Impact on the recovery of bowel function after anal reinfusion of prophylactic stoma drainage fluid after anal preservation surgery for middle and low rectal cancer (STARS-RC04)

Research protocol

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NCTnumber: NCT05461248

Version number: 1.3

Version date: 30 July 2022

Confidentiality statement

The ownership of all information contained in this protocol belongs to the First Hospital of Jilin University, and will be provided only for review by the investigators, co-investigators, ethics committees, and supervisory and management authorities and other relevant medical institutions. Without written approval from the First Hospital of Jilin University, it is strictly prohibited to communicate any information to third parties unrelated to this study, except for necessary explanations to subjects who may participate in this study when signing the informed consent form.

I. Background to the study

Colorectal cancer is one of the common malignant tumours of the digestive tract in China, and its incidence rate ranks 3rd in the country and is on the rise year by year, with an annual incidence of 388,000 people in 2015, of which rectal cancer accounts for more than half of the total[1]. The incidence of rectal cancer in China is characterised by the predominance of middle and low rectal cancer, accounting for about 70% of the total number of cases. At present, surgery is still the main treatment mode for rectal cancer. Anastomotic leakage (AL) has been a hot issue in colorectal surgery.[2] Anastomotic leakage is defined as a disruption or loss of bowel wall integrity at the site of colorectal or colorectal-anal tube anastomosis, which results in interstitial communication (including leakage at the site of reconstruction of the rectal pouch suture, e.g., J **-** pouch), and the development of a pelvic abscess adjacent to the anastomosis site.[3] AL is a common and serious complication after anal preservation surgery for rectal cancer, with an incidence of 6.7%-16.7%.[4-5] The morbidity and mortality rate after AL can be up to 16%.[6] The 2019 Chinese Expert Consensus on the Diagnosis, Prevention, and Management of Anastomotic Leakage in Rectal Cancer Surgery identifies the protective stoma as a protective factor against anastomotic leakage.[2] .

Protective stomas are most common with collared ileostomies, defined as ileal collars that are fixed to the skin surface and create an opening to allow bowel contents to flow out through the artificial stoma. The purpose is to protect the anastomosis between the colon and the rectum or anal canal. Ileostomies require a secondary surgical closure in addition to triggering temporary care problems. The incidence of surgical complications ranges from 11% to 45%, with a mortality rate of 0.06% to 6.4%[7-10]. The most common postoperative complication is intestinal obstruction. Bowel obstruction not only directly causes physical and psychological pain, but also leads to increased rates of nosocomial infections, other surgery-related complications, postoperative mortality, and hospitalisation costs.

A large number of beneficial bacteria (e.g. Bifidobacterium, Lactobacillus, etc.) normally exist in the human intestinal tract, which are not only non-toxic and

harmless to the organism, but also participate in the process of digestion, nutrition, metabolism, absorption, immunity and anti-infection of the host. Research has proved that it plays an important role in maintaining a healthy microecological balance of the organism. The intestinal flora is essential for the maintenance of the host's physiological processes, including the epithelial barrier and immune function[11] . The stressful effects of surgery can cause damage to the intestinal mucosa, and an absent intestinal segment following a protective stoma can weaken intestinal motility, leading to a proliferation of pathogenic intestinal flora and causing intestinal dysbiosis[12] .

Previous studies have shown that the mucosa and villi of the open bowel segments after intestinal diversion produce atrophy, decreased absorptive capacity, and loss of rhythmic contractions. It has been suggested that transanal irrigation may help to prevent and control colorectal anastomotic fistulae and improve patients' postoperative life quality[16-18] . Accordingly, it is hypothesised that if preoperative stimulation of stoma discharge reinfuison to the open bowel segment through the anus may help to promote the recovery of bowel function and intestinal flora disorders after stoma closure surgery.

To address this hypothesis, in the present study we propose to conduct a prospective, randomised controlled study in patients with protective stoma, aiming to investigate whether stimulation of stoma drainage fluid through the anus to an open intestinal segment prior to stoma closure is beneficial for the recovery of bowel function, reduction of complications and improvement of intestinal dysbiosis, and to provide high-level evidence for the clinic.

II. Purpose of the study

To analyse the occurrence of defecation complications, rectal function and quality of life indicators after collecting stoma discharge for anal re-infusion to patients after performing protective ileostomy in anus-preserving surgery for middle and low rectal cancer, so as to evaluate the impact of collecting stoma drainage fluid for anal re-infusion on the recovery of patients' intestinal function.

III. Subject of the study

(i) Inclusion criteria

1. Age: 18~75 years old, male or female;

2. Pathological diagnosis of adenocarcinoma of the rectum on preoperative biopsy;

3. Clinical staging was T1-4aN0-2M0;

4. No distant multiple metastases;

5. ECOG rating 0-2;

6. Cardiac, pulmonary, hepatic and renal functions met the criteria for surgical tolerance

7. Clinical diagnosis of middle and low rectal cancer, the lower edge of the tumour is within 10cm from the anal verge, and it is proposed to perform radical rectal surgery and prophylactic ileostomy at stage I, and intestinal closure at stage II;

8. Patients and their families were able to understand and willing to participate in this clinical study and signed an informed consent form.

(ii) Exclusion criteria

1. Previous history of malignant colorectal tumour or recently diagnosed combination of other malignant tumours;

2、Patients with combined intestinal obstruction, intestinal perforation, intestinal haemorrhage, etc. requiring emergency surgery;

3. Neighbouring organs requiring combined organ removal;

4. ASA classification ≥ Grade IV and/or ECOG physical status score > 2;

5. Those who have serious liver and kidney dysfunction, cardiopulmonary dysfunction, coagulation dysfunction or combined serious basic diseases cannot tolerate the surgery;

6. Have a history of serious mental illness;

7. Pregnant or breastfeeding women;

8. Those who have a history of taking steroid drugs;

9. Patients with other clinical and laboratory conditions considered by the investigator to be inappropriate for participation in the trial;

10. One week before the operation, there are signs of infection, body temperature rises >37.5°C, blood WBC >10.0×109/L;

11. History of antibiotic use 1 week prior to surgery (excluding preoperative shock medication);

12. Preoperative neoadjuvant patients

(iii) Exit criteria

1. Accompanied by other non-oncological conditions that make it impossible for the patient to continue to receive this treatment plan;

2, After enrolment in the study, patients who required emergency surgery due to intestinal obstruction, perforation, or bleeding,et al. prior to stoma closure;

3. Patients with pathologically confirmed distant metastases after rectal surgery, including liver, pelvis, ovary, peritoneum, and distant lymph node metastases;

4. Intraoperative exploration for middle and low rectal cancer in anus-preserving surgery for those who need combined organ resection;

5. After enrolment in the study, patients requested to withdraw from the study cohort for various reasons, or were unable to complete the study programme and follow-up for various reasons;

6. Anastomotic fistula, severe anastomotic stenosis (inability to pass through enteroscopy or oesophageal finger and inability to dilate via oesophageal finger) after radical rectal surgery.

IV. Study endpoints

(i) Primary study endpoints:

Incidence of major LARS after 6 months of stoma closure.

(ii) Secondary research endpoints:

1, Bacteriological sequencing 1 month after stoma closure

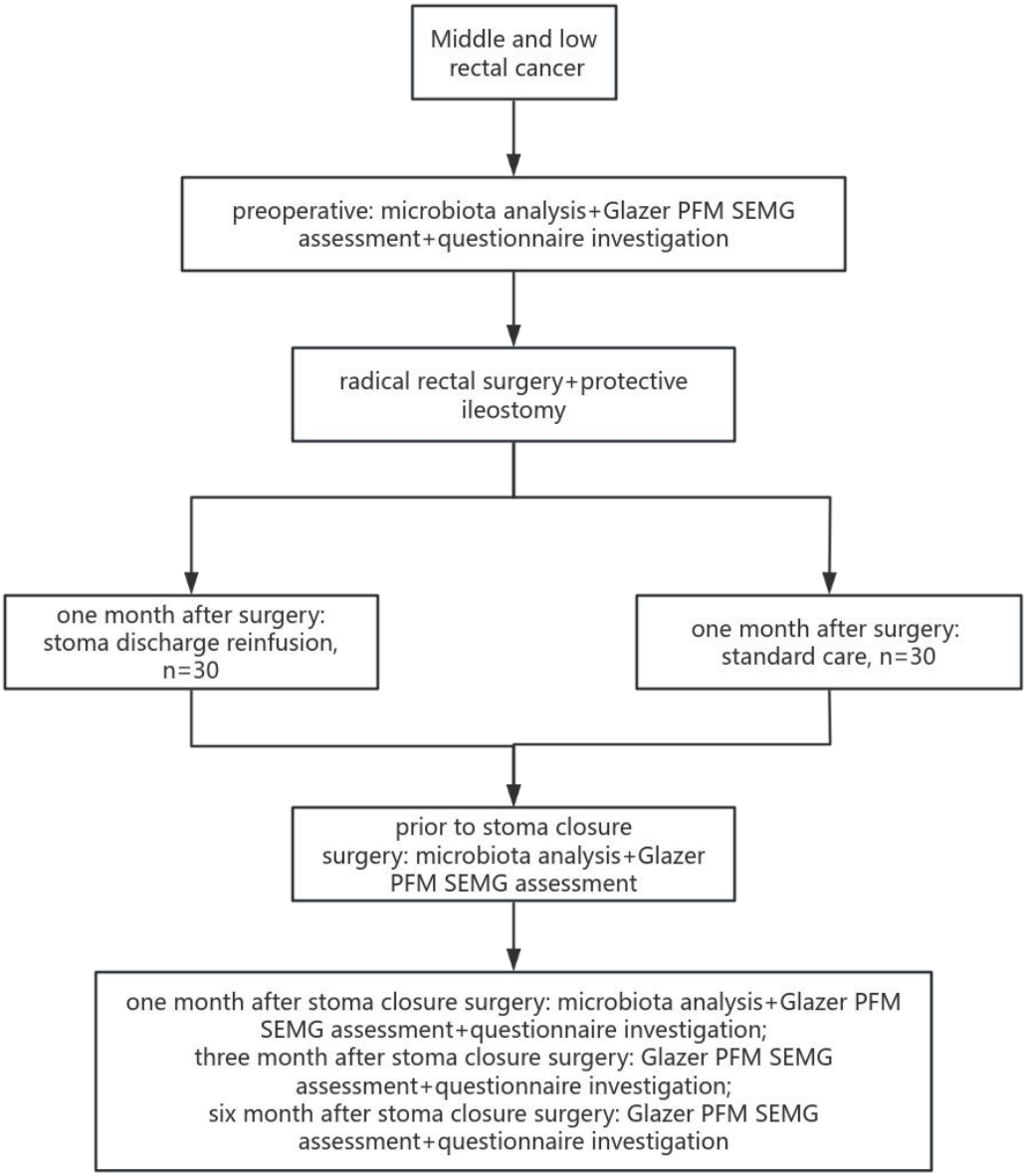
2. Anorectal function (LARS questionnaire, Wexner[15] incontinence score, MSKCC[13-14] bowel function questionnaire), Glazer pelvic floor muscle surface electromyography, and quality of life scores after 1 month of stoma return.

3. Recovery of postoperative bowel function

After reversal surgery, time to oral feeding, time to anal defecation after reduction surgery, and rate of intestinal obstruction (intestinal obstruction was defined as ,inability to tolerate food for more than 72 H or the need for re-fasting or gastrointestinal decompression) were observed.

V. Research design

The study was a prospective randomised design with simple randomised grouping, randomised by prior computer-generated random number tables. The expected recruitment cut-off date for all subjects was 1 November 2022, with a predictable sample size of 60 cases to be enrolled based on patient admissions to the hospital. The enrolment process is as follows


Middle and low rectal cancer
preoperative: microbiota analysis+Glazer PFM SEMG assessment+questionnaire investigation
radical rectal surgery+protective ileostomy
one month after surgery: stoma discharge reinfusion, n=30
one month after surgery: standard care, n=30
prior to stoma closure surgery: microbiota analysis+Glazer PFM SEMG assessment
one month after stoma closure surgery: microbiota analysis+Glazer PFM SEMG assessment+questionnaire investigation;
three month after stoma closure surgery: Glazer PFM SEMG assessment+questionnaire investigation;
six month after stoma closure surgery: Glazer PFM SEMG assessment+questionnaire investigation

(i) Transanal reinfusion of stoma discharge

Experimental group:

Starting from 1 month after radical rectal surgery, the infusion is performed once a week for 2 months. Each infusion was performed with a liquid diet on the day before, and 400-600 mL of stoma discharge was collected on the same day (if the stoma fluid was limited, it could be blended with warm water), and the reinfusion was performed from the patient's anus using an enema bag, with a flow rate of about 100 mL/min being controlled.

Control group:

No special treatment.

(ii) Preoperative preparation for protective stoma reduction

Stoma closure was performed 3 months after surgery. All patients were reviewed in an outpatient clinic at least 7 days before preparation for stoma closure.

The surgeon is responsible for performing rectal palpation and Lower gastrointestinal tract imaging to rule out anastomotic leakage and anastomotic stenosis.

(iii) Pelvic floor muscle function assessment

Pelvic floor muscle function tests were performed "prior to radical rectal surgery", "prior to stoma closure surgery","1 month after stoma closure surgery", "3 months after stoma closure surgery" and "6 months after stoma closure surgery"to compare the recovery of pelvic floor muscle function.

(iv) Sequencing of intestinal flora

faecal sampling

Gut microbiological samples were collected using the rectal swab method. Firstly, the perianal area was cleaned using soap, water and 70% alcohol respectively, then a sterile swab was inserted into the anus 4-5cm at the anal sphincter after moistening with saline and gently rotated to take a sample at the anal crypt (traces of faeces were clearly visible on the swab), then inserted into a sterile freezing tube (or the head of the swabs was clipped and dropped into a sterile freezing tube, 3-5 swabs were provided for each sample) and placed in a box containing ice/ dry ice in a foam box,

transported to the laboratory within 24h and stored in a -80°C refrigerator.

Sample delivery

A. DNA: total amount >500ng, concentration >20ng/ul, no significant degradation, 2g of faecal or intestinal contents;

B. The sample volume of a single delivery should be ≥20 samples, the delivery tube (freezing tube) must be clearly labelled with the sample number, the mouth of the tube should be sealed with Parafilm sealing film (to prevent cross contamination between samples), and the completed delivery order should be sealed in a self-sealing bag and sent to the laboratory with the samples transported on dry ice.

sampling node

Before radical rectal surgery, before stoma closure surgery, and 1 month after stoma closure surgery.

(v) Hospitalisation and discharge criteria after stoma closure surgery

1. Hospitalisation

Discontinue all IV medications on postoperative day 2 if they meet the following criteria:.

- Haemodynamically stable
- Temperature < 37.3 degrees Celsius
- Pain score < 5 (on a scale of 0 to 10)
- Tolerates oral diet without nausea or vomiting
- Clear urination

If all criteria are not met the morning after surgery, the patient will continue rehydration, anti-infective, and pain control therapy until the criteria are met. In addition, even if all criteria for stopping intravenous medication are met, treatment may continue to be given if the surgeon feels that it would be beneficial for the patient to have continued treatment. Patients are checked in daily to see how they are doing to ensure they are progressing well.

2. Discharge criteria

The patient is in good general condition, basically resuming normal diet and intestinal function; body temperature is normal and there are no positive signs on

abdominal examination; relevant laboratory findings are basically normal; and the abdominal incision is healing well (II/A or II/B).

(vi) Adverse events

1. The patient is unable to operate the transanal reinfusion process

Treatment: Each patient who needs transanal reinfusion will have the first process performed by the doctor, who will instruct the patient and his/her family on the spot. The doctor and the patient leave each other's phone number or WeChat to keep in touch.

2、Abnormalities in the patient's transanal reinfusion

Handling: If the patient has abdominal distension or the urge to defecate during transanal reinfusion, the patient should be instructed to take deep breaths to alleviate the discomfort. During transanal reinfusion, pay attention to the patient's condition changes at any time, such as the discovery of rapid pulse, pallor, cold sweat, severe abdominal pain, panic and shortness of breath, you should immediately stop the enema and contact the doctor in time to take emergency measures.

VI. Follow-up programme

Functional learning follow up:

(1) Items: including LARS score, Wexner incontinence score, MSKCC bowel function questionnaire; quality of survival score. The questionnaire follow-up was conducted by a professional pelvic floor follow-up team. The investigators of the pelvic floor follow-up team had appropriate professional training and were unaware of the patient grouping. The method of answering the questionnaires was explained to the patients before the questionnaire assessment, and after detailed enquiry, the patients were asked to answer the questionnaires in a specific way.

(2) Time: before radical rectal surgery, 1 month after stoma closure, 3 months after stoma closure and 6 months after stoma closure.

Survival follow-up:

Patient survival at 1 year post-stoma closuren, 2 years post-stoma closure, 3 years post-stoma closure, and 5 years post-stoma closure follow up.

VII. Observation indicators

1. Baseline information: gender, age, height, weight, ASA, past medical and treatment history, co-morbidities, laboratory tests and imaging.

2. Sequencing of intestinal flora: before radical rectal surgery, before stoma closure, and 1 month after stoma closure.

3. Perioperative period: also include time to first postoperative defecation, time to first postoperative semi-liquid diet, and incidence of postoperative intestinal obstruction.

4. Follow-up indicators: LARS syndrome score, Wexner score, MSKCC Bowel Function Questionnaire, QLQ-C30 Quality of Life Scale.

VIII. Signing of informed consent and registration of subjects

(i) Informed consent signing:

The study will be conducted in accordance with clinical trial protocols, GCP principles and the Declaration of Helsinki. The informed consent form will be signed by the PI or a qualified, trained and authorised clinical staff member. The trial process needs to be explained in detail to the subject and/or authorised person, and it is important to avoid over-informing and to give the subject and/or authorised person enough time to consider whether to participate or not. Subjects/authorised persons will be enrolled in the experimental group once they have agreed and signed the informed consent form. The original informed consent form is kept on file at the research centre and a copy is retained by the subject.

(ii) Subject registration

After signing the informed consent form, patients are registered with subject information, baseline data, and oncology-related data, which should include all data from the screening phase of this study.

IX. Sample size calculation

The sample size was calculated using PASS 15 software, with the major LARS incidence rate at 6 months after stoma closure surgery as the primary outcome. Based on retrospective data from the authors' centre, the major LARS rate at 6 months after stoma closure surgery was estimated to be 14% in the stoma discharge reinfusion group and 47% in the control group. Thus, a sample size of 27 patients was required to achieve 80% power in detecting differences, with a two-sided level of significance of 0.05.

Assuming a dropout rate of up to 10%, 60 patients were enrolled.

X. Methods of statistical analysis

(i) Definition of analysis set

1. Full Analysis Set (FAS)

According to the basic principle of intentional analysis (ITT), all enrolled subjects who were given a randomisation number will be included in the FAS. the FAS is the primary dataset for the evaluation of the efficacy of this study.

2. Compliance with the programme set (Per-Protocol Set, PPS)

PPS is defined as all cases in which planned treatment and visits were completed as specified in the protocol and there were no protocol violations that significantly affected outcomes. Patients with protocol violations that significantly affect the protocol will be excluded from this analysis set. Protocol violations that significantly affect efficacy will be identified at the time of data review. PPS is a secondary data set for the efficacy evaluation of this study.

3. Safety Set (SS)

Cases that completed at least one safety evaluation data after enrolment constituted the safety population of this study. The safety population was the primary population for the safety evaluation of this study.

(ii) Methods of statistical analysis

1. General principles: All statistical tests will be two-sided, and $P< 0.05$ will be considered statistically significant for the differences tested. The description of quantitative indicators will calculate the mean, standard deviation, median, minimum value, maximum value, if it meets the normal variance chi-square, expressed as the mean $\pm$ standard deviation, and use the t-test to compare the differences between the two groups; data that do not meet the normal variance chi-square are expressed as the median (quartile), and the rank sum test is used for comparison. Categorical indicators were described by the number of cases and percentages in each category, and the chi-square test was used to compare the differences between the experimental and control groups.

2, The main outcome indicators of the occurrence of LARS at 6 months after the

reduction were expressed as the number of cases (percentage), and the chi-square test was used to compare the differences between the experimental group and the control group.

Secondary outcome indicator colony species results will be tabulated based on the top 15 species in abundance using cumulative histograms to compare species composition differences between samples. Based on the species abundance information of each sample at the genus level, the top 50 genera of abundance will be selected, and the samples and species will be clustered based on the abundance information of each sample, and heat maps will be drawn. And Shannon diversity index, Simpson index and Chao1 richness index were calculated for Alpha diversity analysis Comparative analysis of microbial community composition of samples between different groups was performed using Beta diversity analysis.

Secondary outcome indicators Wexner score, MSKCC Bowel Function Questionnaire, and QLQ-C30 Quality of Life Scale scores were analysed for repeated-measures data between the two groups, Mauchly's test of sphericity was performed, and ordinary one-way ANOVA or multifactorial ANOVA was performed according to the test results.

x. schedule of visits

sports event	Pre-radical rectal surgery	pre-discharge	Pre-stoma closure surgery	Post-stoma closure 1 month	Post-stoma closure 3 months	Post-stoma closure 6 months
Demographic information	√					
Baseline assessment	√					
bacterial colony sequencing	√		√	√		
Pelvic floor muscle examination	√		√	√	√	√
surgical treatment		√				
postoperative pathology		√				
postoperative follow-up				√	√	√

rectal examination			√	√	√	√
Pelvic floor surface electromyography assessment	√		√	√	√	√
Functioning, quality of life questionnaire	√			√	√	√

Schedule 1

LARS Bowel Function Questionnaire

Does the patient complain of abnormal bowel movements: ☐Yes ☐No
Patient complained of abnormal defecation as: ☐ increased frequency ☐ incontinence ☐ painful defecation ☐ inability to distinguish between gas and faeces ☐ other _____

Whether the patient is satisfied with the current state of defecation: ☐ Satisfied ☐ Unsatisfied
Does the patient think that the current state of defecation affects daily life:
☐ No effect ☐ Yes effect
Use of medication to improve bowel movements: ☐ Yes Name _____ ☐ No
Prophylactic fistula ☐Yes ☐No
Prophylactic Fistula Payback Time ☐ is time Year Month Day ☐ No

1. Have you ever had uncontrollable flatulence (farting)?	
☐Never	0 points
Yes, less than 1 time per week	4 points
Yes, at least once a week	7 points
2. Have you ever had an accidental leakage of loose stool?	
☐Never	0 points
Yes, less than 1 time per week	3 points
Yes, at least once a week	3 points
3. How many times a day do you have a bowel movement?	
☐ More than 7 times per day (24 hours)	4 points
□4~7 times per day (24 hours)	2 points
□1~3 times per day (24 hours)	0 points
☐ Less than 1 time per day (24 hours)	5

points

4. Have you ever had to have another bowel movement within an hour of having one?

☐Never 0 points

Yes, less than 1 time per week 9 points

Yes, at least once a week 11 points

5. Have you ever had to flush to the loo because of an urgent bowel movement?

☐Never 0 points

Yes, less than 1 time per week 11 points

Yes, at least once a week 16 points

The total score of the questionnaire was calculated by adding the scores of the 5 items. A total score of 0-20 indicates "no anterior resection syndrome", and a score of 21-29 indicates "no anterior resection syndrome".
"Mild anterior resection syndrome", 30-42 means "severe anterior resection syndrome".

LARS Rating:___ Points **Functional classification □ N o LARS** **□ Mild LARS ☐ Severe LARS**

Schedule 2

ASA Classification Criteria

Refers to the six classes into which the American Society of Anaesthesiologists (ASA) classifies patients prior to anaesthesia based on their physical condition and risk to surgery.

(military) rank	condition	Perioperative mortality rate
first level	Physical health, good development and nutrition, and normal functioning of organs.	0.06 per cent-0.08 per cent
second level	In addition to surgical disease, there is mild coexisting disease with sound functional compensation.	0.27 per cent - 0.40 per cent
third level	Coexisting conditions are severe and physical activity is limited, but can still manage daily activities.	1.82 per cent-4.30 per cent
fourth level	Severe coexisting conditions, loss of ability to perform daily activities, and frequent life-threatening situations.	7.80 per cent-23.0 per cent
fifth level	Dying patients who have difficulty sustaining life for 24 hours, with or without surgery.	9.40 per cent-50.7 per cent
sixth level	Confirmed brain death and his organs are intended for organ transplants.	

First and second class patients tolerate anaesthesia and surgery well and pass through anaesthesia smoothly.

Anaesthesia for Class III patients carries certain risks, and it is important to make adequate preparations before anaesthesia, and to take effective measures to actively prevent any complications that may occur during anaesthesia.

Class IV patients are extremely dangerous to anaesthesia and have a high perioperative mortality rate even with adequate preoperative preparation.

Grade 5 is a dying patient who is unusually dangerous to anaesthesia and surgery and should not undergo elective surgery.

Schedule 3:

ECOG Physical Fitness Status Scale

(military) rank	functional status
0	Mobility was completely normal and did not differ in any way from the mobility before the onset of the disease.
1	Can move around freely and perform light physical activities, including general household or office work, but cannot perform heavier physical activities.
2	(b) Tolerates the symptoms of the tumour, is able to move freely and take care of himself, is incapacitated for work, but spends no more than 50 per cent of his time in bed during the day.
3	The tumour is so symptomatic that it is bedridden or wheelchair-bound for more than 50 per cent of the day, but it is still able to get up and stand, and is only partially self-sufficient.
4	Seriously ill and bedridden, unable to care for himself.
5	Death.

Schedule 4:

Wexner Constipation Score

frequency of defecation	Time: time in toilet (min)
1-2 times every 1-2 days 0 ☐	Less than 5 0 ☐
2 times per week 1 ☐	5-10 1 ☐
1 time per week 2 ☐	10-20 2 ☐
Less than 1 time per week 3 ☐	20-30 3 ☐
Less than 1 time per month 4 ☐	Greater than 30 4 ☐
Difficulty: pain **assessment**	Auxiliary: auxiliary **forms**
Never 0 ☐	No 0 ☐
Very little 1 ☐	Stimulant laxatives 1 ☐
Sometimes 2 ☐	Finger-assisted or enema 2 ☐
Usually 3 ☐	Failure: **number of** failed defecation attempts in 24h
Always 4 ☐	No 0 ☐
Completeness: incomplete sensory **assessment**	1-3 times 1 ☐
Never 0 ☐	3-6 times 2 ☐
Very little 1 ☐	6-9 times 3 ☐
Sometimes 2 ☐	More than 9 times 4 ☐
Usually 3 ☐	Medical history: duration of constipation (years)
Always 4 ☐	0 0 ☐
Pain: Abdominal **pain**	1-5 1 ☐
Never 0 ☐	5-10 2 ☐
Very little 1 ☐	10-20 3 ☐
Sometimes 2 ☐	More than 20 4 ☐
Usually 3 ☐	
Always 4 ☐	Total Score:___

Schedule 5:

Bowel symptoms (MSKCC Bowel Function Questionnaire)	Always/often	Sometimes/rarely	non-occurrence
constipation			
When you feel like having a bowel movement, can you wait 15min before going to the toilet?			
Do you have another bowel movement within 15 minutes after the previous one?			
Are your bowel function issues affecting your daily activities?			
During the day, do you ever use tissues, nappies or pads under your underwear to prevent leakage?			
Have you ever had loose stools? (Slightly formed, paste-like)			
Have you ever soiled your underwear during the day?			
Have you ever had diarrhoea? (unformed, watery stools)			
Have you ever soiled (leaked) your underwear while sleeping?			
Have you ever used medication (e.g. diarrhoea, antidiarrhoea) to reduce the frequency of bowel movements?			
Bowel movements are affected by diet			
Have you ever controlled your bowel movements by limiting the types of solid foods you consume?			
Does the intake of certain solid foods increase the number of bowel movements per day?			
Have you ever controlled your bowel movements by limiting the types of liquid foods you consume?			
Does drinking a certain liquid increase the number of bowel movements per purpose?			
Abnormal bowel movements			

Do you go to the toilet regularly?			
Do you feel like you have completely emptied your bowels after a bowel movement?			
Can you control your bowel movements?			
Do you know the difference between the sensation of having to pass gas (fart) and having a bowel movement?			

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