A randomized, parallel-group, 30-day, difference analysis study to investigate the efficacy of the transanal drainage tube (TDT) for anastomotic leakage (AL) prevention following the laparoscopic low anterior resection for rectal cancer

Clinical Study Protocol

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Version: 4.0

Date: 2020-Oct-30

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72 **Protocol Synopsis**

Study Title	Use of the TDT for Prevention of Anastomotic Leakage After Laparoscopic Anterior Resection for Rectal Cancer
Scientific Title	A randomized, parallel-group, 30-day, difference analysis study to compare the efficacy of the transanal drainage tube (TDT) for anastomotic leakage (AL) prevention following the laparoscopic low anterior resection for rectal cancer
Contact Investigator	Prof. Weidong Tong
Primary sponsor	Army Medical Center (Daping Hospital), Army Medical University
Secondary sponsor(s)	Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine Department of Gastrointestinal Surgery, The First Affiliated Hospital of Air Force Medical University Department of Colorectal and Anal Surgery, The 940th Hospital of Joint Logistics Support Force of The Chinese People's Liberation Army Department of gastrointestinal and hernia surgery, Second People’s Hospital of Yibin Department of Gastrointestinal Surgery, Yongchuan Hospital of Chongqing Medical University Department of Epidemiology, College of Preventive Medicine, Army Medical University (Third Military Medical University) Department of Gastrointestinal and breast surgery, The People's Hospital of Kaizhou District
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT02686567

Date of Registration In Primary Registry	02/19/2016
Funding Support	Chongqing Health Commission (No.2018MSXM207)
Study Objective	To evaluate whether the TDTs can reduce the incidence of anastomotic leakage after laparoscopic anterior resection for rectal cancer
Intervention(s)	For patients who were assigned to the TDT group, a silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery.
Groups	● TDT group: application of TDT after laparoscopic low anterior resection for rectal cancer ● Non-TDT group (control): without TDT application
Key Inclusion And Exclusion Criteria	Ages Eligible for Study: ≥18 years Sexes Eligible for Study: both Accepts healthy volunteers: no **Inclusion criteria:** ● age from 18 to 8o years old ● primary rectal adenocarcinoma ● tumor location ≤ 10 cm ● ASA I, II, or III ● laparoscopic LAR + DST ● patients and their families can understand and are willing to participate in this study and provide written informed consent **Exclusion criteria:** ● emergency operation

	● patients with preoperative radiotherapy ● patients with IBD, FAP, recurrent rectal cancer, or synchronous cancer, other types of surgeries for rectal cancer ● patients with serious mental illness or uncontrolled infections before surgery ● pregnant or breastfeeding women ● patients with other clinical and laboratory conditions considered by the investigator should not participate in the trial
Study Type	● Interventional ● Allocation: randomized ● Intervention model: the parallel assignment ● Masking: no ● Primary purpose: comparison
Target Sample Size	560
Recruitment Status	Study completion: Sep 2020
Primary Outcome(s)	AL rate within 30 days after surgery in 2 groups
Key Secondary Outcomes	● Grades of AL ● Postoperative anal pain score ● TDT-related adverse events: bleeding ● TDT-related adverse events: iatrogenic colonic perforations(ICP)
Sample Size Estimation	Based on the synthesis of information from multiple published studies with large sample sizes, we assume that the AL rate will be reduced from 10.5% to the expected 4% due to the TDT intervention. With an 80% power and a 5% significance level, and an expected crossover rate of 1%, and a dropout rate of 10%, we needed to recruit 560 patients overall

Study Method	1. Eligible patients are randomly assigned to two groups with a 1:1 allocation ratio (TDT and non-TDT group) after the laparoscopic LAR and DST procedures are chosen during the operation 2. Simple randomization was obtained through computer-generated random number sequence allocation by the ***Quality Control Committee.*** 3. Allocation concealment was performed: After completion of the anastomosis and further DS construction if necessary, the surgeon was notified to implement the intervention based on the randomization results by the circulating nurse 4. Quality requirements: All perioperative treatments must comply with relevant guidelines. The preservation of the left colonic artery was assessed by the surgeon according to his or her own experiences and assessment of the patient's conditions 5. The decision regarding DS construction was made by the surgeon 6. A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery in patients of TDT group 7. The tube is fixed with a skin suture and connected to a drainage bag 8. TDT is planned to remove 3-7 days after surgery according to the surgeon's discretion when the discharge of feces or flatus was clearly and repeatedly observed and/or when surgeons confirmed the absence of signs of AL 9. Early removal is allowed if the patient experienced intolerable pain 10. AL will be recorded within 30 days after surgery (the definition of AL is detailed in the following text ,see 8.1)

	11. Grades of AL will be identified and recorded 12. The numerical rating scale (NRS) is used to assess the anal postoperative pain score of patients in the TDT group. The assessment will be performed every day postoperatively until the TDT is removed 13. TDT-related adverse events such as bleeding and ICPs will be identified and recorded

1 Background

Anastomotic leakage (AL) is one of the most dreadful complications after LAR and is associated with increased medical costs, longer hospital stay, higher postoperative morbidity, and mortality for patients, even higher rate of recurrence(1). Diverting stoma (DS) is still one of the most common methods used in AL prevention, despite the clinical benefit of reducing morbidity from anastomotic leaks, DS remains a large source of morbidity for patients, with increased postoperative stay, readmission, dehydration, etc(2-4). It has been reported that the transanal drainage tube (TDT) is valuable and safe to prevent AL after LAR, but doubts about this never ceased. The potential role of applying a TDT is supposed to be beneficial for endoluminal pressure reduction as well as fecal diversion, resulting in a protective effect on anastomotic healing (5). Several meta-analytical studies have reported that the TDT is effective in AL prevention (6). However, the majority of previous studies have the limitation of retrospective observation, a small sample size or utilization of a nonrandomized control group. Moreover, inconsistent results have also been reported, failing to prove the effectiveness of the implementation (7-9). Cong and his colleagues reported that the AL rate in the TDT group was unexpectedly higher than that in the non-TDT group (15.1% vs. 4.9%, $P = 0.008$)(9). Zhao supposed that the TDT would reduce anastomotic complications but found that the AL rate was not significantly different between the two groups (2.5% vs. 7.8%, $P = 0.160$)(8). In a study using propensity score matching (PSM), Yang reported no significant difference in the overall AL rate between the two groups (9.8% vs. 11.8%, $P = 0.652$). A similar result was concluded by Lee in their retrospective study, both before and after PSM (5.8% vs. 10.7%, $P = 0.652$; 5.8% vs. 9.1%, $P = 0.278$, respectively)(7). Therefore,

due to the lack of a high level of evidence, the role of TDTs in AL prevention after LAR is still unclear.

2 Study Title

Use of the TDT for Prevention of Anastomotic Leakage After Laparoscopic Anterior Resection for Rectal Cancer.

3 Objective

3.1 Research Hypothesis

The null hypothesis is that the AL rate of patients with TDT is the same as that without TDT within 30 days following laparoscopic LAR. (H0)

The alternative hypothesis is that the AL rate of patients with TDT is different from that without TDT within 30 days following laparoscopic LAR. (H1)

3.2 Study Objective

To evaluate whether the TDTs can reduce the incidence of anastomotic leakage after laparoscopic anterior resection for rectal cancer.

4 Intervention(s)

A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery in patients from the TDT group.

5 Trial Design

This trial is designed as a randomized, controlled, open-label, multicenter, difference analysis study with two parallel groups and a primary endpoint of anastomotic leakage within 30 days after laparoscopic low anterior resection for rectal cancer.

5.1 Groups:

Randomization will be performed with a 1:1 allocation ratio.

- TDT group: application of TDTs after laparoscopic low anterior resection for rectal cancer.
- Non-TDT group (control): without TDT application.

6 Eligibility Criteria

Patients (or a representative) must provide written, informed consent before any study procedures occur.

6.1 Inclusion criteria

All patients should meet the surgical conditions under the Chinese guideline for the diagnosis and treatment of colorectal cancer. Besides, patients eligible for the trial must comply with all of the following at randomization:

- Age from 18 to 8o years old
- Primary rectal adenocarcinoma
- Tumor location ≤ 10 cm
- ASA I, II, or III
- Laparoscopic LAR + DST

6.2 Exclusion criteria

- Emergency operation
- Patients with preoperative radiotherapy
- Patients with IBD, FAP, recurrent rectal cancer, or synchronous cancer, other types of surgeries for rectal cancer
- Patients with serious mental illness or uncontrolled infections before surgery
- Pregnant or breastfeeding women
- Patients with other clinical and laboratory conditions considered by the investigator should not participate in the trial

7 Sample Size Estimation

Based on the synthesis of information from multiple published studies with large sample sizes (5, 10-15), we assume that the AL rate will be reduced from 10.5% to the expected 4% due to the TDT intervention. With an 80% power and a 5% significance level, and an expected crossover rate of 1%, and a dropout rate of 10%, we needed to recruit 560 patients overall

8 Standard operating procedures (SOP)

8.1 All patients should meet the surgical conditions under the Chinese guideline for the diagnosis and treatment of colorectal cancer

8.2 Perioperative management should comply with relevant guidelines. For example, routinely implement mechanical bowel preparation combined with antibiotics before surgery, nutritional risk assessment and support; postoperative antibiotics and nutritional support treatment must strictly comply with the requirements of the local health department; pay attention to pain management.

8.3 After reporting relevant information to the ***Quality Control Committee***, eligible patients are randomly assigned to two groups with a 1:1 allocation ratio (TDT and non-TDT group) after the laparoscopic LAR and DST procedures are chosen during the operation.

8.4 Simple randomization was obtained through computer-generated random number sequence allocation by the ***Quality Control Committee.***

8.5 Allocation concealment was performed: After completion of the anastomosis and further DS construction if necessary, the surgeon was notified to implement the intervention based on the randomization results by the circulating nurse.

8.6 Quality requirements: All procedures must be performed by experienced surgeons who had performed at least 300 laparoscopic LARs before the study. All perioperative treatments must comply with relevant guidelines. The preservation of the left colonic artery was assessed by the surgeon

according to his or her own experiences and assessment of the patient's conditions.

8.7 The decision regarding DS construction was made by the surgeon.

8.8 A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery in patients from the TDT group.

8.9 The tube is fixed with a skin suture and connected to a drainage bag.

8.10 TDT is planned to remove 3-7 days after surgery according to the surgeon's discretion when the discharge of feces or flatus was clearly and repeatedly observed and/or when surgeons confirmed the absence of signs of AL.

8.11 Early removal is allowed if the patient experienced intolerable pain.

8.12 Record whether the patient has AL-related symptoms and signs, collect blood routine, albumin, prealbumin and other laboratory test results on the day after the operation, postoperative day (POD) 1, 3, 5, and so on. Record the pelvic drainage volume and fluid properties every day after the operation, and combine the above inspection results as an important supporting result for evaluating the presence or absence of AL and the grades.

8.13 AL will be recorded within 30 days after surgery (the definition of AL is detailed in the following text)

8.14 Grades of AL will be identified and recorded

8.15 The numerical rating scale (NRS) is used to assess the anal postoperative pain score of patients in the TDT group.

8.16 TDT-related adverse events such as bleeding and ICPs will be identified and recorded.

8.17 Discharge criteria: able to take a liquid or semi-liquid diet; there are signs of recovery of intestinal function; normal body temperature; no positive signs in abdominal examination; able to go to the ground and have a certain ability to take care of themselves.

9 Follow-up plan

9.1 Follow-up period: within 30 days after surgery;

9.2 Designate a investigator to keep in touch with discharged patients, and instruct patients to return to the hospital for follow-up treatment if they feel unwell;

9.3 The follow-up content focuses on the presence or absence of AL-related symptoms or signs such as abdominal pain, chills, fever, and acute abdomen after discharge, as well as other symptoms that observers believe are related to AL (this can be determined by discussion with lead observers).

10 Outcomes Measures

10.1 Primary Outcome Measures

The primary endpoint is the AL rate within 30 days after surgery.

AL was defined when the following symptoms were noticed: abdominal pain; fever; peritonitis; leukocytosis; increased procalcitonin (PCT) or C-reactive protein (CRP); discharge of feces, pus, or gas from the drainage tube or the vagina; and septicemia with pelvic abscess. All clinically suspicious symptoms were confirmed by digital rectal examination, computed tomography (CT) scan, or surgery when necessary(5, 7-9, 16-20).

10.2 Secondary Outcome Measures

- The grades of AL. The severity grading of AL was defined according to the International Study Group of Rectal Cancer(21). In the present study, AL was referred to as grades B and C, and asymptomatic AL (grade A) was not considered because no active therapeutic intervention was required.
- Anal postoperative pain score. The numerical rating scale (NRS) is used to assess the anal postoperative pain score of patients in the TDT group. The assessment will be performed every day postoperatively until the TDT is removed.
- TDT-related adverse events such as bleeding and ICPs. Only 2 cases of iatrogenic colonic perforations (ICPs) were reported in all cases of previous studies. The underline benefit will be a significant reduction of AL rate in patients with TDTs while the underline harms may be bleeding, ICP, or discomfort caused by TDTs.

11 Data Collection Methods

The data to be collected includes but is not limited to the following: preoperative information including gender, age, contact information; basic hospitalization information of the patient; related examination results including colonoscopy, CT, MRI, etc.; surgery related including operation methods, operation time, blood loss, etc. The postoperative related information includes laboratory results such as blood routine, albumin, patient symptoms, signs, pelvic drainage and traits, and related measurement results of TDT. See the Case Report Forms (CRFs) for details.

11.1 Case report form (CRF)

In this trial, the required observation or inspection items need to be recorded in the case report form. The contents of the case report form must be completely consistent with the original data. For the results calculated from the original data, the calculation basis should be traceable.

11.2 Original data record

All information should be recorded in the CRFs in a timely, truthful and detailed manner. The ***Data Manager*** will check the completeness and accuracy of the CRF and make necessary modifications or additions.

11.3 Quality control

Perform corresponding inspections and evaluations as required and record them in the CRFs. All forms must be completed, signed, and dated by the investigators. The ***lead investigators*** check every 6 months, supervise the completion of the CRF forms, and conduct a review and signature. All items should have a corresponding objective basis, be prepared for review and use, and should not be fabricated. The ***Data Manager*** should carefully check each CRF and sign it after confirming that it is complete and correct. The medical records required to be recorded are true and reliable, properly kept, and subject to random inspections at any time. If you make

any mistakes and modify them, you should sign and date them, and the original modification can be identified.

12 Statistical Analysis Plan

- Public health statisticians and ***lead investigators*** formulate statistical analysis plans based on the research plan; ***Data Manager*** will perform statistical analysis according to the statistical plan.
- Sample size estimation was performed using PASS, version 11 (NCSS, LLC, Kaysville, UT, USA).
- Statistical analysis will be performed using SPSS, version 25.0 (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA).
- All analyses are two-sided, and a $P < 0.05$ is considered statistically significant.
- Analyses of the primary and secondary endpoints are based on the intention-to-treat (ITT) principles. Per-protocol (PP) analysis is restricted to the participants who fulfilled the protocol in the terms of eligibility, interventions, and outcome assessment.
- A chi-square test or Fisher's exact test is used for the comparison of categorical variables, as appropriate. This mainly involves the baseline data, the primary outcomes (AL rate) and the grades of AL of the two groups of patients.
- Continuous variables are expressed as the median and interquartile range (IQR) and are analyzed using a Mann -Whitney U test if not normally distributed, or are expressed as mean ± standard deviation (SD) and analyzed using Student's t-test if normally distributed. This mainly involves the baseline data of the two groups of patients.
- The comparison of the AL rate in two arms is performed using a chi-square test and is present as relative risk (RR) with a 95% confidence interval (CI).
- Subgroup analysis is not considered at this stage, post hoc subgroup analysis will be planning to perform when suitable.
- Univariate and multivariate logistic regression analysis can be performed to identify the factors which would facilitate the surgeon's decision of DS construction or the factors of high risk of AL.

- Missing values handling：This study does not fill in missing values

13 Research Ethics Approval

13.1 Ethical Committees Approval

This protocol and the template informed consent forms will be reviewed and approved by the sponsor and the applicable ***ethical committees*** concerning scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific consent forms, participant education, and recruitment materials, and other requested documents - and any subsequent modifications - also will be reviewed and approved by the ethical review bodies.

13.2 Informed Consent

Trained residents will introduce the trial to patients. Patients will also receive information sheets. Research residents will discuss the trial with patients in light of the information provided in the information sheets. Patients will then be able to have an informed discussion with the participating consultant. Research residents will obtain written consent from patients willing to participate in the trial.

13.3 Participant confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information

will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released outside of the study without the written permission of the participant.

13.4 Protocol Amendments

After this protocol has been approved by the ***ethical committees***, if there are major changes during the implementation process, the contact investigator will draft an instruction about the amendments and sign it, and report to the ***ethical committees*** for approval before implementation. The ***Quality Control Committee*** will discuss with methodologists and sign together. Administrative changes to the protocol are minor corrections and/or clarifications that do not affect the way the study is to be conducted. These administrative changes will be agreed upon by the ***Quality Control Committee*** and will be documented in a memorandum.

Revision Chronology:

Date	Version	Overview of the Amendment
2016-Feb-20	version 1.0	Original
2016-Dec-26	version 2.0	Seven additional secondary sponsors are mentioned on page 3
2018-Sep-1	version 3.0	Funding information was revised on page 4
2020-Oct-30	version 4.0	Recruitment status changed on page 5

14 Committee

Before the start of the trial, organize project team members to study this clinical research plan to fully understand and master the requirements and content of this research.

14.1 Lead Investigators

In each participating center, a lead investigator will be identified, to be

responsible for the identification, recruitment, data collection, and completion of CRFs, along with follow-up of study patients and adherence to study protocol and investigators brochure. Lead investigators will be quality control committee members.

The ***lead investigators*** check every 6 months, supervise the completion of the CRF form, and conduct a review and signature. All items should have a corresponding objective basis, be prepared for review and use, and should not be fabricated. The original data related to this experiment include: 1) Medical records: case registration form, case registration confirmation form, informed consent, patient background investigation, symptoms and signs, treatment and treatment content;2) Inspection report (pathological examination, imaging diagnosis result; 3) Laboratory test data (blood biochemical test, etc.). The investigator must save the relevant data of the clinical trial for five years after the end of the clinical trial.

14.2 Data Manager

Be responsible for data collection and verification. He or She will check the completeness and accuracy of the CRF and make necessary modifications or additions.

14.3 Quality control committee (QCC)

It consists of lead investigators and the data manager. They are responsible for agreement of final protocol; reviewing the progress of the study and if necessary agreeing to changes of the protocol and/or investigator brochure to facilitate the smooth running of the study; study planning; responsible for trial master file and randomization.

15 Adverse Events

ICPs were the adverse event reported by previous studies. In this study, the height of most anastomoses is expected to be less than 6cm. Theoretically, the possibility of perforation is small, but we still need to be alert. The investigator will

be trained to voluntarily report from time to time when an adverse event occurs to the subject. In addition, the investigators should check the occurrence of the adverse events through consultation and interviews at regular visits during the study period. The situation of patients with adverse events should be discussed and reported to the ***Quality Control Committee*** to analyze the reasons. After discussion, if the actual existence is directly related to the research design, the plan should be modified.

15.1 Classification of adverse events

For the evaluation of adverse events in this research, please refer to the Chinese version of CTCAE v4.02 and [Accordion Severity Grading System]. Grade refers to the severity of the adverse event. CTCAE provides a specific clinical description of the severity of each adverse event (grades 1 to 5) according to the following general guidelines:

Grade 1: Mild; asymptomatic or mild; only clinically or diagnostically seen; no treatment is required.

Grade 2: Moderate; requires minor, topical, or non-invasive treatment; age-appropriate instrumental limitation of activities of daily living*.

Grade 3: Severe or medically significant but not immediately life-threatening; leading to hospitalization or prolonging the hospital stay; disabled; personal activities of daily living are restricted**.

Level 4: Life-threatening; urgent treatment is required.

Level 5: Death related to it.

Activities of Daily Living (ADL)

*Instrumental activities of daily living refer to cooking, buying clothes, using the phone, managing finances, etc.

**Personal activities of daily living refer to bathing, dressing, and undressing, eating, washing, taking medicine, etc., who are not bedridden.

15.2 Records of Adverse Events

All adverse events must be recorded on the adverse event report form, attached to the case report form. For each adverse event, the lead investigator must evaluate and record its severity, duration, relationship with surgery or TDTs, measures, and the outcome of the event.

15.3 Report of Adverse Events

If any "serious adverse event" or "unexpected adverse event" occurs, the researcher must report the adverse event to the ***Quality Control Committee*** within 24 hours after learning of the adverse event, the ***Quality Control Committee*** responsible for handling serious adverse events, regardless of whether the event is related to treatment. The results of all reported serious adverse events (death, etc.) will be followed up and recorded. Reporting to relevant authorities by national regulations will be done by the responsible unit; in any case, all participants must comply with local legal regulations and requirements.

406 **Appendix 1**

407 Current Definitions and ASA-Approved Examples

ASA PS Classification	Definition	Adult Examples, Including, but not Limited to:	Pediatric Examples, Including but not Limited to:	Obstetric Examples, Including but not Limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use	Healthy (no acute or chronic disease), normal BMI percentile for age	
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease	Asymptomatic congenital cardiac disease, well controlled dysrhythmias, asthma without exacerbation, well controlled epilepsy, non-insulin dependent diabetes mellitus, abnormal BMI percentile for age, mild/moderate OSA, oncologic state in remission, autism with mild limitations	Normal pregnancy*, well controlled gestational HTN, controlled preeclampsia without severe features, diet-controlled gestational DM.
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.	Uncorrected stable congenital cardiac abnormality, asthma with exacerbation, poorly controlled epilepsy, insulin dependent diabetes mellitus, morbid obesity, malnutrition, severe OSA, oncologic state, renal failure, muscular dystrophy, cystic fibrosis, history of organ transplantation, brain/spinal cord malformation, symptomatic hydrocephalus, premature infant PCA <60 weeks, autism with severe limitations, metabolic disease, difficult airway, long term parenteral nutrition. Full term infants <6 weeks of age.	Preeclampsia with severe features, gestational DM with complications or high insulin requirements, a thrombophilic disease requiring anticoagulation.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis	Symptomatic congenital cardiac abnormality, congestive heart failure, active sequelae of prematurity, acute hypoxic-ischemic encephalopathy, shock, sepsis, disseminated intravascular coagulation, automatic implantable cardioverter-defibrillator, ventilator dependence, endocrinopathy, severe trauma, severe respiratory distress, advanced	Preeclampsia with severe features complicated by HELLP or other adverse event, peripartum cardiomyopathy with EF <40,

			oncologic state.	uncorrected/decompensated heart disease, acquired or congenital.
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction	Massive trauma, intracranial hemorrhage with mass effect, patient requiring ECMO, respiratory failure or arrest, malignant hypertension, decompensated congestive heart failure, hepatic encephalopathy, ischemic bowel or multiple organ/system dysfunction.	Uterine rupture.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes			

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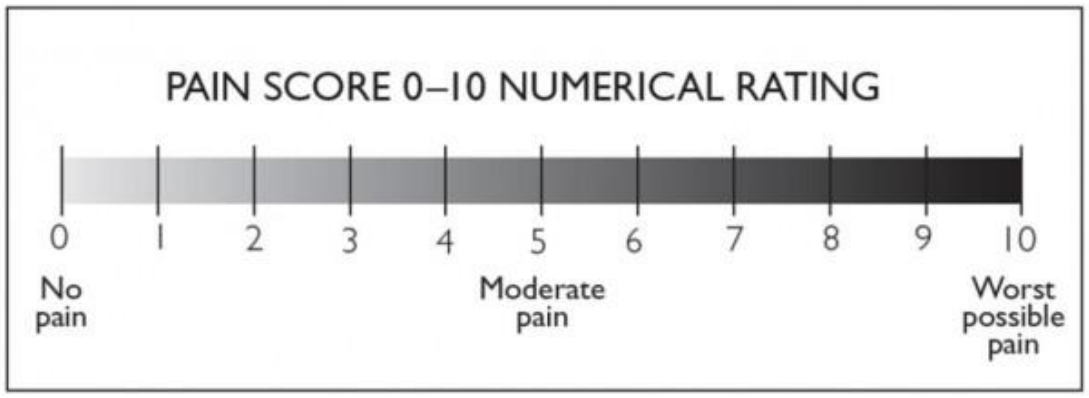
409 * Although pregnancy is not a disease, the parturient' s physiologic state is significantly altered from when the woman is not pregnant, hence the assignment of ASA 2 for a woman with uncomplicated pregnancy.

410 **The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

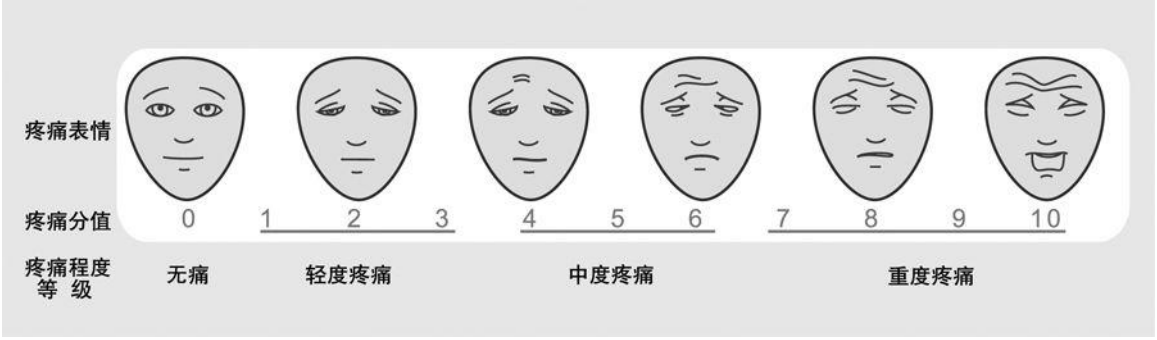
Appendix 2

Pain Scales

The (NPRS-11) is an 11-point scale for self-report of pain. It is the most commonly used unidimensional pain scale. The respondent selects a whole number (integers 0–10) that best reflects the intensity (or other quality if requested of his/her pain. The anchors are 0 = no pain and 10 = extreme pain/worst possible pain (there are various wordings of the upper anchor). It is often categorized into: no pain = 0, mild pain = 1-3, moderate pain = 4-6, severe pain = 7-10, but these categories do not necessarily reflect patient meanings, and are poor for any assessment of change. The categories might be used to set targets for intervention outcomes. The NPRS can be administered verbally (therefore also by telephone) or graphically for self-completion.



Pain scales (visual analog scale method):



Reference

1. Salvans S, Mayol X, Alonso S, Messeguer R, Pascual M, Mojal S, et al. Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vitro: an insight into the association between anastomotic leak and recurrence after surgery for colorectal cancer. Ann Surg. 2014;260(5):939-43; discussion 43-4.
2. Hanna MH, Vinci A, Pigazzi A. Diverting ileostomy in colorectal surgery: when is it necessary? Langenbecks Arch Surg. 2015;400(2):145-52.
3. Phatak UR, Kao LS, You YN, Rodriguez-Bigas MA, Skibber JM, Feig BW, et al. Impact of ileostomy-related complications on the multidisciplinary treatment of rectal cancer. Ann Surg Oncol. 2014;21(2):507-12.
4. Kye BH, Kim HJ, Kim JG, Cho HM. The nutritional impact of diverting stoma-related complications in elderly rectal cancer patients. Int J Colorectal Dis. 2013;28(10):1393-400.
5. Xiao L, Zhang WB, Jiang PC, Bu XF, Yan Q, Li H, et al. Can transanal tube placement after anterior resection for rectal carcinoma reduce anastomotic leakage rate? A single-institution prospective randomized study. World J Surg. 2011;35(6):1367-77.
6. Ha GW, Kim HJ, Lee MR. Transanal tube placement for prevention of anastomotic leakage following low anterior resection for rectal cancer: a systematic review and meta-analysis. Ann Surg Treat Res. 2015;89(6):313-8.
7. Lee SY, Kim CH, Kim YJ, Kim HR. Impact of anal decompression on anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis. Langenbecks Arch Surg. 2015;400(7):791-6.
8. Zhao WT, Hu FL, Li YY, Li HJ, Luo WM, Sun F. Use of a transanal drainage tube for prevention of anastomotic leakage and bleeding after anterior resection for rectal cancer. World J Surg. 2013;37(1):227-32.
9. Cong ZJ, Fu CG, Wang HT, Liu LJ, Zhang W, Wang H. Influencing factors of symptomatic anastomotic leakage after anterior resection of the rectum for cancer. World J Surg. 2009;33(6):1292-7.
10. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257(4):665-71.
11. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg. 2013;148(1):65-71.
12. Snijders HS, Wouters MW, van Leersum NJ, Kolfschoten NE, Henneman D, de Vries AC, et al. Meta-analysis of the risk for anastomotic leakage, the postoperative mortality caused by leakage in relation to the overall postoperative mortality. Eur J Surg Oncol. 2012;38(11):1013-9.
13. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative

complications following surgery for rectal cancer. Ann Surg. 2010;251(5):807-18.
14. den Dulk M, Marijnen CA, Collette L, Putter H, Pahlman L, Folkesson J, et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg. 2009;96(9):1066-75.
15. Kawada K, Hasegawa S, Hida K, Hirai K, Okoshi K, Nomura A, et al. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. Surg Endosc. 2014;28(10):2988-95.
16. Kim MK, Won DY, Lee JK, Kang WK, Kim JG, Oh ST. Comparative study between transanal tube and loop ileostomy in low anterior resection for mid rectal cancer: a retrospective single center trial. Ann Surg Treat Res. 2015;88(5):260-8.
17. Hidaka E, Ishida F, Mukai S, Nakahara K, Takayanagi D, Maeda C, et al. Efficacy of transanal tube for prevention of anastomotic leakage following laparoscopic low anterior resection for rectal cancers: a retrospective cohort study in a single institution. Surg Endosc. 2015;29(4):863-7.
18. Nishigori H, Ito M, Nishizawa Y, Nishizawa Y, Kobayashi A, Sugito M, et al. Effectiveness of a transanal tube for the prevention of anastomotic leakage after rectal cancer surgery. World J Surg. 2014;38(7):1843-51.
19. Adamova Z. Transanal Tube as a Means of Prevention of Anastomotic Leakage after Rectal Cancer Surgery. Viszeralmedizin. 2014;30(6):422-6.
20. Montemurro S, De Luca R, Caliandro C, Ruggieri E, Rucci A, Sciscio V, et al. Transanal tube NO COIL(R) after rectal cancer proctectomy. The "G. Paolo II" Cancer Centre experience. Tumori. 2012;98(5):607-14.
21. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010;147(3):339-51.