoma [2]. However, anterior resection carries the risk of anastomotic leakage, a complication associated with costly postoperative morbidities and a negative impact on long-term outcomes, including reduced overall survival [3].

Several preventive methods have been introduced to mitigate the risk of anastomotic leakage following anterior resection for rectal cancer. Among others, these techniques include preoperative mechanical bowel preparation, oral antibiotics, intraoperative testing of anastomotic integrity and perfusion, anastomotic buttressing, anastomotic reinforcement, and creation of a protective stoma [4].

Use of a protective stoma has been common practice in low anterior resection for decades [5]. Diverting feces is thought to reduce intraluminal pressure and decrease the bacterial load at the distal anastomosis [6]. Although a protective stoma does not reduce the incidence of anastomotic leakage [7, 8], it does limit morbidity by lowering the risk of fecal peritonitis and septicemia in the event of leak [9].

Loop ileostomy and loop colostomy are the two methods used to create a temporary protective stoma [4]. Despite their long-standing use, no clear superiority of one over the other has been established, resulting in a large variation in the stoma type used between surgeons, centers, and countries.

We are aware of five randomized controlled trials in which the use of loop ileostomy and loop colostomy during anterior resection for rectal cancer have been compared (**Table 1).** These trials took place more than 2 decades ago, used small sample sizes, and had various outcomes. Several retrospective series have also compared the two stoma types, but these studies were limited and biased by diverse confounding factors. Meta-analyses, including also retrospective series, indicate differing risk–benefit profiles for the two types of stomata: Loop ileostomy may result in fewer parastomal hernias, prolapses, and stoma retractions, whereas loop colostomy appears to result in fewer problems related to dehydration [10, 11]. Regarding stoma closure, loop ileostomy may be associated with a lower incidence of infection at the surgical site but a higher incidence of postoperative bowel obstruction [10,

11]. Adding to this debate, one nationwide study reported an alarming rate of renal failure in patients with loop ileostomy [12] and another, recent, study linked loop ileostomy with a high incidence of low anterior resection syndrome [13].

Table 1. Randomized controlled trials in which loop ileostomy and loop colostomy in patients undergoing anterior resection were compared

Author, Publication year	Number	Primary outcome	Main findings	Conclusions
Williams et al., 1986 [14]	47 (23 LI vs. 24 LC)	Stoma-related morbidity	LI: 3 (18%) LC: 11 (58%)	Favored: LI
Khoury et al., 1987 [15]	61 (32 LI vs. 29 LC)	Anastomotic leakage after primary surgery	LI: 2 (6%) LC: 6 (21%)	Favored: LI
Gooszen et al., 1998 [16]	76 (37 LI vs. 39 LC)	Stoma-related morbidity	LI: 9 (24%) LC: 1 (3%)	Favored: LC
Edwards et al., 2001 [17]	70, (34 LI vs. 36 LC)	Clinically relevant anastomotic leakage	LI: 2 (6%) LC: 1 (3%) More other stoma-related complications in the LC group	Favored: LI
Law et al., 2002 [18]	80 (42 LI vs. 38 LC)	Ileus after primary surgery	LI: 6 (14%) LC: 1 (3%) 5 cases of postoperative ileus, 2 of intestinal obstruction before stoma closure	Favored: LC

Abbreviations: LC, loop colostomy; LI, loop ileostomy.

In recent years, a relationship between pathological imbalance in the colonic microbiome and colorectal cancer has been discerned [19]. The colonic microbiome is known to play a role in carcinogenesis [19, 20], as well as progression [21, 22] and treatment of colorectal cancer [22, 23]. We are aware of only one study that compared the microbiomes of patients with colorectal cancer with or without loop ileostomy or colostomy; this recent observational cohort study conducted in Japan involved 165 patients [24]. In that study, patients with stoma had fewer microbes favorable for cancer immunotherapy than patients without. No studies comparing the differences in microbiomes between loop ileostomy and loop colostomy are available. Given that the colonic microbiome is recognized to play a significant role in treating colorectal cancer, important differences in the colonic microbiomes of patients undergoing loop ileostomy and loop colostomy may exist [19-23].

To provide Level 1 evidence for clinical practice, we designed the PROtective ileoStomy versus ProtectivE colostomy in anterior Rectal resectIon – a multicenter, open-label, randomized conTrolled studY (PROSPERITY). This trial primarily aims to compare loop ileostomy to loop colostomy in terms of stoma-related adverse events. The study also includes microbiological analyses to assess the changes in, and role of, the microbiome in patients undergoing either of the stomata. In this study, we hypothesized that protective loop colostomy will result in fewer and or less severe stoma-related adverse events than a loop ileostomy within 60 days.

METHODS AND ANALYSIS

Study design

The PROSPERITY trial is a multicenter, open-label, superiority, individually randomized study. The trial will be coordinated by the Helsinki University Hospital, which will oversee study implementation and ensure adherence to the protocol. The Steering Committee, composed of adjunct professors from Helsinki University Hospital, will provide scientific guidance and strategic oversight throughout the trial. The Outcome Adjudication Committee consists of three consultant gastroenterological surgeons who are not involved in patient recruitment, clinical care, data collection, or data processing. All data presented to the Outcome Adjudication Committee will be blinded for the allocation group by the Data Management Team to ensure impartial assessment of the outcomes. The Data Management Team will be responsible for collecting, processing, and validating data to maintain the integrity and accuracy of the study findings. The participating hospitals include all the university hospitals in Finland, namely, Helsinki University Hospital, Turku University Hospital, Tampere University Hospital, Oulu University Hospital, and Kuopio University Hospital. More hospitals may join the trial after its commencement. The study was registered with ClinicalTrials.gov (NCT06650085) prior to commencement and the Ethical Committee of Helsinki University Hospital approved the study design (approval number 4579/2024). This protocol is reported according to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Inclusion criteria

Patients undergoing elective anterior resection—resection of the rectum with colorectal or coloanal anastomosis—due to rectal neoplasia, with a protective stoma planned, will be

assessed for eligibility.

Exclusion criteria

The exclusion criteria are: (1) the patient already has a stoma or an additional stoma is created during surgery; (2) technical inability to perform ileostomy or colostomy, e.g., previous bowel resection or anatomical factors; (3) aged <18 years; and (4) inability of the patient to adequately cooperate.

Trial intervention

The intervention groups will be the (1) loop colostomy and (2) loop ileostomy groups. Both types of protective stomata will be created using standard surgical techniques: Stoma sites, both for ileostomy (typically lower right quadrant) and colostomy (typically upper right quadrant, right transversostomy) are marked preoperatively, with the patient in a sitting position. A circular or transverse incision is made into the surface of the skin at the place thus marked. The subcutaneous tissue is dissected in a cylindrical shape. A cross shaped or horizontal incision is made in the external fascia of the rectus sheath. The rectus muscle is separated, not transected, to reach the internal fascia of the rectus sheath; a cross-shaped or horizontal incision, the approximate length of two finger widths, is made in the sheath. A loop of the transverse colon and or ileum is brought to the surface of the skin with two lumens draining into a stoma pouch. The transverse colon and or ileum is attached to the skin using absorbable sutures, preferably with three-point sutures. A stoma bridge can be used if warranted. The stoma incision should not be made outside the rectal sheath and the distance from the costal margin should be sufficient to allow for proper fixation of the stoma pouch. All surgeries should be performed by a consultant colorectal surgeon, or by a surgeon under the direct supervision of a consultant colorectal surgeon, who has experience in performing both types of stoma surgeries. All participating hospitals follow Enhanced Recovery After Surgery (ERAS) principles, although the specific protocols may vary slightly between centers.

Randomization

Recruitment will take place before surgery, preferably at the preoperative clinical visit. The patient will need to provide written informed consent before enrolment to the trial. The final inclusion and randomization will occur during surgery, after the anterior resection and colorectal or coloanal anastomosis have been completed and the surgeon has confirmed that a protective stoma is required and that both ileostomy and colostomy are technically feasible.

Patients will be individually randomized in a 1 to 1 ratio to undergo either loop ileostomy or loop colostomy. The randomization sequence will be generated by computer using a variable block size of 4 to 6. The randomization sequence will be stratified according to: (1) center, (2) body mass index (<30 kg/m^2 and ≥30 kg/m^2), and (3) any neoadjuvant treatment administered (yes/no; radiotherapy, chemotherapy, or a combination of the two). Allocation will be performed using the Research Electronic Data Capture (REDCap) software.

Blinding

The study will be conducted as an open-label trial because blinding of patients, treating personnel, or data collectors is not considered feasible. However, to minimize bias in the open-label design, the primary outcome has been carefully designed to be as objective as possible. Furthermore, outcomes that are not predefined will be assessed by committee blinded to the study group.

Study outcomes

The primary outcome is the occurrence of prespecified stoma-related adverse events within 60 days from primary surgery, reported using the Comprehensive Complication Index (CCI). What constitutes a stoma-related adverse event can be subjective; therefore, these events have been predefined and are listed in **Table 2**. Similarly, adverse events that are not considered stoma-related are detailed in **Table 3**. The list of stoma-related adverse events was compiled based on a comprehensive literature search conducted using the term *ileostomy and colostomy and complications* from 2022 to 2023. In total, 99 publications were assessed, and all relevant complications were included in the list. From this list, a panel of 10 consultant surgeons assessed if an adverse event was stoma-related or not. A second round of assessment was performed for those adverse events that did not achieve 90% agreement. Any other adverse event that occurs within 60 days from primary surgery and is not included in the list will be reviewed by the Outcome Adjudication Committee. The committee members will be blinded to the allocation group. The time frame of 60 days was chosen in consideration of the recommendation that protective stomata be closed within 2 to 3 months of the primary surgery. Should a stoma be reversed within 60 days, data regarding the adverse events will be collected up to the point of reversal surgery. The CCI is based on Clavien–Dindo classification and takes into account the cumulative burden of adverse events [25]. Index values can range from 0 to 100, with a value of 0 indicating no events and one of 100 indicating death due to an adverse event. Details of types of adverse events will be reported, but not statistically analyzed.

Table 2. Stoma-related adverse events

Complication
Stoma necrosis*, **
Stoma prolapse*, **
Parastomal hernia*, **
Bleeding from stoma site*, **
Stoma retraction or lift of the stoma from the surface of the skin*, **
Peristomal skin irritation requiring a change in treatment (additional changes of the stoma bag, use of topical creams, etc.)*, **
Stoma stenosis or obstruction*, **
Peristomal fistula or abscess*, **
Mucosal hypertrophy of the stoma requiring a change in treatment
Ileus, included if occlusion related to the stoma site is present, but excluded if a specific other reason for ileus is identified (e.g., internal hernia unrelated to stoma or mechanical bowel obstruction not at the site of stoma)
Pneumonia, if caused by aspiration due to ileus (ileus, as described above)
Surgical site infection at stoma or another incision site
Fascial dehiscence, if occurring with surgical site infection or ileus (ileus, as described above)
Electrolyte imbalance or acute kidney failure (Kidney Disease: Improving Global Outcomes stage 1 (increase in serum creatinine of >1.5 × baseline or >26.5 μmol/L or more, or requirement for intravenous fluids due to high stoma output (>1500 mL/day); each day on which intravenous fluids are required is counted as one complication
Cerebrovascular, cardiovascular, or thromboembolic event, if occurring at a time of dehydration and high-output stoma (>1500 mL/day)
Atrial fibrillation or other arrhythmia, if occurring with dehydration or electrolyte imbalance and high-output stoma (>1500 mL/day)

* Clavien–Dindo class 1 if no intervention is required, otherwise according to intervention based on Clavien–Dindo classification.

** Counted once for first occurrence; subsequently, only an additional visit(s) to the medical unit (including stoma nurse, emergency department, or other) for the same reason is counted as another cumulative adverse event.

Table 3. Adverse events that are not considered stoma-related

Complication
Pneumonia, if not caused by aspiration due to ileus
Urinary tract infection
Cerebrovascular, cardiovascular, or thromboembolic event, if occurring without dehydration
Bleeding, other than at the stoma site
Delirium, if occurring without dehydration or electrolyte imbalance
Urinary retention
Peripheral nerve paresthesia and or paralysis
Fever, unknown origin

Clostridium difficile infection
Respiratory distress
Cholecystitis
Atrial fibrillation or other arrhythmia, if occurring without dehydration or electrolyte imbalance
Ascites
Epidural complications (headache, hematoma, etc.)
Fascial dehiscence, if occurring without surgical site infection and without ileus
Intestinal perforation, if not anastomotic leakage and not at the stoma site
Hematuria
Allergic reactions
Abnormal pain
Anastomosis stricture
Pleural effusion
Ureteral complications (stone, stricture, lesion, etc.)
Bowel obstruction, if the mechanical obstruction is not caused by the stoma site
Bowel necrosis, not at the stoma site
Anastomotic leakage
Intra-abdominal abscess, not located at the stoma site
Acute kidney injury without concomitant high-output stoma (>1500 mL/day)

The secondary outcomes include: (1) all complications within 30 days from primary surgery, reported using the CCI to capture all—not only stoma-related—postoperative complications; (2) all complications within 30 days from stoma closure, reported using the CCI and including only patients who have undergone stoma closure within 1 year from primary surgery; (3) number of hospital-free days within 30 days from the primary surgery; (4) quality of life at 2 months from primary surgery, measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires Core 30 and Colorectal 29 (QLQ-C30+QLQ-CR29). Two months was chosen as the time point to reflect quality of life while the stoma is still in place, but with enough time having passed to recover from the primary surgery; and (5) change in kidney function at 1 year, compared with initial kidney function, measured using the difference in estimated glomerular filtration rate (eGFR) before and 1 year after primary surgery. Tertiary outcomes include: (1) 5-year overall survival; (2) 5-year disease-free survival, including only patients with M0 at primary surgery undergoing radical R0/1 surgery; (3) change in kidney function at 5 years, compared with initial kidney function, that is, difference in eGFR before and 5 years after primary surgery; (4) number of incision hernias at the ostomy site within 5 years from the primary surgery. Only patients who have undergone successful stoma closure and are alive at 5 years will be included in this analysis; (5) cumulative death-censored successful stoma closure, within 5 years from primary surgery.

If a stoma closure is attempted but, for example, an anastomotic dehiscence occurs and the stoma is modified, it will not be considered a successful stoma closure; and (6) quality of life at 5 years, measured using the European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L), QLQ-C30, QLQ-CR29, and—only for patients without stoma—low anterior resection syndrome scores. The exploratory outcomes/variables are: (1) quality of life within 1 year (EQ-5D-5L at 2 months, 6 months, and 1 year after primary surgery, low anterior resection syndrome score (LARS) at 6 months and 1 year after primary surgery (only for patients without a stoma), and QLQ-C30, QLQ-CR29 at 6 months and 1 year after primary surgery), (2) total number of anastomotic leakages reported with grading [26] within 60 days of primary surgery, and (3) intestinal microbiome composition and functional potential (only for patients at Helsinki University Hospital) during the stoma phase and stabilization of the microbiome after stoma closure. We will correlate bacterial taxa with the clinical outcomes to study whether microbiome characteristics are linked to clinical outcomes in short term (1 year) or long term (5 years).

Follow-up

Computed tomography imaging with per rectal contrast medium, colonography, or endoscopy will be used to assess colorectal and or coloanal anastomosis at approximately 6 weeks after primary surgery. At this time, contact will be made either through an outpatient visit or by telephone. Patients will also be telephonically monitored every 2 weeks by the study nurse to identify any potential postoperative or stoma-related adverse events for up to 60 days after primary surgery. A follow-up call will be made 30 days after the surgery to close the stoma. If, via a telephone call, suspicion of a complication is raised or the patient reports a complication, patients will be requested to undergo a physical assessment as necessary. Patients will be contacted by letter or telephone at 1 and 5 years after primary surgery. Creatinine tests will be conducted at 1 and 5 years after primary surgery to calculate eGFR. Outcomes will also be assessed from patient records and, if necessary, by requesting patient records from other hospitals. Patients will be asked to complete the EQ-5D-5L [27], QLQ-C30 [28], QLQ-CR29 [29], and low anterior resection syndrome score (LARS) [30] assessments before and at 2 months, 1 year, and 5 years after primary surgery. If necessary, the patient can be contacted by letter or telephone at any time.

Costs and funding

The hospitals involved in this study will not carry any additional costs concerning the surgical

treatment administered to patients. This is because both interventions included in this study are standard procedures used daily in clinical practice when treating patients with rectal tumors. Patients will not require additional visits or examinations due to their participation in the study. Follow-up will be conducted via telephone by a study nurse. Routine follow-up according to normal clinical practice after rectal surgery is up to 5 years and includes the necessary laboratory tests. The cost of handling and analyzing microbiome samples, and researcher and study nurse salaries will be paid from research grants. This is an investigator-initiated study without any commercial funders.

Intestinal microbiome analysis

Samples will be obtained from feces stored in the colon and the mucous membrane biopsies of all patients undergoing preoperative endoscopy at Helsinki University Hospital. Mucous membrane biopsies will be obtained at the planning visit, during the primary surgery, at the stoma closure, and at the 1-year follow-up visit. Stool samples will be collected preoperatively, during the primary surgery, and during the stoma closure, from the stoma pouch (**Table 4**). Additional samples will be taken 3, 6, and 12 months after stoma closure. Microbial swab samples will be taken from the rectum during stoma closure. Samples will be used to analyze the microbiome and mucosal gene expression. Mucosal samples will be directly stored in RNAlater solution for analysis and fecal samples will be frozen and stored at −80 °C within 1 day of defecation.

Table 4. Participant timeline

	Enrollment	Primary surgery	Follow-up 60 days after primary surgery, phone call	Follow-up 6 months after primary surgery, phone call/letter	Follow-up 1 year after primary surgery, phone call/letter	Stoma closure	Follow-up 30 days after stoma closure, phone call	Follow-up 5 years after primary surgery, phone call/letter
CRF	CRF1	CRF2–3	CRF4	CRF5	CRF6	CRF8	CRF9	CRF7
Written informed consent	X							

Inclusion/exclusion evaluation	X	x						
Randomization		x						
QOL	X		x	x	x			x
Medical history	X					x		
eGFR and creatinine	X	x	x		x	x		x
Operative details	X	x				x		
Assessment for adverse events/complications		x	x				x	
Assessment for stoma site hernia								x
Assessment for recurrence					x			x
Assessment for survival					x			x
Microbiome samples	MMB, SS	MMB, SS			MMB, SS	MMB, SS, S		

Abbreviations: CRF, case report form; eGFR, estimated glomerular filtration rate; MMB, mucous membrane biopsy; SS, stool sample; S, swab sample from rectum; QOL, quality of life.

The primary method of analysis for mucosal samples will be high-throughput sequencing of the 16S rRNA genes of bacteria. Profiling of 16S rRNA genes reveals the composition of the bacterial population. The primary method of analysis of fecal samples will be shotgun metagenomic sequencing, in which the genetic material of the microbes is extensively sequenced, enabling the functional potential of the microbiome, in addition to its composition, to be studied. The analyses will be performed using methods and bioinformatic pipelines that are routinely used and frequently updated within the research group. The research group has extensive experience studying the composition of the intestinal microbiome, therapeutic use of intestinal bacteria (fecal transplants), and host–microbe interactions [31-34].

Sample size

For power calculation purposes, a sample of 95 consecutive patients who underwent anterior resection with loop colostomy for rectal cancer at Helsinki University Hospital for the previous trial [35] were assessed. The mean and standard deviation stoma-related CCI values in this group were 2.5 and 6.2 points, respectively. The sample size calculation was based on detecting a 5-point difference in the CCI mean values between the groups, hypothesizing 2.5 points in the loop colostomy group and 7.5 points in the loop ileostomy group, with a standard deviation of 14. A 10-point difference in the CCI mean values reflects a single grade difference in the established Clavien–Dindo classification [36] and stoma-related adverse events are usually minor; therefore, we considered a 5-point difference would indicate a clinically meaningful threshold. With a power of 90% and significance level set at 5%, 330 patients are required [37]. Taking into account a loss to follow-up of up to 5%, the final sample size required was calculated to be 350 patients.

Statistical analysis plan

Primary analyses will be conducted on an intention-to-treat basis. The primary outcome will be analyzed using either the Mann–Whitney U test or t-test, bootstrapped or log-transformed if necessary. Secondary outcomes will be analyzed using either the Mann–Whitney U test or t-test for continuous variables, depending on the distribution, and the chi-square or Fisher's exact test for categorical variables. If necessary, log transformation or a bootstrapped t-test will be performed on non-normally distributed continuous variables. Tertiary outcomes will be analyzed separately when a minimum of the 5-year follow-up data for all patients is available. Survival analysis will be conducted using the Kaplan–Meier method and log rank test; the eGFR will be analyzed using the Mann–Whitney U test or t-test. The Kaplan–Meier method and log rank test will be used to estimate the cumulative incidence of incisional site hernias. Statistical significance will be set at a two-tailed p value of <0.05. Effect sizes will be reported using relative risk, corrected from the odds ratios with 95% confidence intervals, or as Wilcoxon effect sizes ($r = z \sqrt{n}$).

Prespecified subgroup analyses according to (1) body mass index (<30 kg/m^2 and >30 kg/m^2), (2) surgical approach (minimally invasive vs. open surgery), (3) neoadjuvant treatment (yes/no), (4) adjuvant treatment (yes/no), and (4) cancer stage (stages 1–3 vs. stage 4) will be conducted.

Conducting interim analyses is not planned as both arms are currently standard care and considered safe.

Data collection and management, and post-trial care

Data will be collected using Case Report Forms 1 to 8 within the REDCap web application. Table 4). Data will be monitored by the Clinical Research Institute Helsinki University Hospital monitoring services for researcher-initiated clinical studies, or similar services for the other university hospitals. Monitoring will be performed in accordance with currently valid official rules and regulations and the Good Clinical Practice guidelines. Access to data will be restricted to monitors, investigators, and study nurses. Post-trial care is not warranted since the interventions used in this trial are standard, widely accepted treatments for rectal cancer and patients will receive standard clinical care outside of the trial.

Schedule

The research project is scheduled to begin during 2024 or once the study protocol has been peer reviewed and potentially updated. Patient recruitment is estimated to take approximately 2 to 3 years to reach the sample size determined by the power calculation. The follow-up phase is estimated to continue until the end of 2032, 5 years from the time the last patient undergoes primary surgery.

Patient and public involvement

Two patients who underwent anterior resection with a protective colostomy as well as a stoma nurse contributed to developing the study design and consent forms. The patients wished to remain anonymous.

ETHICS AND DISSEMINATION

The study plan has been approved by the Ethics Committee of Helsinki University Hospital (approval number 4579/2024). Permission to conduct the study will be sought from each participating centers' institutional review board. All patients meeting the inclusion and or exclusion criteria are eligible to participate in the trial, regardless of their gender, sex, or race. All patients in the study will be adults and must have sufficient comprehension of the Finnish, Swedish, or English language and information provided in the written informed consent form (**supplemental material**). The recruiting surgeon will inform each patient in verbal and written form. Participation in the study will be voluntary and will not affect the patient's other treatment. The informed consent form must be signed by the patient and the recruiting surgeon before inclusion in the study. Patients may withdraw their consent at any time without losing

any of their rights as a patient.

Both intervention arms (loop ileostomy and loop colostomy) are standard treatments and the choice between them is based on surgeon or center preference outside the trial. Thus, randomizing patients to either intervention is considered ethical.

During the study, patient identification data will be collected in a study folder. The data collected during the study will be stored and analyzed without the patient identification data. At randomization, each study patient will receive a study number, which will be linked to their identification information in the study folder. Data will be stored in a locked room and electronic data will be stored on password-protected drives of hospital computers. Data will be processed in accordance with the General Data Protection Regulation and data processing will be conducted based on Article 6 (e) in conjunction with Article 9 (i) of the regulations.

The results will be reported in a scientific paper submitted to an international peer-reviewed journal. The first report will cover primary, secondary, and exploratory outcomes up to the 1-year follow-up examination. The second report will address outcomes up to 5 years. Microbiological analyses will be reported separately once 1- and 5-year outcomes are available. All reports will be published with open access, provided the journal has an open access option and funding for article processing charges is obtained. The use of professional writers is not intended.

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Data availability statement: Data from the study, once available, may be shared if appropriate permissions are first sought and obtained, if the study permissions obtained allow it, and if sharing is compliant with Finnish law.

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TIEDOTE TUTKIMUKSESTA

Suojaava ohutsuoliavanne tai suojaava paksusuoliavanne peräsuolisyöpäleikkauksessa - prospektiivinen satunnaistettu tutkimus

Pyyntö osallistua tutkimukseen

Sinua pyydetään mukaan tutkimukseen, jossa selvitetään, onko suojaavalla paksusuoliavanteella vähemmän haittoja potilaalle verrattuna suojaavaan ohutsuoliavanteeseen. Tutkimus suoritetaan samanaikaisesti useassa suomalaisessa yliopistosairaalassa. Tämä tiedote kuvaa tutkimusta ja sinun mahdollista osuuttasi siinä.

Lue rauhassa tämä tiedote. Jos sinulla on kysyttävää, ota yhteyttä tutkijalääkäriin tai muuhun tutkimushenkilökuntaan (yhteystiedot löytyvät asiakirjan lopusta).

Jos päätät osallistua tutkimukseen, sinua pyydetään allekirjoittamaan erillinen suostumus.

HUS alueellinen lääketieteellinen tutkimuseettinen toimikunta on antanut tutkimussuunnitelmalle puoltavan lausunnon.

Mitä tutkitaan ja miksi

Teidän hoitava lääkäri on arvioinut, että leikkauksessanne tarvitsee tehdä avanne. Mikäli leikkauksessa ei tarvitsisikaan tehdä avannetta, teidän osallistumisenne tutkimukseen päättyy, eikä teille tehdä avannetta. Tämä tutkimus ei siis vaikuta siihen tehdäänkö teille avannetta vai ei, vaan ainoastaan siihen minkä tyyppinen avanne teille tehdään.

Tämän tutkimuksen tavoitteena on selvittää, onko suojaavalla paksusuoliavanteella vähemmän haittoja potilaalle verrattuna suojaavaan ohutsuoliavanteeseen peräsuolen syöpää sairastavilla potilailla, joille suoritetaan leikkaushoito. Teidän leikkauksessanne on tarkoitus tehdä suoliliitos paksusuolen ja jäljelle jääneen peräsuolen tai peräaukkokanavan välille sekä tätä suoliliitosta suojaava avanne. Suojaavalla avanteella pyritään vähentämään suoliliitoksen paranemiseen liittyviä mahdollisia ongelmia. Suojaavan avanteen voi tehdä joko paksusuolesta tai ohutsuolesta. Tutkimuksemme tarkoituksena on vertailla näiden kahden avannetyypin eroja. Tutkimus on satunnaistettu tutkimus, jossa potilaat arvotaan kahteen ryhmään, joista toiselle ryhmälle tehdään suojaava ohutsuoliavanne ja toiselle ryhmälle tehdään suojaava paksusuoliavanne. Te itse tai teitä hoitava lääkäri ei voi vaikuttaa kumpaan ryhmään tulette tutkimuksessa kuulumaan.

Tutkimuksen aikana on myös tarkoitus selvittää suoliston bakteerikantojen eroja eri avannetyyppien välillä. Osalta tutkittavista tullaan tutkimuksen aikana keräämään ulostenäytteitä sekä paksusuolen limakalvonäytteitä. Näistä ei koidu ylimääräisiä käyntejä potilaalle.

Tutkimukseen pyydetään mukaan henkilöitä, jotka ovat yli 18-vuotiaita, joilla on todettu peräsuolen syöpä ja heille suunnitellaan leikkausta, joka edellyttää suojaavan avanteen. Tutkimusryhmän edustaja keskustelee kanssasi arvioidessaan, oletko soveltuva osallistumaan tutkimukseen.

Tutkimus toteutetaan HUS Helsingin yliopistollisessa sairaalassa, Tampereen yliopistollisessa sairaalassa ja Turun yliopistollisessa sairaalassa. Tutkimukseen osallistuu yhteensä noin 350 tutkittavaa.

Miten tutkitaan

Tutkimukseen osallistuvat potilaat käyvät tavanomaisilla lääkärin ja avannehoitajan vastaanottokäynneillä. Tutkimukseen ei sisälly ylimääräisiä käyntejä. Tutkimushenkilökunta voi olla sinuun yhteydessä myös puhelimitse.

Tutkimukseen liittyvä seuranta kestää noin 5 vuotta.

Tutkimus toteutetaan siten, että tutkittava satunnaistetaan toiseen kahdesta ryhmästä. Toisen ryhmän potilaat saavat suojaavan paksusuoliavanteen ja toisen ryhmän potilaat saavat suojaavan ohutsuoliavanteen. Satunnaistaminen on tärkeää, jotta voidaan tutkia eri hoitojen vaikutusta. Satunnaistetussa tutkimusasemassa tutkija ei aseta potilaita ryhmiin, vaan potilaat jakautuvat ryhmiin satunnaisesti.

Lisäksi sinulta saatetaan ottaa ylimääräisiä suolen limakalvon näytteitä tavanomaisen lääkärinkäynnin, suolen tähystyksen tai leikkauksen yhteydessä, ja sinua saatetaan pyytää antamaan ulostenäytteitä.

Osallistumisen vapaaehtoisuus, keskeyttäminen ja suostumuksen peruuttaminen

Tähän tutkimukseen osallistuminen on vapaaehtoista. Voit kieltäytyä osallistumasta tutkimukseen, keskeyttää osallistumisesi tai peruuttaa jo annetun suostumuksesi tähän tutkimukseen syytä ilmoittamatta, milloin tahansa tutkimuksen aikana ilman, että se vaikuttaa oikeuteesi saada tarvitsemaasi hoitoa.

Halutessasi peruuttaa tutkimukseen osallistumisesi ota yhteyttä: Laura Koskenvuo, dosentti, erikoislääkäri Puh. 050 427 4957, laura.koskenvuo@hus.fi

Jos päätät keskeyttää osallistumisesi tai peruuttaa suostumuksesi, sinusta siihen mennessä kerättyjä tietoja ja/tai näytteitä käytetään osana tutkimusaineistoa, jotta ne eivät vääristyisi.

Tutkimuksen päättyminen

Tutkimustulokset julkaistaan kansainvälisessä vertaisarvioidussa tiedejulkaisussa.

Tutkimuksen alkamisesta sen kaikkien tulosten julkaisuun on arvioitu kestävän kokonaisuudessa 7 vuotta, mistä ajasta tutkittavien osuuden arvioidaan kestävän 5 vuotta.

Tutkimuksen toteuttaja ja rahoittaja

Tutkimus on tutkijalähtöinen. Rahoitus on hankittu / hankitaan julkisista lähteistä ja esimerkiksi säätiöiltä.

Tutkimuksen mahdolliset hyödyt ja haitat

Molempiin avannetyyppeihin liittyy myös mahdollisia haittoja. Tällä hetkellä ei ole selvillä kumpaan avannetyyppiin liittyy vähemmän haittoja. Paksusuoliavanteen haittoja voivat olla avanteen esiinluiskahdus, avannetyrä, avanteen sulkuarven tyrä ja avanteen sulkuarven haavatulehdus. Ohutsuoliavanteen haittoja voivat olla avanteen toimimattomuus heti leikkauksen jälkeen ja toisaalta liikatoiminta ja elimistön kuivuminen.

Tutkimuspotilaalle voi koitua mahdollista hyötyä, jos hän satunnaistuu ryhmään, josta koituu potilaalle vähemmän haittaa.

Tutkimuksen tuottama tieto auttaa selvittämään onko edellä mainittujen hoitomuotojen välillä eroja.

Mahdollisista muista haitoista sinulle kertoo tarvittaessa tutkijalääkäri Laura Koskenvuo.

Tutkimukseen osallistumisesta voi aiheutua myös odottamattomia haittoja. Ne voivat liittyä tutkimuksen aikana tehtävään toimenpiteeseen. Mikäli tutkimustuloksissa havaitaan sattumalta poikkeavia löydöksiä, tutkimusta tekevä lääkäri arvioi niiden merkityksen ja ohjaa sinut asianmukaiseen jatkohoitopaikkaan.

Tutkittavien vakuutusturva ja korvaukset

HUS on vakuuttanut tutkimukseen osallistujat potilasvakuutuslain mukaisesti. Lisätietoja vakuutuksesta antaa Laura Koskenvuo.

Jos tutkimuksen takia tehdystä toimenpiteestä aiheutuu sinulle henkilövahinko, voit hakea korvausta. Henkilövahingosta voi hakea korvausta HUS potilasvakuutuksesta. Lisätietoja vakuutuksesta ja sen hakemisesta antaa Laura Koskenvuo.

Tutkittavalle maksettavat haitta- ja kulukorvaukset

Tähän tutkimukseen osallistumisesta ei makseta palkkiota.

Henkilötietojen käsittely ja tietojen luottamuksellisuus

Tässä tutkimuksessa sovelletaan suomalaista tutkimus- ja henkilötietojen suojaa koskevaa lainsäädäntöä. Tutkijat ja muu tutkimushenkilöstö ovat sitoutuneet noudattamaan hyvää tieteellistä käytäntöä ja tutkimuksen eettisiä ohjeita. Tarkempi kuvaus tutkimuksen oikeusperustasta on tämän tiedotteen lopussa.

Henkilötietojasi käsitellään tieteellistä tutkimustarkoitusta varten. Sinusta kerättyä tietoa ja tutkimustuloksia käsitellään luottamuksellisesti lainsäädännön edellyttämällä tavalla. Kaikki tietojasi käsittelevät tahot ja henkilöt ovat salassapitovelvollisia. Lisää tietoa henkilötietojesi käsittelystä ja oikeuksistasi saat tämän tiedotteen lopusta.

Lisätiedot ja yhteyshenkilöt

Jos sinulla on kysyttävää tutkimuksesta, voit olla yhteydessä tutkijalääkäriin tai muuhun henkilökuntaan. Voit keskustella heidän kanssaan kaikista tutkimuksen aikana mahdollisesti ilmenneistä haittavaikutuksista, epäilyttävistä oireista ja muista mieltäsi askarruttavista asioista.

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KUVAUS TUTKIMUKSESSA TAPAHTUVASTA HENKILÖTIETOJEN KÄSITTELYSTÄ JA SIIHEN LIITTYVÄT TUTKITTAVAN OIKEUDET

Rekisterinpitäjä

Rekisterinpitäjänä tutkimuksessa on HUS, joka vastaa tutkimuksen yhteydessä tapahtuvien henkilötietojen käsittelyn lainmukaisuudesta.

Tutkimusrekisteriin tallennetaan vain tutkimuksen tarkoituksen kannalta välttämättömiä henkilötietoja. Tietojen kerääminen perustuu tutkimussuunnitelmaan.

Henkilötietojen käsittelyperuste

Yleinen etu lääketieteellisessä tutkimuksessa:
Lääketieteellisessä tutkimuksessa henkilötietojen käsittelyperusteena on lääketieteellisestä tutkimuksesta annetun lain 21 a § mukaisesti keskeisten tutkimuksen suorittamiseen liittyvien käsittelytoimien osalta yleinen etu ja kansanterveyteen liittyvä yleinen etu (EU:n yleisen tietosuoja-asetuksen artiklat 6.1.e ja 9.2.j) sekä turvallisuusraportointiin ja muihin viranomaisille tehtäviin ilmoituksiin liittyen osalta lakisääteisen velvoitteen noudattaminen ja kansanterveyteen liittyvä yleinen etu (tietosuoja-asetuksen artiklat 6.1.c ja 9.2.j).

Henkilötietojen käsittely

Tutkimuksessa henkilötietojasi käsittelevät ainoastaan tutkimusryhmään nimetyt henkilöt, joiden työtehtäviin niiden käsittely kuuluu.

Tutkimuksen rekisteriin tallennetaan vain tutkimuksen tarkoituksen kannalta välttämättömiä henkilötietoja. Tutkittavien henkilöllisyyden tietää vain tutkimuksen henkilökunta, joka on salassapitovelvollinen. Kaikkia tutkimuksessa sinusta kerättäviä tietoja käsitellään tietojen keräämisen jälkeen koodattuina, joten tietojasi ei voida tunnistaa tutkimukseen liittyvistä tutkimustuloksista, selvityksistä tai julkaisuista. Tietojen koodaaminen tarkoittaa sitä, että nimesi ja henkilötunnuksesi poistetaan ja korvataan yksilöllisellä koodilla. Tämän jälkeen sinua koskevia tietoja ei voida tunnistaa ilman koodiavainta, jonka säilytyksestä vastaa tutkimuksen toimeksiantaja. Tutkimuksen ulkopuolisilla henkilöillä ei ole pääsyä koodiavaimeen. Tutkimustulokset analysoidaan koodattuna.

Mistä tietoja kerätään

Tutkimuksessa kerätään henkilötietojasi seuraavista lähteistä: sähköinen potilaskertomus, Kanta-arkisto.

Henkilötietojen luovutus

Tässä tutkimuksessa henkilötietojasi tai näytteitäsi ei luovuteta muille tahoille.
Tietojen luovutus Suomessa ja EU:n sisällä

Tässä tutkimuksessa tietojasi ei luovuteta ulkopuolisille tahoille.

Tietojen siirto EU- ja ETA-alueen ulkopuolelle

Tutkimuksessa tietojasi ei siirretä EU:n ja Euroopan talousalueen (ETA) ulkopuolelle.

Henkilötietojen säilytys

Henkilötietojesi säilytysaikaa sääntelee lainsäädäntö sekä hyvä kliininen tutkimustapa. Henkilötietojesi säilytyksestä vastaa HUS. Tietojasi säilytetään tietoturvallisessa ympäristössä 7 vuotta tutkimuksen päättymisestä jälkeen, jonka jälkeen ne hävitetään asianmukaisesti.

Tutkittavan oikeudet

Sinulla on oikeus saada tietoa henkilötietojesi käsittelystä ja pyytää henkilötietojesi käsittelyn rajoittamista. Sinulla on myös oikeus tarkastaa tietosi ja pyytää niiden oikaisemista tai täydentämistä, jos esimerkiksi havaitset niissä virheen tai ne ovat puutteellisia tai epätarkkoja. Sinulla on myös oikeus vastustaa henkilötietojesi käsittelyä.

Tieteellisen tutkimuksen yhteydessä näitä oikeuksia voidaan kuitenkin rajoittaa. Laki voi velvoittaa rekisterinpitäjän säilyttämään tutkimustietosi tietyn määräajan rekisteröidyn oikeuksista riippumatta. Laki sallii poikkeukset rekisteröidyn oikeuksista silloin, kun se on välttämätöntä tieteellisten tutkimustulosten ja tutkittavien turvallisuuden varmistamiseksi.

Voit milloin tahansa tiedustella, käsittelemmekö henkilötietojasi ja vaatia käsittelyn perustelua. Voit myös tiedustella, mistä olemme saaneet tietojasi ja mihin näytteitäsi ja tietojasi on luovutettu. Sinulla on oikeus saada tiedot maksutta ja kohtuullisessa ajassa (yhden kuukauden kuluessa pyynnöstä). Jos tietopyyntösi on hyvin laaja tai jostakin muusta perustellusta syystä tietojen kerääminen on erityisen aikaa vievää, voidaan määräaikaa pidentää enintään kahdella (2) kuukaudella. Määräajan jatkamisesta ja syystä ilmoitetaan sinulle.

Tietosuoja-asioissa suosittelemme ottamaan yhteyttä tutkimuksen vastuuhenkilöön Laura Koskenvuohon.

Tutkimuspaikkakohtaisen johtavan tutkijan yhteystiedot:
Titteli: Dosentti, erikoislääkäri
Nimi: Laura Koskenvuo
Yksikkö/klinikka: HUS Vatsakeskus
Sähköpostiosoite: laura.koskenvuo@hus.fi@hus.fi

Tietosuojavastaava: Petri Hämäläinen, kehittämispäällikkö
HUS-yhtymä, yleishallinto- ja juridiikka, lakiasiat
eutietosuoja@hus.fi
Postiosoite: PL 440, 00029 HUS

Sinulla on oikeus tehdä valitus erityisesti vakinaisen asuin- tai työpaikkasi sijainnin mukaiselle valvontaviranomaiselle, mikäli katsot, että henkilötietojen käsittelyssä rikotaan EU:n yleistä tietosuoja-asetusta (EU) 2016/679 tai tietosuojalakia (1050/2018). Suomessa valvontaviranomainen on tietosuojavaltuutettu.
Tietosuojavaltuutetun toimisto, Lintulahdenkuja 4, 00530 Helsinki, PL 800, 00531 Helsinki
Puhelinvaihde: 029 566 6700, Sähköposti (kirjaamo): tietosuoja@om.fi

TUTKITTAVAN SUOSTUMUS TUTKIMUKSEEN OSALLISTUMISESTA

Suojaava ohutsuoliavanne tai suojaava paksusuoliavanne peräsuolisyöpäleikkauksessa - prospektiivinen satunnaistettu tutkimus (PROSPERITY)

Helsinki, HYKS, vatsakeskus

Minua on pyydetty osallistumaan yllä mainittuun tieteelliseen tutkimukseen, jonka tarkoituksena on selvittää, onko suojaavalla paksusuoliavanteella vähemmän haittoja potilaalle verrattuna suojaavaan ohutsuoliavanteeseen.

Olen lukenut ja ymmärtänyt saamani tutkimustiedotteen ja annan suostumukseni sen mukaiseen tutkimukseen. Olen saanut tiedotteesta riittävästi tietoa tutkimuksesta ja sen yhteydessä suoritettavasta tietojen keräämisestä, käsittelystä ja luovuttamisesta. Tiedotteen sisältö on kerrottu minulle myös suullisesti ja olen saanut riittävän vastauksen kaikkiin tutkimusta koskeviin kysymyksiini.

Minulla on ollut riittävästi aikaa harkita tutkimukseen osallistumista. Olen saanut riittävät tiedot tutkimuksen tarkoituksesta ja sen toteutuksesta, tutkimuksen hyödyistä ja riskeistä sekä oikeuksistani. Minua ei ole painostettu eikä houkuteltu osallistumaan tutkimukseen.

Tiedän, että tietojani käsitellään luottamuksellisesti eikä niitä luovuteta sivullisille. [

Ymmärrän, että tähän tutkimukseen osallistuminen on vapaaehtoista. Olen selvillä siitä, että minulla on oikeus kieltäytyä tutkimukseen osallistumisesta. Voin myöhemmin halutessani myös keskeyttää osallistumiseni tutkimukseen tai peruuttaa suostumukseni milloin tahansa syytä ilmoittamatta, eivätkä ne vaikuta kohteluuni tai saamaani hoitoon millään tavalla.

Voin keskeyttää osallistumiseni missä tahansa tutkimuksen vaiheessa syytä ilmoittamatta. Minulla on myös oikeus peruuttaa antamani suostumus milloin tahansa ennen tutkimuksen päättymistä. Olen tietoinen siitä, että mikäli keskeytän tutkimuksen tai peruutan suostumuksen, minusta keskeyttämiseen ja suostumuksen peruuttamiseen mennessä kerättyjä tietoja ja näytteitä käytetään osana tutkimusta. Tiedän, että tutkimukseen osallistumisesta aiheutuneista kuluista ei makseta korvausta

Suostumusasiakirja FI

Allekirjoituksellani vahvistan osallistumiseni tähän tutkimukseen ja suostun vapaaehtoisesti tutkimushenkilöksi.

Tutkittavan allekirjoitus	Päiväys
Tutkittavan nimenselvennys	Tutkittavan syntymäaika tai henkilötunnus
Tutkittavan osoite	

Suostumus vastaanotettu

Tutkijalääkärin allekirjoitus	Päiväys
Nimenselvennys	

Alkuperäinen allekirjoitettu asiakirja jää tutkijalääkärin arkistoon ja kopio allekirjoitetusta suostumuksesta annetaan tutkittavalle.