Supplemental Digital Content for

Morbidity, Mortality, and Pathologic Outcomes of Transanal vs Laparoscopic Total Mesorectal Excision for Rectal Cancer

Short-term Outcomes from a Multicenter Randomized Controlled Trial

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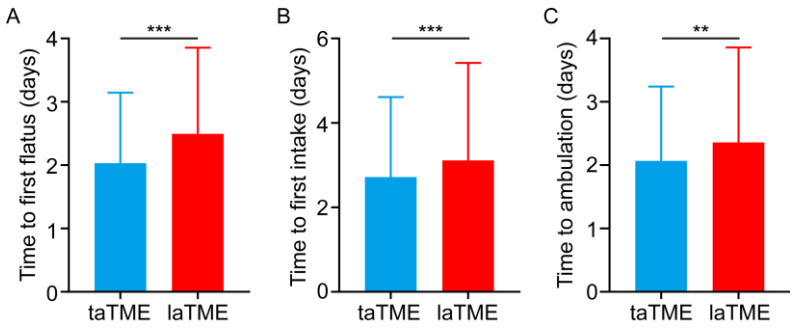
This file includes:

Supplemental Fig 1. A-C



Supplemental Fig 1. Postoperative recovery in the taTME and laTME groups. A- Time to first flatus. B- Time to first intake. C- Time to ambulation. **P < 0.01, ***P < 0.001. All values are mean ± SD.

Title: Transanal Versus Laparoscopic Total Mesorectal Excision for Rectal Cancer: A Randomised, Open-label, Phase 3, Non-inferiority Trial

Study Protocol

Study Group: Chinese Transanal Endoscopic Surgery Collaborative (CTESC) group

Sponsor: Sun Yat-sen University

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Ver. 3.0 (2019/12/18)

Confidentiality Statement:
The information contained in this clinical protocol is only available to the investigators, the Ethics Committee and relevant agencies for review. Without approval from the principal investigator (PI), no information shall be given to a third party irrelevant to this study

Protocol Synopsis

Protocol Title	Transanal Versus Laparoscopic Total Mesorectal Excision for Rectal Cancer: A Randomised, Open-label, Phase 3, Non-inferiority Trial
Protocol Version	Ver. 3.0
PI	Liang Kang
Research Centers	The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong; Shengjing Hospital of China Medical University, Shenyang, Liaoning; The Second People's Hospital of Yibin, Yibin, Sichuan; The Affiliated Nanchong Central Hospital of North Sichuan Medical College, Nanchong, Sichuan; Daping Hospital, Army Medical University, Chongqing; Xinqiao Hospital, Army Medical University, Chongqing; The First Hospital of Jilin University, Changchun, Jilin; Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou; Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai; The First Affiliated Hospital of University of South China, Hengyang, Hunan; Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing; The First Affiliated Hospital of Xi'an Jiaotong University, Xian, Shanxi; Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai; The Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong; Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong; The Third Xiangya Hospital of Central South University, Changsha, Hunan; Sun Yat-sen Global Health Institute, Sun Yat-sen University, Guangzhou, Guangdong
Indications	Patients with clinical stage I-III rectal cancer below peritoneal

	reflection
Research Purpose	The aim of this trial is to confirm the non-inferiority of transanal total mesorectal resection (taTME) to laparoscopic total mesorectal excision (laTME) for the treatment of patients with clinical stage I-III rectal cancer below peritoneal reflection in terms of 3-year disease-free survival and 5-year overall survival as primary endpoints.
Research Design	Multicenter, open label, randomized controlled, noninferiority study
Case Grouping	Study group: transanal total mesorectal resection group Control group: laparoscopic total mesorectal excision group
Determination of Sample Size	The sample size was calculated using PASS software. Sample-size calculation of this trial was on the basis of three-year disease-free survival (DFS) and five-year overall survival (OS); but the sample size according to five-year OS was larger than that based on three-year DFS. The three-year DFS and five-year OS among patients with clinical stage I-III rectal cancer treated with laTME were assumed to be 74·6% and 77·4%, respectively. According to a log-rank test with an α error of 2·5% (in a two-sided test), power of 80%, and a non-inferiority margin of 10%, at least 610 and 910 patients would be required to sufficiently declare taTME noninferior to laTME in three-year DFS and five-year OS, respectively. Assuming a dropout rate of 20%, a total of 1114 patients were planned to enroll for this trial.
Number of Research Centers	16
Inclusion Criteria	1) Age older than 18 and younger than 75 years 2) Patient eligible for surgery, with American Society of

	Anesthesiologists class I-III 3) Primary rectal cancer below peritoneal reflection, with clinical stage I-III based on the 7th edition of the American Joint Committee on Cancer staging system 4) Pathologically confirmed rectal adenocarcinoma before surgery 5) Patients are suitable for a sphincter-sparing procedure 6) Expected curative resection via TME 7) Written informed consent
Exclusion Criteria	1) T1 tumors that can be locally resected 2) Involvement of the circumferential resection margin as indicated by MRI or CT scan 3) Tumors with ingrowth in the internal sphincter or levator ani 4) Previous rectal surgery or pregnancy 5) Absolute contraindications to general anesthesia or prolonged pneumoperitoneum 6) Signs of acute intestinal obstruction or synchronous abdominal surgery 7) Having a medical history of FAP, active IBD, or other carcinomas within 5 years 8) Any psychological, familial, sociological, or geographical conditions that could hamper compliance with the study protocol or the follow-up schedule
Withdrawal Criteria	1) Patients with distant metastasis that is discovered during surgical exploration or confirmed by the postoperative pathologic examination 2) Patients intraoperatively confirmed as unable for a sphincter-sparing procedure to ensure patients' safety 3) Patients intraoperatively confirmed as unsuitable to adhere to

	TME principles 4) Patients requiring simultaneous surgical treatment of other diseases 5) Sudden severe complications during the perioperative period (intolerable surgery or anesthesia), which renders it unsuitable or unfeasible to implement the study treatment protocol as scheduled 6) Patients confirmed to require emergency surgery by attending physicians due to changes in the patient's condition after inclusion in this study 7) Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study 8) Treatment implemented is proven to violate study protocol
Intervention	Surgery for eligible patients will be conducted in accordance with total mesorectal excision principles. Study group: transanal total mesorectal resection Control group: conventional laparoscopic total mesorectal excision
Endpoints	Primary Endpoints: 3-year DFS and 5-year OS Secondary Endpoints: 1) Morbidity and mortality 2) Pathologic outcomes 3) Postoperative recovery course 4) 3-year OS 5) 5-year DFS 6) Time to recurrence 7) Recurrence patterns 8) Delayed surgical complications 9) Functional outcomes

	10) Quality of life
Statistical considerations	All data analyses will be performed using the SAS 9.3 software (SAS Institute, Cary, NC). The noninferiority analysis for the primary endpoints of 3-year DFS and 5-year OS will be conducted by comparing 95% confidence intervals (calculated by Newcombe method with adjustment for randomisation strata as recommended by the FDA and NCCLS) of survival rates between the study and control groups on an intent-to-treat (ITT) population basis. When appropriate, the primary endpoints will also be analyzed on a per-protocol basis. There were no planned interim analyses for 3-year DFS and 5-year OS. Interim analyse was planned for morbidity and mortality rates, as well as pathologic outcomes, when approximately 50% and all of the patients had been enrolled. Continuous variables will be expressed as mean (standard deviation) or median (interquartile range). Categorical variables will be expressed as numbers and percentages. The t test or Wilcoxon rank sum test will be used to compare continuous variables depending on the data distribution, and categorical variables were analyzed by Fisher's exact test or χ^2 test as appropriate. The Newcombe method with adjustment for randomisation strata was used to calculate the 95% CIs for between-group differences in binary data. Survival analysis will be conducted using the Kaplan-Meier method and the log-rank test. The numbers of loss to follow-up participants will be compared using the chi-square test. A two-sided P <0.05 will be considered statistically significant.

Table of Contents

1. Background

About 704,000 patients per year are diagnosed with rectal cancer globally [CA Cancer J Clin. 2015;65(2):87-108]. Total mesorectal excision (TME) was first highlighted in the 1980s by Heald and Ryall [Br J Surg. 1982; 69(10):613-6; Lancet. 1986; 1(8496):1479-82] due to its significant contribution to reducing local recurrence. The procedure has been considered the standard surgical technique for rectal cancer since then.

Along with the development of minimally invasive techniques, laparoscopy has become common practice in colorectal surgery for decades. Even though controversy still exists, laparoscopic TME (lapTME) has been proven to achieve similar resection quality and oncological outcomes compared with open TME (opTME) in several clinical trials. Laparoscopic surgery proved feasible and safe in the COREAN trial; moreover, this procedure has some short-term benefits for patients compared with open surgery, especially those with middle or low rectal cancer who have been treated with neoadjuvant chemoradiotherapy [Lancet Oncol. 2010; 11(7):637-45]. In addition, the COLOR II trial reported no statistically significant differences for treating high- or middle-rectal-cancer patients with either lapTME or opTME, but lapTME had advantages for low-rectal-cancer patients [Lancet Oncol. 2013; 14(3):210-8]. It is also worth noting that, when comparing lapTME with opTME, the former can reduce the operative wound, enhance patient recovery, and reduce wound-related complications [N Engl J Med. 2015; 373(2):194]. As a result, lapTME has become common over the past few decades.

However, it remains difficult to acquire complete TME with a safe surgical margin by conventional transabdominal methods in obese male patients with low rectal cancer have undergone neoadjuvant treatment and have a narrow pelvic floor, etc. [Lancet Oncol. 2010; 11(7):637-45; N Engl J Med. 2015; 373(2):194; Br J Surg. 2009; 96(9):982-9]. In order to tackle these issues, transanal total mesorectal excision (taTME) was introduced by Sylla et al [Surg

Endosc. 2010; 24(5):1205-10]. The feasibility, safety, and advantages of this method have been verified by more recent studies, and it has become a hot topic for rectal cancer both in the literature and at conferences [Surg Endosc. 2010; 24(5):1205-10; Tech Coloproctol 2015; 19:57–61; J Am Coll Surg 2015; 221:415–23]. Theoretically, taTME could achieve better pathological outcomes than lapTME, as it provides better vision to mobilize the distal rectum. Thus, taTME may result in a better oncological outcome for patients [Ann Surg 2015;261:234–6]. However, taTME is still in the early stages of development and the desired or expected oncological outcomes have yet to be achieved before it can become the standard technique for rectal-cancer treatment. Thus, the aim of this trial is to evaluate in patients with clinical stage I-III rectal cancer below peritoneal reflection if 3-year disease-free survival and 5-year overall survival as primary endpoints are noninferior for taTME relative to lapTME; and to compare other long-term oncological efficacy and safety parameters as secondary endpoints.

2. Purpose

To evaluate in patients with clinical stage I-III rectal cancer below peritoneal reflection if 3-year disease-free survival and 5-year overall survival as primary endpoints are noninferior for taTME relative to lapTME; and to compare other long-term oncological efficacy and safety parameters as secondary endpoints.

3. Overall Design

Prospective, multicenter, open labelled, randomized controlled, noninferiority study.

3.1 Multicenter Participation

Sixteen centers from Guangdong, Liaoning, Sichuan, Chongqing, Jilin, Guizhou, Shanghai, Hunan, Beijing, and Shanxi jointly participate in this study.

3.2 Control Group and Grouping

Study group: transanal total mesorectal resection group

Control group: laparoscopic total mesorectal excision group

3.3 Sample Size Estimate

The sample size was calculated using PASS software. Sample-size calculation of this trial was on the basis of three-year disease-free survival (DFS) and five-year overall survival (OS); but the sample size according to five-year OS was larger than that based on three-year DFS. The three-year DFS and five-year OS among patients with clinical stage I-III rectal cancer treated with laTME were assumed to be 74·6% and 77·4%, respectively. According to a log-rank test with an α error of 2·5% (in a two-sided test), power of 80%, and a non-inferiority margin of 10%, at least 610 and 910 patients would be required to sufficiently declare taTME noninferior to laTME in three-year DFS and five-year OS, respectively. Assuming a dropout rate of 20%, a total of 1114 patients were planned to enroll for this trial.

3.4 Randomization

Patients enrolled in this study will be randomly assigned into either the study group or the control group. The random numbers are generated to ensure that patients are randomly divided into two groups with an allocation ratio of 1:1. A central

randomization system will be employed, and all the researchers must register at the website of the research system. When a researcher has chosen a certain patient, he/she should log on to the webpage and upload the basic information on the patient before acquiring the random grouping schemes. Randomization will be stratified for different institutions. All the patients are blinded to the surgical approach that they are going to receive and will be required to sign the informed consent before being enrolled in the study. Obviously, it is impossible to blind the surgeons who will perform the surgeries. However, all the surgeon researchers will be required to limit potential cointerventions as much as possible. Therefore, investigators and patients were not masked to treatment assignment; however, the quality control committee was masked to the randomization details during assessment of the primary and secondary outcomes. The assessment of perioperative complications was not masked, because the research team members were involved in all aspects of patient care.

3.5 Blinding Method

An open design will be used for this study.

3.6 Study Period

Patient Enrollment: the plan is expected to complete the enrollment within 2 years in the 16 centers.

Follow-up period: the enrollment of the first case is used as the starting point of the follow -up, and five years after the last case is included as the end point of follow-up.

4. Research Subjects

All patients meeting all inclusion criteria and without any of the exclusion criteria are eligible for this study.

4.1 Inclusion Criteria

1) Age older than 18 and younger than 75 years
2) Patient eligible for surgery, with American Society of Anesthesiologists class I-III
3) Primary rectal cancer below peritoneal reflection, with clinical stage I-III based on the 7th edition of the American Joint Committee on Cancer staging system
4) Pathologically confirmed rectal adenocarcinoma before surgery
5) Patients are suitable for a sphincter-sparing procedure
6) Expected curative resection via TME
7) Written informed consent

4.2 Exclusion Criteria

1) T1 tumors that can be locally resected
2) Involvement of the circumferential resection margin as indicated by MRI or CT scan
3) Tumors with ingrowth in the internal sphincter or levator ani
4) Previous rectal surgery or pregnancy
5) Absolute contraindications to general anesthesia or prolonged pneumoperitoneum
6) Signs of acute intestinal obstruction or synchronous abdominal surgery
7) Having a medical history of FAP, active IBD, or other carcinomas within 5 years
8) Any psychological, familial, sociological, or geographical conditions that could hamper compliance with the study protocol or the follow-up schedule

4.3 Withdrawal Criteria

1) Patients with distant metastasis that is discovered during surgical exploration or confirmed by the postoperative pathologic examination

2) Patients intraoperatively confirmed as unable for a sphincter-sparing procedure to ensure patients' safety

3) Patients intraoperatively confirmed as unsuitable to adhere to TME principles

4) Patients requiring simultaneous surgical treatment of other diseases

5) Sudden severe complications during the perioperative period (intolerable surgery or anesthesia), which renders it unsuitable or unfeasible to implement the study treatment protocol as scheduled

6) Patients confirmed to require emergency surgery by attending physicians due to changes in the patient's condition after inclusion in this study

7) Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study

8) Treatment implemented is proven to violate study protocol

4.4 Selection of Cases

1) Patients when admitted to hospital and physical examination should meet the following conditions: age >18 and <75 years; non-pregnant or lactating women; no serious mental illness; no history of rectal surgery; no other malignant disease history within five years; no history of a medical history of FAP, active IBD; no signs of acute intestinal obstruction; no history of unstable angina or myocardial infarction within six months; no history of sustained systemic corticosteroid therapy within one month; not requiring simultaneous surgical treatment of other diseases; pulmonary function test with FEV1 ≥50% of the expected value; and no history of cerebral infarction or cerebral hemorrhage within six months.

2) The endoscopic examination of primary lesion of patients and the histopathological

biopsy confirmed rectal adenocarcinoma before surgery.

3) Preoperative imaging examination showed primary rectal cancer was below peritoneal reflection.

4) Patient is explicitly diagnosed with rectal cancer and preoperative staging assessment of clinical stage I-III based on the 7th edition of the American Joint Committee on Cancer staging system, and is expected to undergo a sphincter-sparing procedure via TME to obtain R0 surgical results.

5) Patient's ASA score is I-III.

6) Patient does not require emergency surgery.

7) At this time, the patient becomes a potentially eligible case, and then enter the Standard Operating Procedures.

5. Endpoints

5.1 Primary Endpoint

1) 3-year DFS [Time Window: postoperative 3 years]

2) 5-year OS [Time Window: postoperative 5 years]

5.2 Secondary Endpoints

1) Morbidity and mortality [Time Frame: postoperative 30 days]
2) Mortality [Time Frame: after 31 days after end of surgery]
3) Pathologic outcomes [Time Frame: postoperative 30 days]
4) Postoperative recovery course [Time Frame: postoperatively up to first discharge]
5) 3-year OS [Time Frame: postoperative 3 years]
6) 5-year DFS [Time Frame: postoperative 5 years]
7) Time to recurrence [Time Frame: postoperative 3 years]

8) Recurrence patterns [Time Frame: postoperative 3 years]
9) Delayed surgical complications [Time Frame: postoperative 2 years]
10) Functional outcomes [Time Frame: postoperative 2 years]
11) Quality of life [Time Frame: postoperative 2 years]

6. Diagnostic Criteria for This Study

The 7th edition of the American Joint Committee on Cancer staging system will be used for this study. Diagnostic criteria and classification of rectal cancer: According to the histopathological international diagnostic criteria, patients who were diagnosed as rectal adenocarcinoma will be enrolled.

7. Qualifications of the Participated Surgeons

7.1 Basic Principle

Surgeons were selected from the members of the CTESC group who met the following criteria: 1) have a minimum of 100 laTME and 50 taTME procedures performed by each surgical team; 2) are expected to have ≥50 laTME and ≥30 taTME procedures annually; 3) were confirmed to be qualified surgeons by the CTESC Research Committee based on the evaluation of the unedited videos of 2 laTME and 2 taTME procedures in obese male patients (body-mass index ≥28) with rectal cancer below peritoneal reflection.

7.2 Specific Measures

1) The medical record room of the participating units shall provide written proof of the

number of past cases completed.

2) Video blind review of surgery: The applicant provides videos of laTME and taTME carried out during one recent month (performed in male patients (body-mass index ≥28) with rectal cancer below peritoneal reflection; five cases each) to the CTESC Research Council; the CTESC Research Council will randomly select the videos of two cases of laTME and taTME separately, and randomly assign three peer experts (composed of more than 40 domestic and Japan and America rectal surgery experts) to conduct blind review on the video taken. When the three review experts unanimously approve the surgical techniques and tumor cure degree, the applicant will be permitted to participate in this study as a researcher.

8. Standard Operating Procedures (SOP)

8.1 Case Selection

8.1.1 Selection Assessment Items

All patients should meet the surgical conditions under the Chinese guidelines for the diagnosis and treatment of rectal cancer. Clinical examination data of patients conducted from hospital admission to enrollment into this study (time period is usually 1 week) will be considered baseline data, and must include:

1) Systemic status: height, weight, and ECOG score, etc.

2) Peripheral venous blood: white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), lymphocyte count (LYM), etc.

3) Blood biochemistry: albumin, prealbumin, total bilirubin, AST, ALT, creatinine, fasting glucose, CRP, etc.

4) Serum tumor markers: CEA, CA19-9, CA12-5, etc.

5) Computed tomography (CT) examination of the abdomen and thorax.

6) Magnetic resonance imaging (MRI) scan.

7) Colonoscopy and biopsy.

8) Chest X-ray (AP and lateral views): cardiopulmonary conditions.

9) Resting 12-lead ECG.

10) Respiratory function tests: FEV1, FVC, etc.

11) Other significant data as recorded by clinicians.

8.1.2 Selection Application

For cases that meet all inclusion criteria and none of the exclusion criteria, prior to inclusion in this study, the research assistant of each research participating center will fill out the [Eligibility Application Form], and then fax it to the CTESC Research Committee for review to verify that they belong to eligible cases.

8.1.3 Eligibility Consultation

Contact Information and Working Hours of the CTESC Research Committee:

Address: Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University 26 Yuancun Erheng Road, Guangzhou, Guangdong

Tel: 020-38254084

Fax: 020-38254084

Working Hours: Monday to Friday 9:00 to 17:00 (except holidays and weekends)

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8.1.4 Precautions

1) Application and confirmation of eligibility should be completed preoperatively;

postoperative applications will not be accepted.

2) If [Eligibility Application Form] is inadequately completed, it must be completed; otherwise, it will not be accepted.

3) After being accredited by the CTESC Research Committee, it should be archived and numbered (Baseline Number, BN) and the [eligibility confirmation notice] should be faxed to the applicant.

4) After each research participating center receives the [eligibility confirmation notice], the research assistant of each center is responsible for its custody and recording.

5) Once selected for registration, the content of the [eligibility application form] will be entered into the database; eligibility is not allowed to be artificially canceled (the relevant information cannot be deleted from the database), unless the patient declines for the information to be used in this study.

6) The data center will reject any repeatedly selected information. If this happens, the first registered data will be used (for the first time BN).

7) In the case of repeated selection or registration error, the research assistant of each research participating center should contact the CTESC Research Committee as soon as possible for liaison, recording.

8.2 Preoperative neoadjuvant treatment

The neoadjuvant therapy was performed according to the Chinese protocol of diagnosis and treatment of colorectal cancer (2015 edition) by the Hospital Authority of National Health Commission of the People's Republic of China. Patients with stages cT4 will be recommended for neoadjuvant therapy, and neoadjuvant treatment for patients with stages cT3N+ was decided by the multi-disciplinary team.

8.3 Preoperative Management

After the eligibility is obtained, surgery should be performed within 10 days.

1) For the person failing to accept surgical treatment within 10 days after selected, the reason needs be recorded in the [Pre-treatment Records].

2) In case of any deterioration of the clinical conditions from the selection time to the expected day of surgery, whether to undergo an elective surgery as planned should be decided in accordance with the judgment of the doctor in charge; if an emergency surgery is required, the case should be withdrawn from per-protocol set according to the withdrawal criteria; if the doctor still performs an elective surgery, it should be registered in the [Pre-treatment Records] according to the original recording method; if the doctor cancels the surgery, is should be recorded in the [treatment end table], and the chief physician's judgment basis should be recorded in the [treatment end table] at the same time; if an elective surgery is postponed to be performed after 10 days, the reason should be recorded in the [Pre-treatment Records].

3) For patients with nutritional risks, preoperative enteral/parenteral nutritional support is allowed.

4) For elderly, smokers, high-risk patients with diabetes, obesity and chronic cardiovascular/cerebrovascular or thromboembolic past history, among others, perioperative low-molecular-weight heparin prophylaxis, lower-limb antithrombotic massage, active lower limb massage, training in respiratory function and other preventive measures are recommended. For other potentially high-risk complications not specified in this study protocol, the doctor in charge of each research participating center can decide on the most appropriate approach according to clinical practice and specific needs of each center and should record it in the CRF.

5) For patients who underwent preoperative therapy, assessment of their clinical stage should be after preoperative therapy, and within 10 days before. After assessment, patients with clinical stage I-III rectal cancer will be considered to be enrolled. But if a “watch and wait” management approach was recommended by the treating physician, this patient will be not considered to be enrolled.

6) For the laparoscopic approach of the surgeries in this study, laparoscopic total mesorectal excision should be performed at each research center according to Chinese

Ministry of Health's Colorectal Cancer Diagnosis and Treatment guideline (2015 Edition). The digestive tract reconstruction method, handsewn or stapled, should be selected by the doctor in charge according to his/her experience and the specific intraoperative circumstances.

7) Preoperative fasting and water deprivation and other before-anesthesia requirements on patients should follow the conventional anesthesia program of each research participating center, which is not specified in this study.

8) For prophylactic antibiotics, the first intravenous infusion should begin 30 minutes prior to surgery. It is recommended to select a second-generation cephalosporin (there are no provisions on specific brands in this study); the preparation, concentration and infusion rate should comply with routine practice; and prophylaxis should not exceed postoperative three days at a frequency of one infusion every 12 hours. If patient is allergic to cephalosporins (including history of allergy or allergy after cephalosporin administration), other types of antibiotics are allowed according to the specific clinical situation and when used over the same time period mentioned.

8.4 Randomization

1) The study will use a central, dynamic, and stratified randomization method. The control factors for randomization will be participating center.

2) Upon receipt by research participating centers of an [eligibility confirmation notice], the designated person is responsible for immediately sending the selected patient information (institution) to the randomized enforcement department of the data center.

3) The central randomization department will determine the enrollment of cases after analyzing the case information and will immediately inform the research center.

4) The research assistant of each research participating center should receive in a timely manner the enrollment notices and will assign the patient to the Study Group or Control Group in strict accordance with grouping assignment received.

8.5 Standardization of Surgical Practice

8.5.1 Handling Practices Followed by Both Groups

8.5.1.1 Anesthesia

The operation is to be carried out with endotracheal intubation under general anesthesia; whether epidural assisted anesthesia is applied or not is left at the discretion of the anesthetist and is not specified in this study protocol.

8.5.1.2 Intraoperative Exploration

Surgical exploration should typically include a thorough assessment of the peritoneal cavity and the abdominal organs to detect or rule out metastatic disease (eg, radiographically occult metastasis, carcinomatosis), more advanced local disease (eg, fixation to adjacent organs), synchronous lesions, or coexisting pathology.

8.5.1.3 Regulations on Total Mesorectal Excision

Total mesorectal excision is a standard component of radical rectal cancer surgery. An adequate mesorectal excision is required to extent 5 cm below distal edges of tumors. In the distal rectal cancers, less than 5cm from anal verge, negative distal bowel wall margin of 1-2cm may be acceptable. Lymphatic adipose tissue in the mesorectum should be removed.

8.5.1.4 Regulations on the Extent of Lymph Node Dissection

All lymphatic and fatty tissues in the drainage area should be removed. Lateral

lymph node dissection will not be included in this study.

8.5.1.5 Regulations on Digestive Tract Reconstruction

The digestive tract reconstruction method is to be determined by the surgeon according to his/her own experience and the intraoperative situation, which may be any of such anastomoses as a handsewn or stapled anastomosis. If instrumental anastomosis is used, whether the manual reinforced stitching is to be performed or not on anastomotic stoma is determined by the surgeon and not specified in this study protocol.

8.5.1.6 Regulation on the Stoma

whether the stoma should be performed is to be determined by the surgeon according to his/her own experience and the intraoperative situation, and not specified in this study protocol.

8.5.1.7 Regulations on the Drainage Tubes

Whether the drainage tubes (possibly including splenic fossa drainage tube, pelvic drainage tube, peritoneal cavity drainage tube, and transanal drainage tube) are left or not after operation are determined by the surgeon in charge of the research participating center according to his/her own experience and actual need, and are not specified in this study protocol.

8.5.1.8 Regulations on Surgery-related Equipment and Instruments

Energy equipment, vascular ligation method, digestive tract cutting closure, and digestive tract reconstruction instruments are determined by the surgeon in charge of the operation according to his/her own experience and actual needs and are not specified

in this study protocol.

8.5.1.9 Regulations on Performance of Other Concurrent Operations

If any other system/organ disease is found during surgery, the responsible surgeon and the consultants of relevant departments should jointly determine performance of a concurrent operation if there is such necessity. The priority of operations is determined according to clinical routine. The patients meeting the Exclusion Criteria will be excluded from the per-protocol and modified intention-to-treat population.

8.5.1.10 Regulations on Handling Excluded Patients as Identified Intraoperatively

If the surgeon in charge judges and determines that the patient undergoing surgery belongs to the exclusion case group, then the research approach is suspended and the surgeon will follow routine clinical practice of the research participating center to decide subsequent treatment (therapeutic decisions as to whether to excise gastric primary focus and metastases are made by the surgeon in charge); whether to proceed with laparoscopic surgery or convert it to laparotomy will be determined by the surgeon in charge; such subsequent treatments are not specified in this study protocol.

8.5.1.11 Regulations on Surgical Videos

For all study patients, intraoperative videos of all the surgeries were retained. No video data shall disclose the personal information of patients. When the videos are viewed or reviewed, the personal information must be processed with mosaics or be covered. The videos should be marked with unified Chinese name.

For example:

Video name: [laTME-subject's random number-centre]/ [taTME-subject's random

number-centre]

8.5.1.12 Criteria for Confirming Operation Quality

To confirm the appropriateness of the operations, the procedures of rectal mobilization, the rectum and mesorectum resection, vessel skeletonization and vascular ligation, colonic mobilisation, and specimen integrity will be assessed in the videos saved (as stated above). The whole surgery procedure will be videotaped and the unedited video files will be saved. The CTESC Research Committee will conduct review and monitoring of the surgical quality as mentioned above.

8.5.1.13 Saving of Surgical Videos

All videos will be saved in the hard disk in digital form, and within two weeks after the operation, they should be submitted to CTESC data center for unified saving. All research participating units can back up one copy; the research participating units shall keep the surgery video for future inspection. If failure to provide the complete video according to “Regulations on Surgical Videos” is confirmed, the CTESC Research Committee will judge and record the surgery quality as unqualified; however, the case will remain in the per-protocol set data of this study.

8.5.2 Regulations on Transanal Total Mesorectal Excision

The transanal surgery will be conducted according to TME principles. In patients undergoing taTME, the transanal endoscopic device was used for rectal mobilization, and the rectum and mesorectum resection in a “bottom-to-up” fashion. The taTME procedures were permitted to be done by one team (the transabdominal phase followed by the transanal phase was performed by one surgical team) or two teams (with separate transabdominal and transanal teams operating at the same time). The brands of transanal

endoscopic device, pneumoperitoneum support system, energy equipment, clip and video storage devices are not specified in this study.

8.5.2.1 Regulations on Pneumoperitoneum

In the transabdominal phase, carbon dioxide pneumoperitoneum will be used to maintain the pressure at 12-13 mmHg. In the transanal phase, carbon dioxide pneumoperitoneum will be used to maintain the pressure at 12-15 mmHg.

8.5.2.2 Regulations on Punctures and Auxiliary Incision

For the transabdominal procedures, the positions of punctures and auxiliary small incision are not specified; the number of punctures should not exceed 5. There should be only one auxiliary small incision whose length shall not exceed the maximum tumor diameter and necessarily will be less than 10 cm in normal cases. If the auxiliary small incision needs to be longer than 10 cm, the surgeon in charge should make a decision and record the reasons in the CRF.

8.5.2.3 Definition of Transanal total mesorectal excision (taTME)

The whole operations must be performed using surgical instruments with the support of a camera system. A digital camera (8 million pixels at least) will be used to take pictures which shall contain the following contents (See the Figure1-11 below). The procedures of rectal mobilization, the rectum and mesorectum resection are completed under endoscopic guidance. The taTME procedures were permitted to be done by one surgical team (the transabdominal phase followed by the transanal phase was done by the same surgical team) or two surgical teams (with separate transabdominal team and transanal team operating at the same time). During the transabdominal phase, the surgeons firstly conducted abdominal exploration. Then they

skeletonized the inferior mesenteric vessels and performed mobilization of the splenic flexure (if necessary), left colon, and rectosigmoid colon until the peritoneal reflection was reached. These procedures were done in a “up to down” manner. During the transanal phase, the anal retractor system was applied to expose the anorectum sufficiently after digital anal dilation. Afterward, two 2/0 prolenes were adopted to perform the purse-string suture to occlude the rectal lumen. The purse-string closure should be at least 1 cm away from the lower margin of the tumor. The time to do purse-string suture was not uniform in all study patients, as it could be placed either before (under direct vision) or after (under endoscopic assistance) the introduction of the transanal platform according to the tumor location. Before incising the rectal wall, rectal lavage with at least 200 mL iodophor and 200 mL saline was required. After introduction of the transanal endoscopic device into the anal cavity, a pneumo-anorectum (12-15 mmHg) was created by insufflating CO_2. Then a full-thickness circumferential dissection or extension of the inter-sphincteric plane (if inter-sphincteric resection is required) was performed until reaching the “holy plane”. On the basis of the principles of total mesorectal excision, the rectal mobilization, and the rectum and mesorectum resection were performed until the peritoneal reflection was reached, and these procedures were done in a “bottom-to-up” fashion. Lastly, the specimen is allowed to be extracted through anus or through an auxiliary incision and will be determined by the surgeon in charge; this facet is not specified in this study protocol.

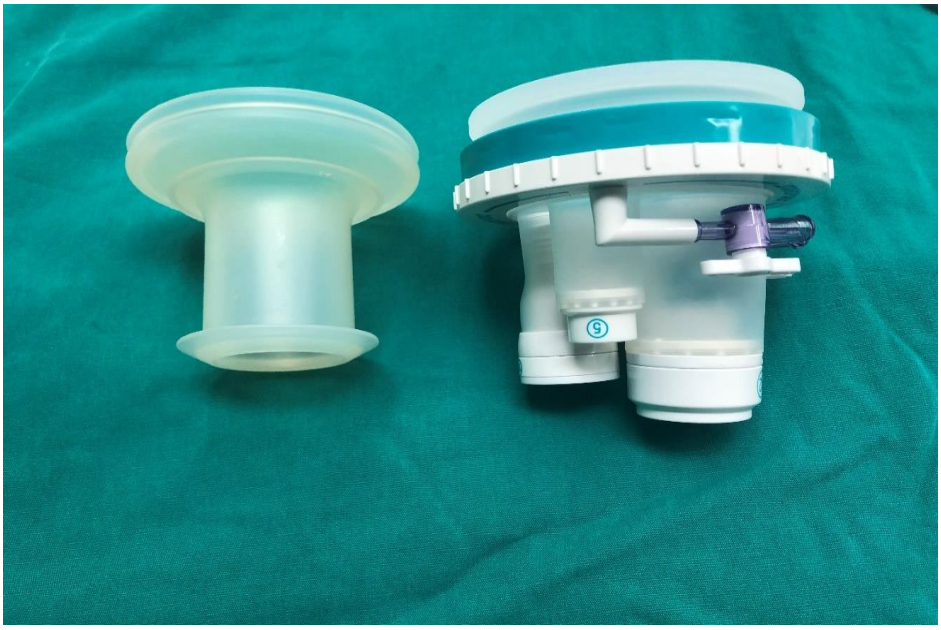

Figure 1. Transanal operative platform

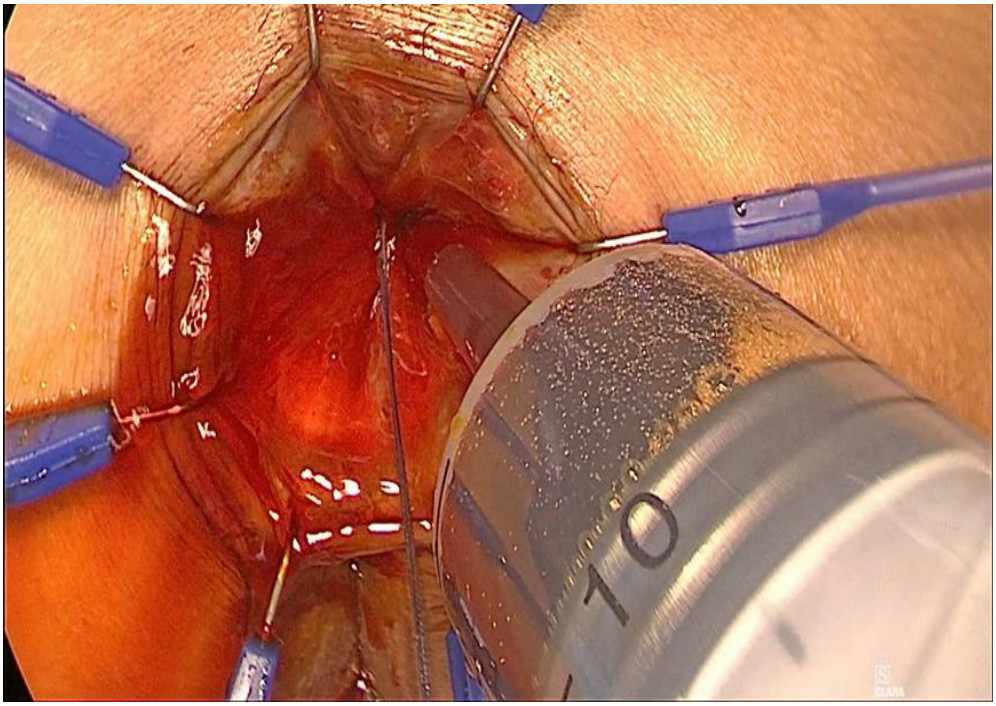

Figure 2. Purse-string suture

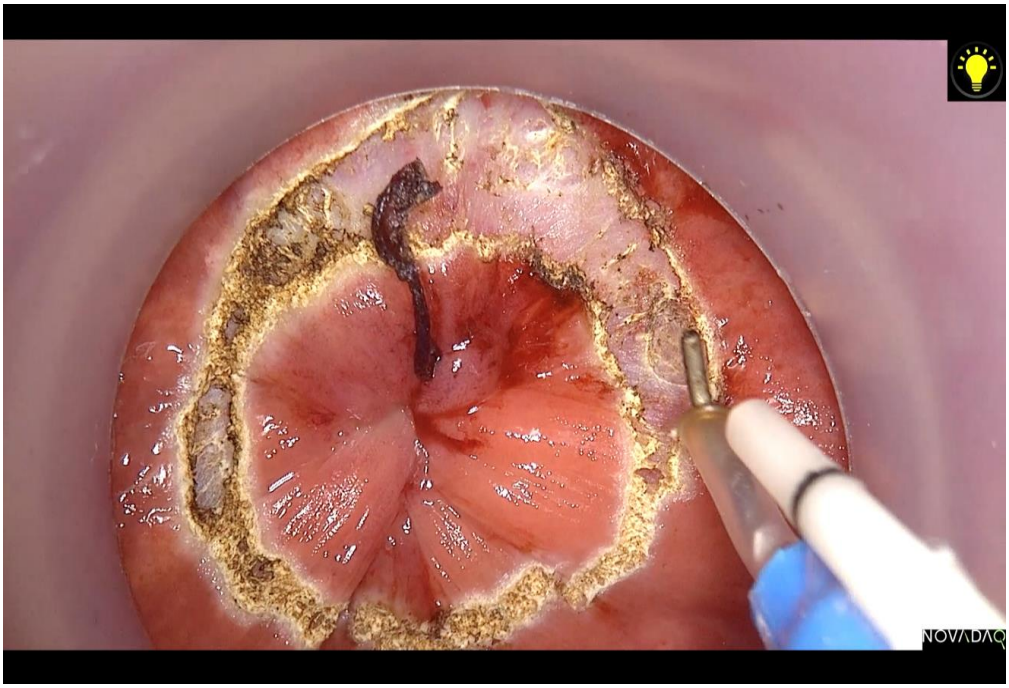

Figure 3. Full-thickness circumferential dissection

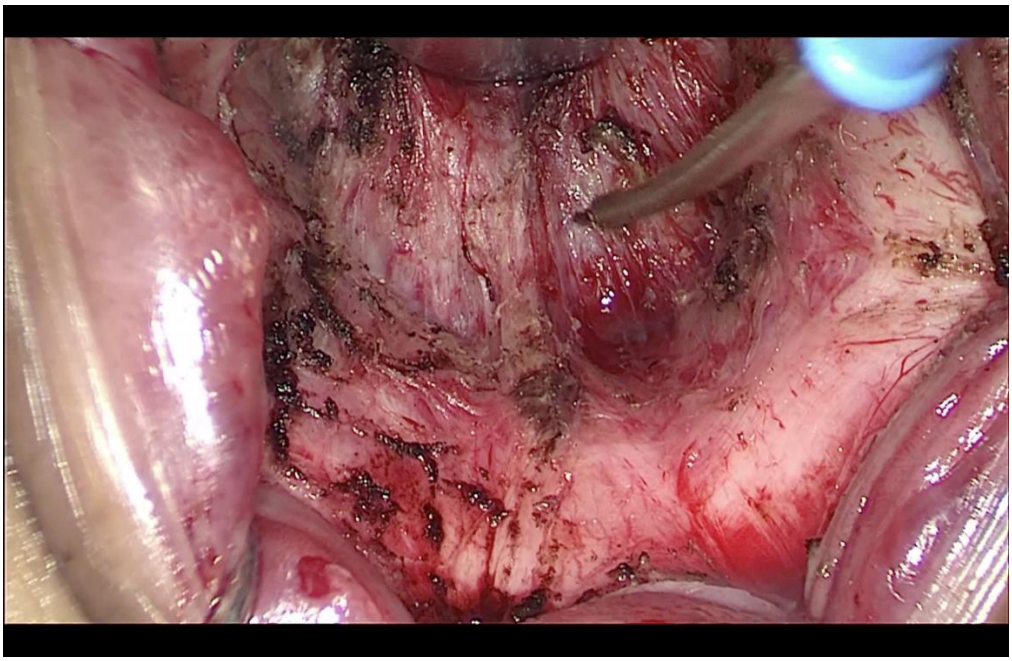

Figure 4. The conjoined longitudinal muscle

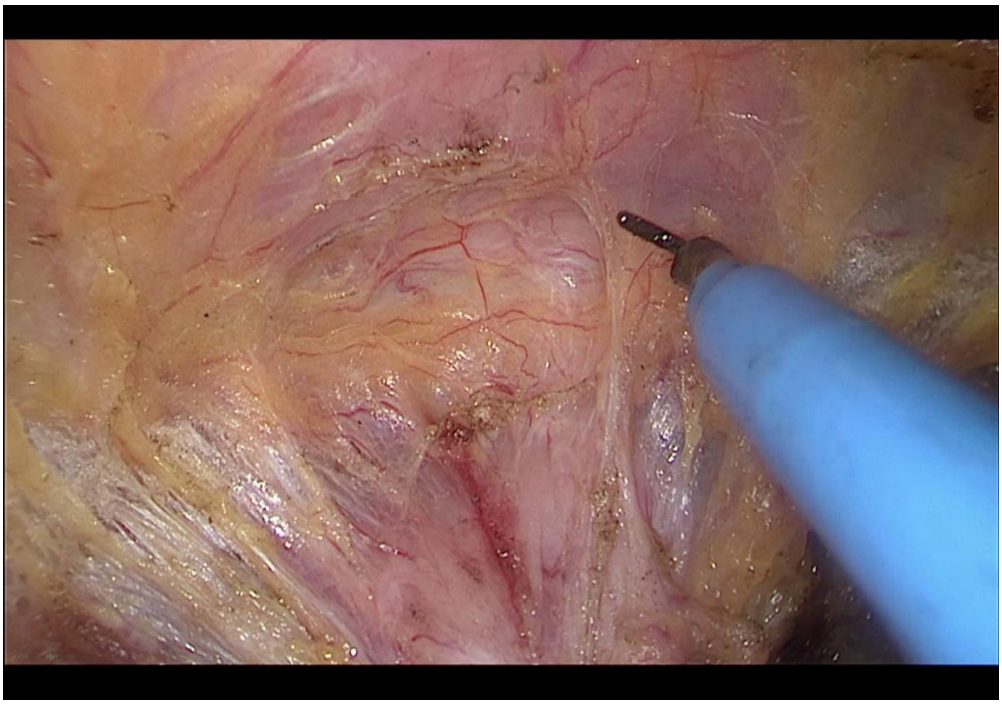

Figure 5. Anterior surgical plane

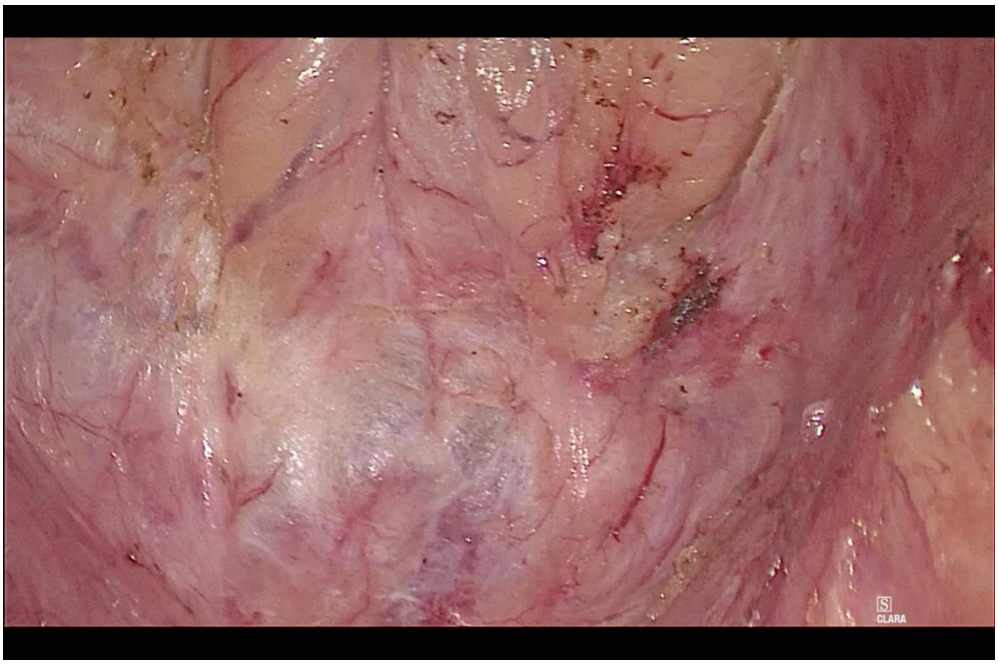

Figure 6. Posterior surgical plane

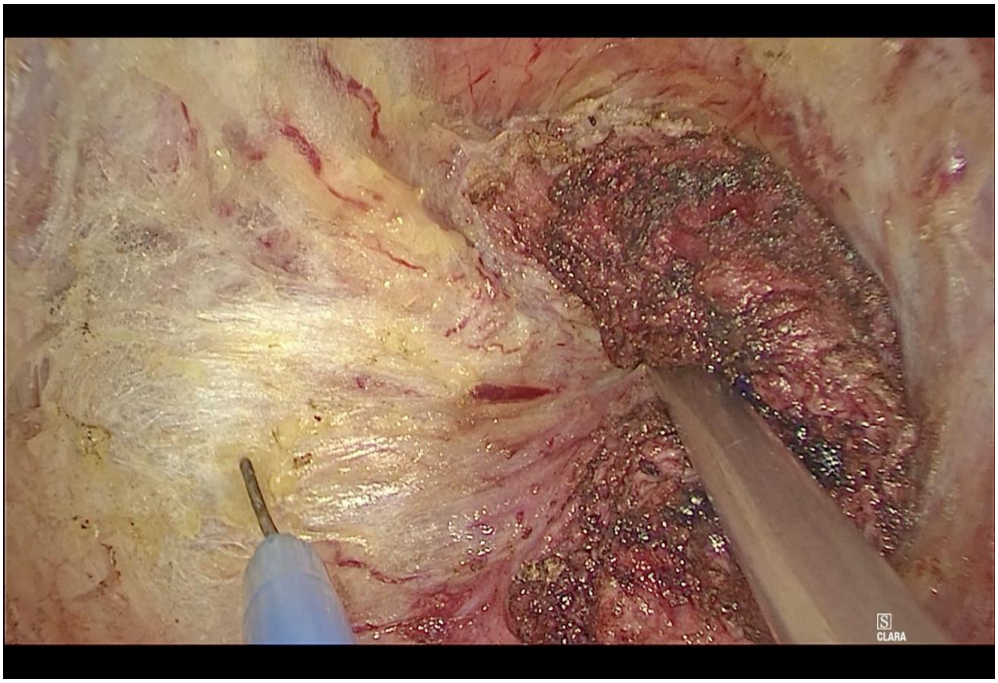

Figure 7. Right surgical plane

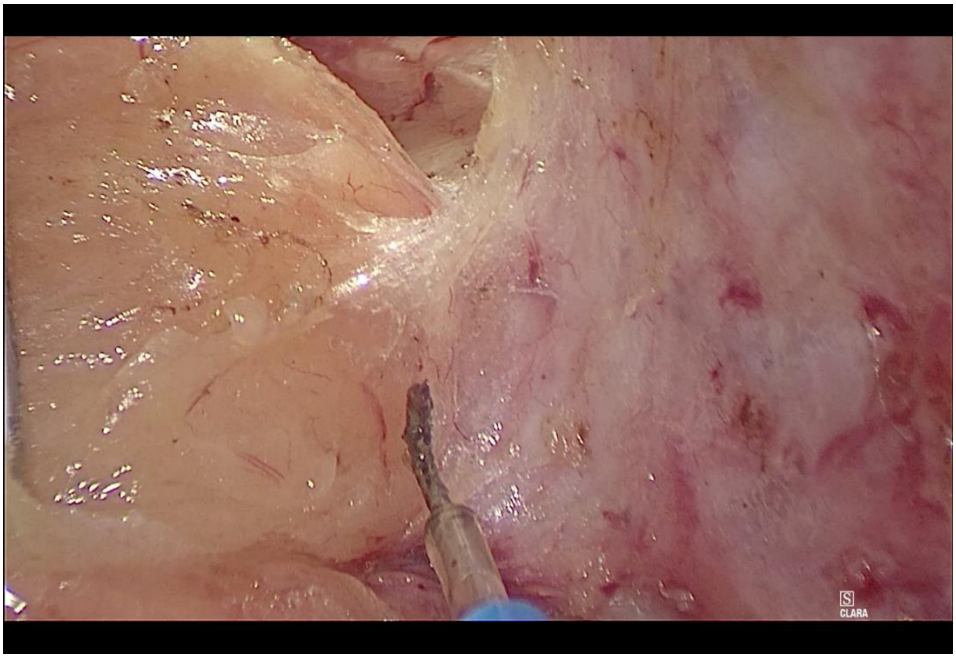

Figure 8. Left surgical plane

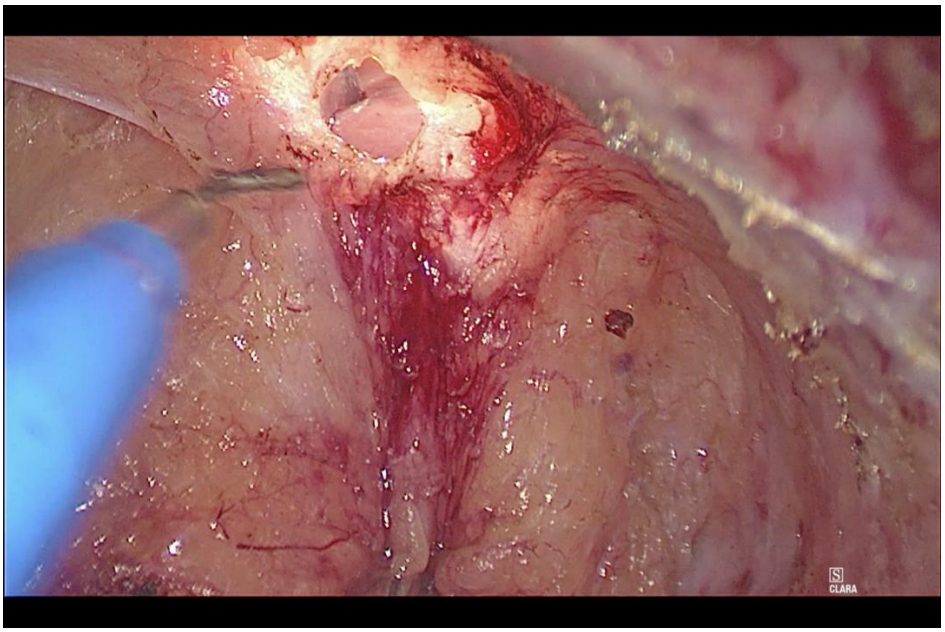

Figure 9. Peritoneal reflex (transanal view)

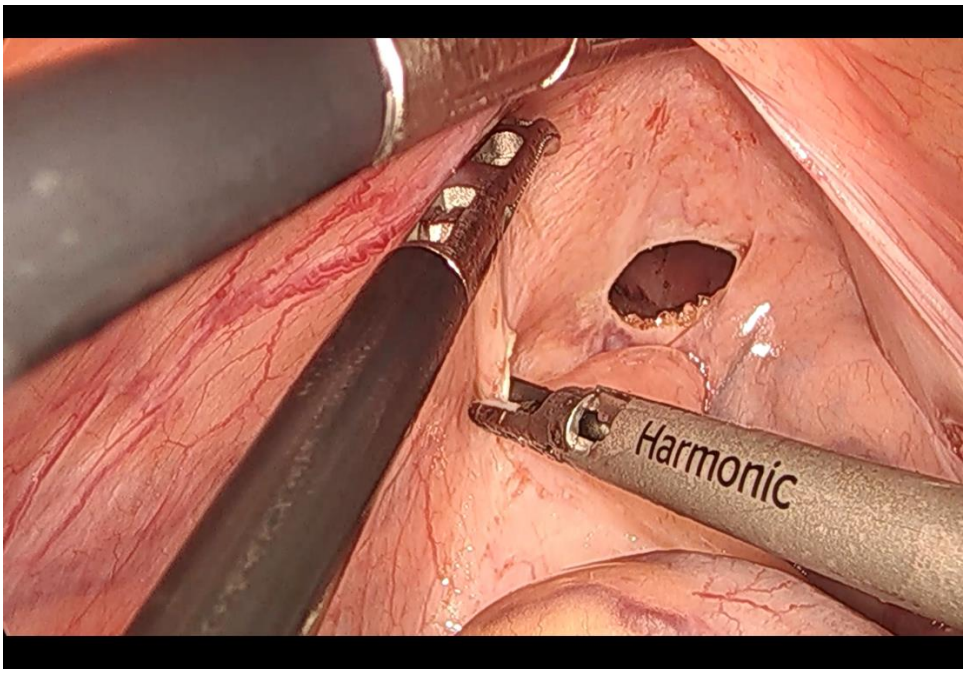

Figure 10. Peritoneal reflex (transabdominal view)

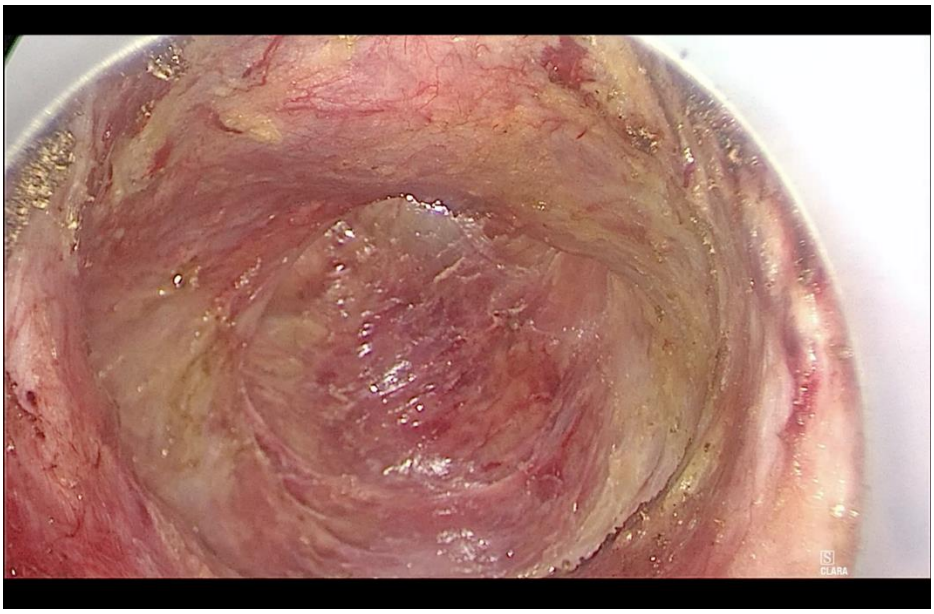

Figure 11. Postoperative surgical area (transanal view)

8.5.2.4 Definition of laparoscopic total mesorectal excision (laTME)

Transabdominal total mesorectal excision with laparoscopic technology (laTME) was performed using a five-trocar laparoscopic technique. A digital camera (8 million pixels at least) will be used to take pictures which shall contain the following contents (See the Figure12-18 below). After tracheal intubation and general anesthesia, the patients experienced the abdominal and perineal disinfection in a lithotomy position. Afterward, the surgeons firstly conducted abdominal exploration. Then they performed vascular ligation, colonic mobilization, and anterograde total mesorectal excision with a nerve-sparing dissection in a ‘‘up-to-down’’ manner.

The procedures that are up to the level of peritoneal reflection are similar with those of the taTME during the transabdominal phase. When the peritoneal reflection was reached, the surgeons opened the peritoneal reflection in the front of rectum, separated the front wall of rectum with the adjacent organ through the space among Denonvilliers Fascia, and mobilized the rectum laterally. Then, they cut the rectum with a laparoscopic cutting stapler at least 1 cm below the tumor. After the TME was accomplished, the patients underwent a handsewn or stapled anastomosis. Saline was then used to test the anastomosis.

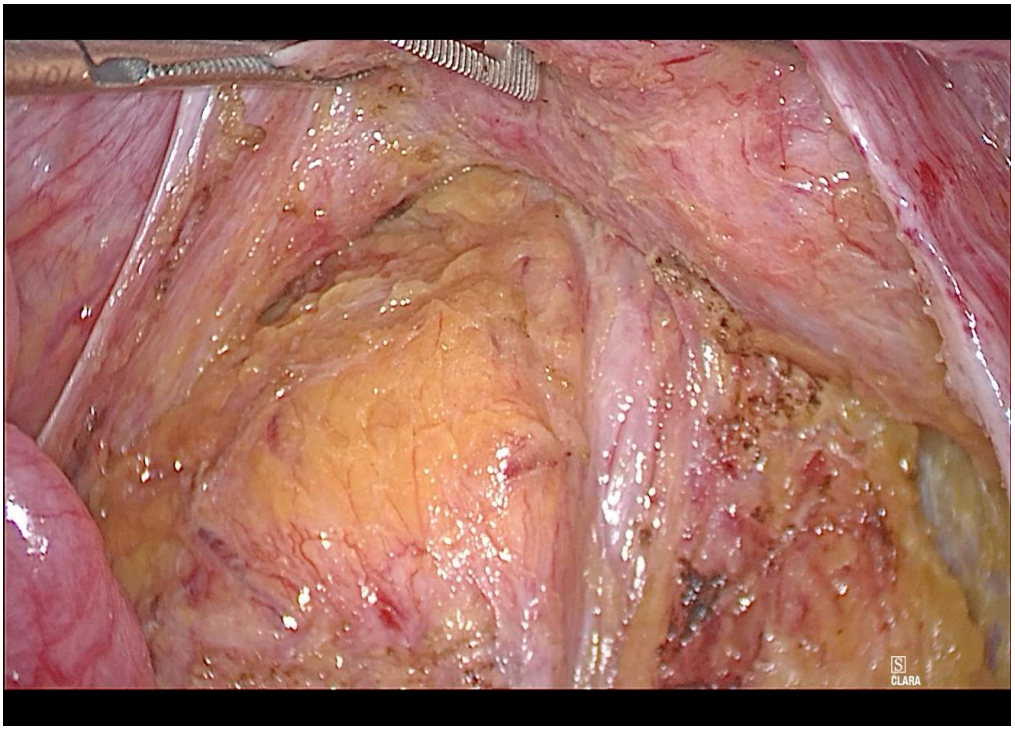

Figure 12. Anterior surgical plane

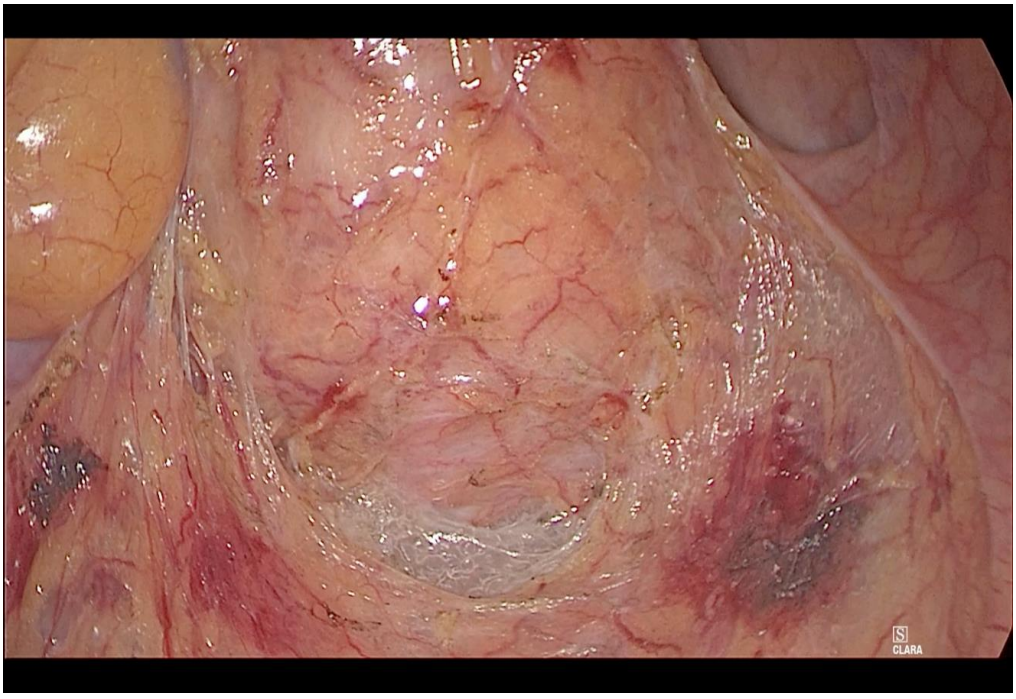

Figure 13. Posterior surgical plane

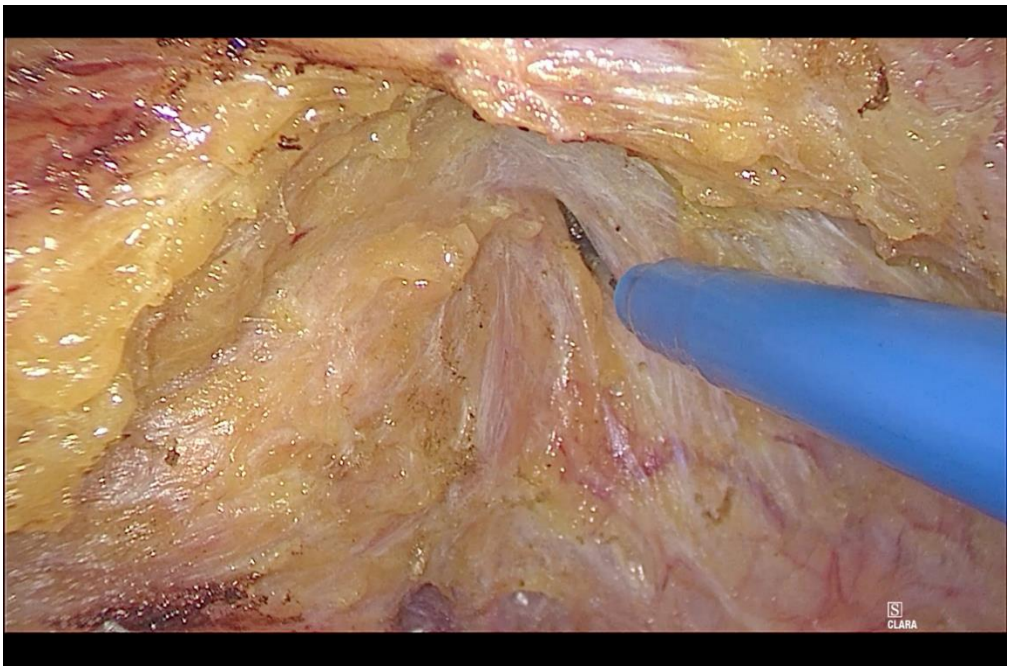

Figure 14. Right surgical plane

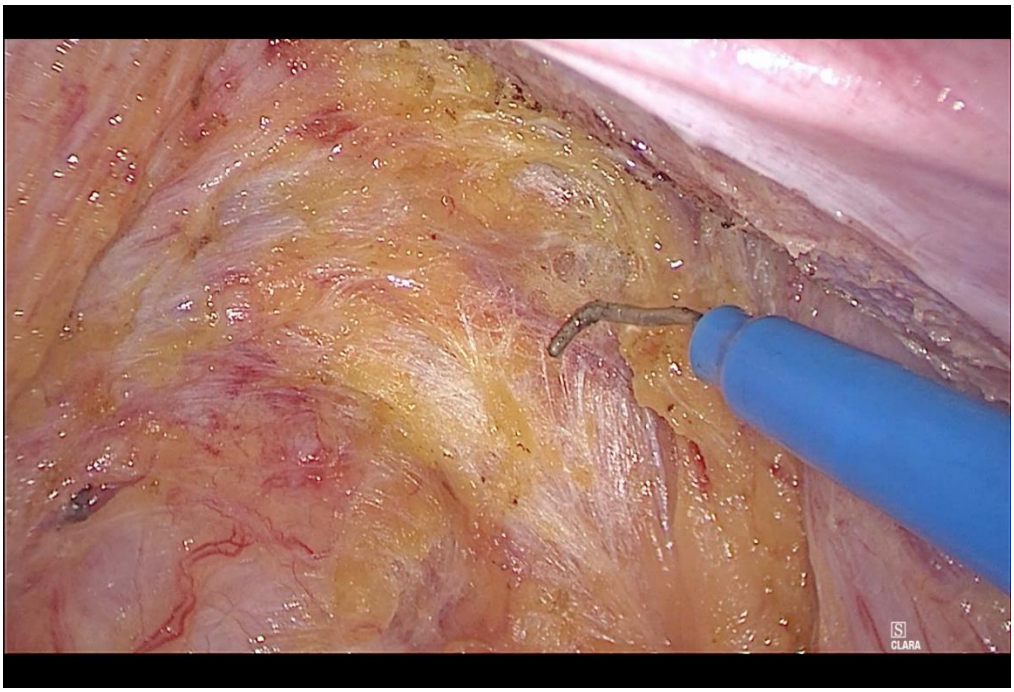

Figure 15. Left surgical plane

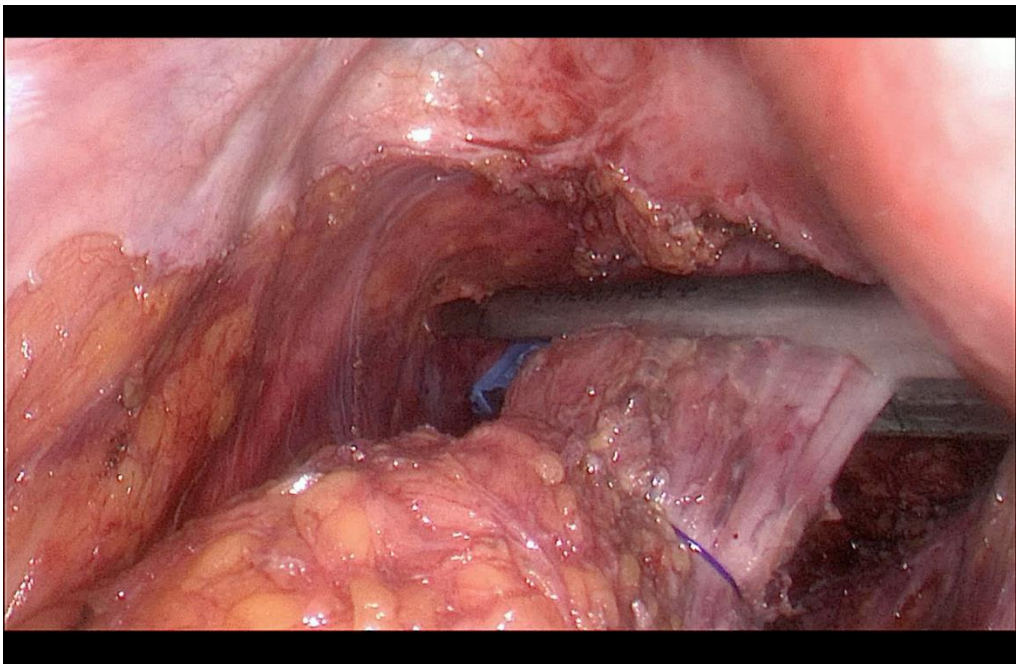

Figure 16. Stapler resection

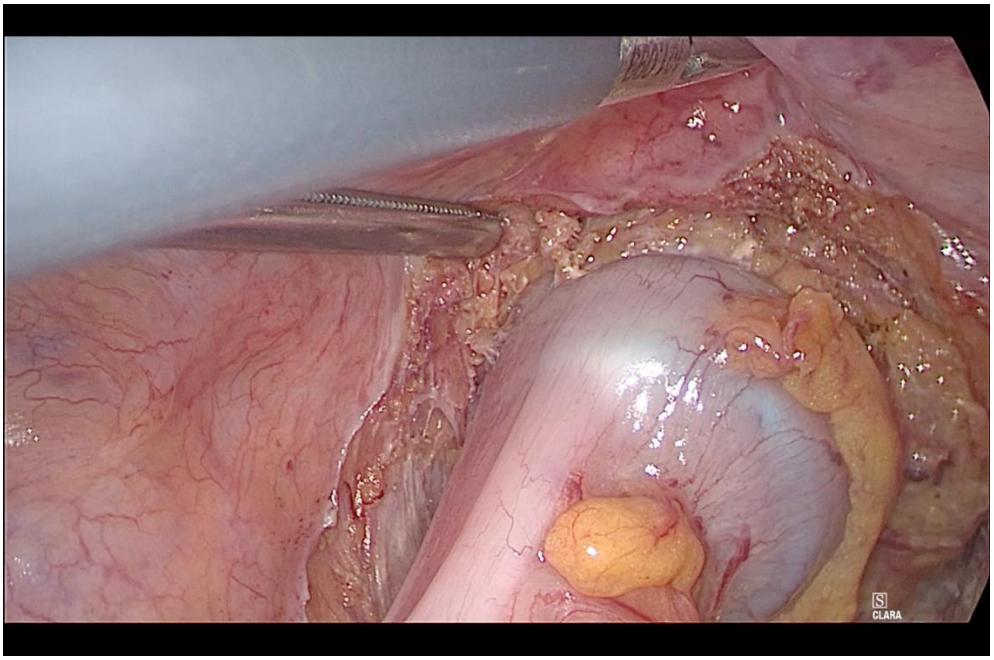

Figure 17. Anastomosis

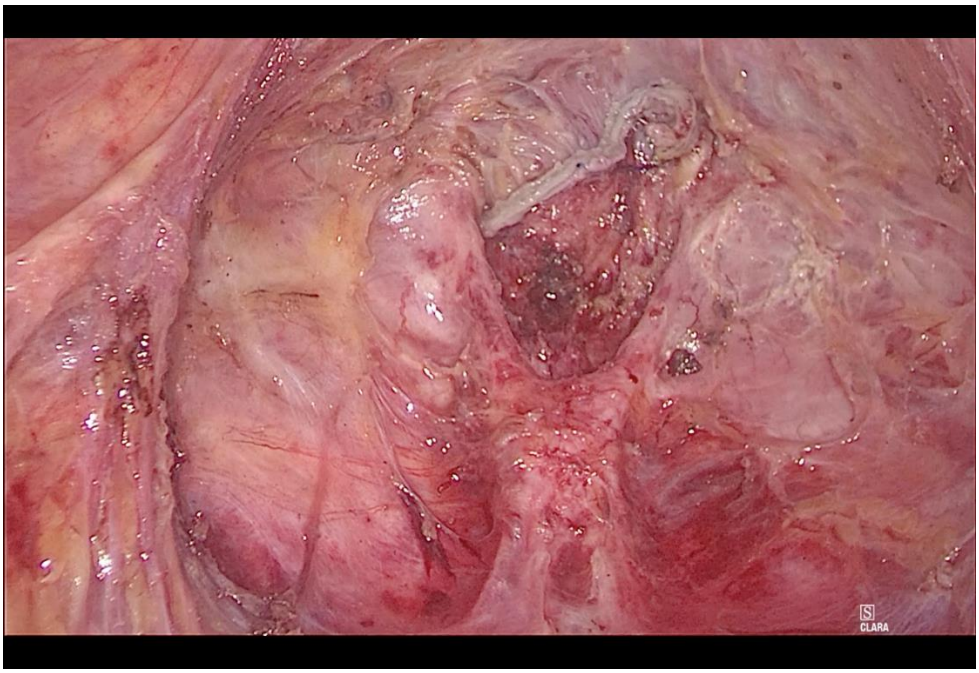

Figure 18. Postoperative surgical area (transabdominal view)

8.5.2.5 Regulations on Conversion

In the taTME group, we defined conversion when “bottom-to-up” transanal TME could not be performed due to technical challenges or complications, thereby requiring either laparoscopic or open TME. Conversion in the laTME group was defined as TME procedures that were completed by a conventional open abdominal or transanal surgery. The need for conversion is based on the decisions of the surgical teams with regards to the patients’ safety, technical challenges, inability to complete TME, or other factors which require treatment. The reasons for the any conversion to open must be clearly recorded in the CRF. When intraoperative hemorrhage, organ damage and other serious/life-threatening complications which are difficult to control occur during taTME or laTME, it is necessary to actively convert to open surgery. If the anesthesiologist and surgeon consider intraoperative complications caused by carbon dioxide pneumoperitoneum may threaten the patient’s life, it is necessary to actively convert to open. The surgeon in charge can decide to convert to open surgery driven by other technical or equipment reasons and will record said reasons. The incision length of >10 cm is considered as a case of conversion to open surgery in this study.

8.5.2.6 Subsequent Treatment of Excluded Patients from the Transanal Group

Whether the patients continue to undergo surgery under taTME or converted to open surgery is at surgeon’s discretion according to clinical experience.

8.5.3 Conventional open surgery

Conventional open surgery will be also performed according to TME principles.

8.5.4 Observation Items during Surgery (same for both groups)

The research assistant should fill in appropriate content on the day of surgery. The specific items include:

1) Name of surgeon in charge

2) Operation duration (min)

3) Operation type, reconstruction method

4) Incision length (cm), number of punctures

5) Whether the operation is switched to other surgery and reasons

6) Intraoperative estimated blood loss (ml; from skin cutting to stitching)

7) Blood transfusion (ml): in this study, the blood transfusion event is defined as transfusion of red cell suspension (ml) or whole blood (ml)

8) Tumor location

9) Tumor size (maximum diameter, in mm)

10) Length of proximal margin (mm), distal margin (mm), radical degree of operation (R0/R1/R2)

12) Intraoperative complications: Intraoperative complications were defined as unexpected surgical adverse events occurring during surgery (eg, iatrogenic injury of the blood vessels, bowel, or other organs; haemorrhage; CO_2 embolism; mechanical factor-related problems, cardiopulmonary dysfunction due to hypercapnia, and others.). Vascular injury was defined as laceration or break of the presacral vessels. Intraoperative haemorrhage was defined as blood loss of more than 200 mL in the absence of vascular injury. CO_2 embolism was defined as an abrupt decrease in end-tidal CO_2 and oxygen saturation in the setting of venous bleeding. Any diagnosis on intraoperative complications will be made by the surgeons based on the intraoperative situation and our trial protocol, and reviewed and confirmed by the CTESC Research Committee according to the unedited surgical videos.

13) Intraoperative death (occurring during the time period from skin cutting to skin stitching completion) regardless of reason.

14) Other significant findings as reported by surgeons.

8.6 Postoperative Management (same for both groups)

8.6.1 Preventive Use of Analgesics

Preventive use of analgesics will be determined by the clinicians in charge; this facet is not specified in this study protocol. Continuous postoperative prophylactic intravenous analgesia is allowable but not mandatory within postoperative 48 hours; its dose, type, and rate of infusion should be determined by the anesthesiologist according to clinical practices and specific patient conditions. The repeated use of prophylactic analgesics is not allowed beyond 48 hours after the end of surgery unless it is judged necessary.

8.6.2 Fluid Replacement and Nutritional Support

Postoperative fluid infusion (including glucose, insulin, electrolytes, vitamins, etc.) or nutritional support (enteral/parenteral) will be performed based on doctor's experience and routine clinical practices and is not specified in this study. After oral feeding, it is allowable to stop or gradually reduce fluid infusion/nutritional support.

8.6.3 Postoperative Rehabilitation Management

Postoperative rehabilitation management will be determined by the clinicians in charge; this facet is not specified in this study protocol. Management methods of drainage tube: Follow regular diagnosis and treatment approaches. Eating recovery time, diet transition strategies: follow regular diagnosis and treatment approaches.

8.6.4 Patient Discharge Standards

Patients needed to meet the following criteria for discharge: 1) satisfactory intake of a soft diet for two meals; 2) satisfactory self-care ability; and 3) absence of complications by routine clinical examinations.

8.6.5 Postoperative Observation Items

Definition of "postoperative day n": One day from 0:00 to up to 24:00. Up to 24:00 on the day of surgery is "postoperative day 0;" the next day from 0:00 to up to 24:00 is "postoperative day 1;" and so on. From the first postoperative day until hospital discharge, the research assistant should timely fill in the following items and specific observation items including: Time to first flatus, time to first intake, time to ambulation and duration of hospital stay, complications, etc.

8.6.6 Pathological Results

Reports of pathologic outcomes will include the total mesorectal excision quality, circumferential resection margin, distal resection margin, number of harvested lymph nodes and number positive, length from the inferior of tumor to distal resection margin, length of resected sample, lymphovascular invasion, and nerve invasion, pathology stage, tumor differentiation and tumor types.

8.7 Follow-up

8.7.1 Follow-up Period and Strategy

Each research center will arrange to have its own team and assigned staff member

responsible for the follow-up to carry out the follow-up of all cases enrolled in the study. Within 1 year after the surgery, a follow-up should be carried out every 3 months; after 1 year, a follow-up should be carried out every 6 months; after 2 years, a follow-up should be carried out every 12 months (i.e., follow-up at postoperative 3, 6, 9, 12, 18, 24, 36, 48 and 60 months).

In this study, it is recommended that follow-up assessment should be conducted at the surgical center, however, other means of follow-up will not be excluded. If follow-up takes place at another hospital, it is recommended that it be a tertiary hospital. The investigators who are responsible for follow-up should tract and record the results of each examination:

1) To consolidate the results of each examination, and to assess and record postoperative survival status, and the presence/absence of tumor recurrence or metastasis for all patients.

2) If the patient refuses follow-up according to the above protocol, it will be recorded as lost to follow-up to at the time of follow-up, and will be analyzed together with the cases meeting the study criteria at the end of the study.

8.7.2 Examination Items during Follow-up

1) Systematic physical examination: The doctor in charge will regularly conduct a systematic physical examination at the time of each follow-up, giving particular attention to superficial lymph nodes, abdomen, rectum, and signs of recurrence and metastases, among others.

2) Blood examination: peripheral blood routine assessment, blood biochemistry, and serum tumor markers.

3) Imaging examination: pelvic MRI, chest and abdomen CT, colonoscopy (histopathological biopsy if needed).

4) Other examinations as suggested by clinicians.

8.8 Postoperative Adjuvant Therapy

8.8.1 Indications for Postoperative Adjuvant Chemotherapy

1) After the surgical treatment is completed, according to the postoperative pathologic results, R0 resection cases at Phase II or above should receive postoperative adjuvant chemotherapy according to the protocol.
2) For relapse cases after R0 resection or progression after non-R0 resection, no provisions on the follow-up treatment protocols are specified for this study; all research participating centers will decide on their own a follow-up treatment protocol according to their clinical treatment practices.

8.8.2 Postoperative Adjuvant Chemotherapy Program

The chemotherapy program refers to the NCCN guidelines and the Chinese Ministry of Health's Colorectal Cancer Diagnosis and Treatment guideline (2015 Edition). In this study, a chemotherapy program based on 5-Fu or 5-Fu analogs will be recommended. The Capeox or capecitabine single-drug program or FOLFOX will be recommended. The cycle of postoperative chemotherapy does not exceed 6 months.

8.8.3 Safety Evaluation Indicators of Postoperative Adjuvant Chemotherapy

The safety evaluation indicators for the patients enrolled in the study should be immediately filled out by the investigators before and after each postoperative adjuvant chemotherapy cycle, with specific items including:
1) performance Status (ECOG);
2) subjective and objective status (according to records of CTCAE v3.0 Short Name);
3) blood tests: peripheral venous blood assessment: WBC, Hb, PLT Blood biochemistry: albumin, Na, K, total bilirubin, AST, ALT, creatinine, Serum tumor markers: CEA,

CA19-9, CA12-5;

4) safety evaluation items to be implemented during chemotherapy when necessary (refer to CTCAE v3.0): neurotoxicity, cardiovascular system (cardiac toxicity, ischemic heart disease, etc.), bone marrow suppression and infections due to immune dysfunction, others.

8.9 Study Calendar

	Perioperative		Follow-up (months)								
	preoperative	Surgery-discharge	3	6	9	12	18	24	36	48	60
General information	√										
Colonoscopy	√		√			√		√	√	√	√
Tumor markers	√		√	√	√	√	√	√	√	√	√
Blood biochemistry	√	√	√	√	√	√	√	√	√	√	√
Pelvic MRI	√		√			√		√	√	√	√
Chest and abdomen CT	√		√			√		√	√	√	√
Electrocardiogram, respiratory function	√										
Intraoperative assessment		√									
Pathological assessment		√									
Postoperative assessment		√									
LARS Score and Wexner Score	√		√	√		√		√			
EORTC QLQ-C30 and EORTC QLQ-CR38	√		√	√		√		√			

8.10 Definitions Involved in SOP

8.10.1 ECOG Performance Status Score

According to the simplified performance status score scale developed by the ECOG, the patients' performance status can be classified into 6 levels, namely 0-5, as follows:

0: Fully active, able to carry on all pre-disease performance without restriction

1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work

2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5: Dead

Patients at level 3, 4, and 5 are generally considered to be unsuitable for surgical treatment or chemotherapy.

8.10.2 ASA Classification

According to the patients' physical status and surgical risk before anesthesia, the American Society of Anesthesiologists (ASA) has categorized patients into 5 levels (I-V levels) as follows:

ASA I: Well-developed patients with physical health and normal function of various organs.

ASA II: Patients with mild complications and good functional compensation in addition to surgical diseases.

ASA III: Patients with severe complications, restricted physical activity, but still capable of coping with day-to-day activities.

ASA IV: Patients with serious complications, who have lost the ability day to day activity, often with life-threatening conditions.

Class V: Moribund patients receiving surgery or not, little chance for survival.

Generally, ASA I/II patients are considered good for anesthesia and surgical tolerance, with a smooth anesthesia process. ASA III patients are exposed to some anesthesia risks, and therefore good preparations should be fully made before

anesthesia, and effective measures should be taken to prevent potential complications during the anesthesia. ASA IV patients are exposed to the most risks, even if good preoperative preparations are made, with the perioperative mortality rate is being very high. ASA V patients are moribund patients and should not undergo elective surgery.

8.10.3 Oncology-related Definitions

In this study, tumor staging is according to AJCC-7th.

8.10.3.1 Primary Focus Location

The Primary tumor location will be recorded based on the distance between the inferior of the tumor and anal verge.

8.10.3.2 Tumor Staging Record

8.10.3.2.1 Recording Principle

The two staging records for clinical classification and pathological classification involve T (invasion depth), N (regional lymph node) and M (distant metastasis) which are expressed in Arabic numerals and denoted as X if indefinite.

8.10.3.2.2 Records of Tumor Invasion Depth

Tumor invasion depth is defined as follows:

T_X: primary tumor cannot be assessed.

T_0: no evidence of primary tumor.

Tis: carcinoma in situ: intraepithelial or invasion of lamina propria.

T_1: tumor invades submucosa.

T_2: tumor invades muscularis propria.

T_3: tumor invades through the muscularis propria into pericolorectal tissues.

T_{4a}: tumor penetrates to the surface of the visceral peritoneum.

T_{4b}: tumor directly invades or is adherent to other organs or structures.

8.10.3.2.3 Records of Tumor Metastasis

Lymph node metastasis (N):

N_X: number of lymph node metastasis is unknown.

N_0: no lymph node metastasis.

N_1: metastasis in 1 to 3 regional lymph nodes.

N_{1a}: metastasis in 1regional lymph node.

N_{1b}: metastasis in 2 to 3 regional lymph nodes.

N_{1c}: tumor deposits in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional lymph nodal metastasis.

N_2: metastasis in 4 or more regional lymph nodes.

N_{2a}: metastasis in 4-6 regional lymph nodes.

N_{2b}: metastasis in 7 or more regional lymph nodes.

Distant metastasis (M)

M_X: presence of distant metastasis is unclear.

M_0: no distant metastasis outside of the regional lymph nodes.

M_1: distant metastasis outside of the region lymph nodes.

Record the specific sites under M1 condition: peritoneum (PER), liver (HEP), lymph node (LYM), skin (SKI), lung (PUL), bone marrow (MAR), bone (OSS), pleura (PLE), brain (BRA) and meninges (MEN), intraperitoneal exfoliated cells (CY), and others (OTH).

8.9.3.2.4 Tumor Staging

	N0	N1	N2a	N2b	M1
T1	I	IIIA	IIIA	IIIB	
T2	I	IIIA	IIIB	IIIB	
T3	IIA	IIIB	IIIB	IIIC	
T4a	IIB	IIIB	IIIC	IIIC	
T4b	IIC	IIIC	IIIC	IIIC	
Any T/N	IV				

8.10.3.3 Pathologic Types and Classifications

8.10.3.3.1 Type

1) Tubular adenocarcinoma

2) Mucinous adenocarcinoma

3) Papillary adenocarcinoma

4) Signet ring cell carcinoma

8.10.3.3.2 Grading

G_X: classification cannot be assessed.

G_1: well differentiated.

G_2 moderately differentiated

G_3: poor differentiated.

G_4: undifferentiated.

8.10.3.4 Evaluation of Pathologic Outcomes

Reports of pathologic outcomes will include the total mesorectal excision quality,

circumferential resection margin, distal resection margin, number of harvested lymph nodes and number positive, length from the inferior of tumor to distal resection margin, length of resected sample, lymphovascular invasion, and nerve invasion, pathology stage, tumor differentiation and tumor types.

8.10.3.4.1 Records of total mesorectal excision quality

A complete TME is defined as a rectal resection specimen that has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transection with no coning in of the mesorectum above the point of transection. The surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat. A nearly complete TME is defined as a rectal resection specimen where the mesentery is all present, without coning or missing fat. A < 5 mm deep defect may be present in the envelope covering the mesenteric fat caused either by a wayward incision or traction injury during extraction of the TME specimen through a small extraction site.

8.10.3.4.2 Records of resection margins

The involvement of the circumferential resection margin was considered if the distance was ≤1 mm from the tumor to the mesorectal fascia. A positive distal resection margin was defined if the distance between the closest tumor to the cut edge of the tissue was ≤1 mm.

8.10.3.4.3 Records of number of harvested lymph nodes

All lymph nodes are included in the resected specimens should be evaluated. Pathologists should make every effort to identify at least 12 lymph nodes in the surgical specimen. Efforts to locate lymph nodes should be included in the pathology report.

9. Endpoints and Definitions for Determination of Relevant Results

9.1 Definition of Relapse and Recurrence Day

Recurrence is considered to occur in the situations described below, and the basis of diagnosis of recurrence should be recorded in the CRF.

1) Determined by any imaging evaluation (X-ray, ultrasound, CT, MRI, PET-CT, endoscopy, etc.), without discrepancy among the results of several imaging examinations. When recurrence is diagnosed according to the results of several imaging examinations, the date of first discovery via imaging examination is defined as the recurrence day.

2) Clinical recurrence is diagnosed only through clinical history and physical examination without imaging or pathology diagnosis, and the date the diagnosis is made is the recurrence day.

3) Recurrence also could be diagnosed without imaging or clinical findings but through only cytology or tissue biopsy; the earliest cytology or tissue biopsy examination date is the recurrence day.

4) The increase in CEA and other tumor markers alone cannot be the basis for recurrence diagnosis.

9.2 Endpoint Definitions

9.2.1 **Disease (tumor)-free survival: DFS**

Disease-free survival (DFS) is defined as the time from intervention to disease or death of any cause, and it is censored at the last day when the patient is alive without any evidence of disease. If there is no follow-up data on death or a tumor recurrence event, the final date of no relapse should be confirmed (eventually relapse-free survival

confirmation date: the outpatient day or the last date to accept the inspection) as the termination point.

9.2.2 Morbidity

Morbidity was defined as intraoperative or postoperative surgical complications, which were diagnosed by evaluation of imaging or clinical symptoms and signs. Postoperative complications were stratified according to the Clavien-Dindo classification.

Intraoperative complications were defined as unexpected surgical adverse events occurring during surgery (eg, iatrogenic injury of the blood vessels, bowel, or other organs; haemorrhage; CO2 embolism; and Subcutaneous emphysema). Correction of preoperative anemia will not be included as a complication. The decision to transfuse will be made at the surgeon's discretion. Vascular injury was defined as laceration or break of the presacral vessels. Intraoperative haemorrhage was defined as blood loss of more than 200 mL in the absence of vascular injury. CO2 embolism was defined as an abrupt decrease in end-tidal CO2 and oxygen saturation in the setting of venous bleeding. Any diagnosis on intraoperative complications will be made by the surgeons based on the intraoperative situation and our trial protocol and confirmed by the CTESC Research Committee according to the unedited surgical videos.

Post-operative complications were recorded as follows: Anastomotic leakage; Anastomotic bleeding; Intestinal obstruction; Uroschesis; Incisional infection; Abdominal/pelvic infection; Deep vein thrombosis; Pulmonary embolism; Cerebral infarction; Lymphatic leakage; and Others. Diagnosis on any specific postoperative complication was established according to the specific image-based physical examinations, laboratory evaluations, or significant clinical manifestations. Once a specific complication was diagnosed, the severity was assessed according to the

Clavien-Dindo classification. The diagnosis on any post-operative complications will be reviewed and confirmed by the CTESC Research Committee according to the available evidence (including specific image-based physical examinations, laboratory evaluations, or significant clinical manifestations).

1) Anastomosis-related complications (leakage, stenosis, or bleeding) were confirmed by intestinal X-ray imaging, endoscopy, or angiography. Anastomotic leakage was defined as clinical evidence of a defect of the integrity of the intestinal wall at the anastomotic site. 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 for anastomotic leakage were confirmed by digital rectal examination, computed tomography (CT) scan, or surgery when necessary. Anastomotic bleeding was defined as clinically significant rectal bleeding, active and continuous fresh blood from the drain with a drop in hemoglobin for which no other cause was established.

2) Postoperative intraperitoneal hemorrhage was defined as an amount of hemorrhage exceeding 200 mL.

3) Abdominal/pelvic/incisional or other organ infections will be defined by the need for antibiotic treatment and/or drainage. Abdominal/pelvic infection was proven by ultrasonography or computed tomography examination and resulted in a systemic inflammatory response for at least 24 hours. Incisional infection is defined as an infection that occurs within 30 days after the operation and involves the skin/subcutaneous tissue and deep soft-tissue infection of the incision. The criteria for diagnosis of incisional infection include at least one of the following signs or symptoms: redness, heat, pain or tenderness, localized swelling and purulent drainage.

4) Intestinal obstruction will include primary ileus and secondary ileus. Primary ileus

will be defined as the condition of bowel dysfunction (NPO status) that occurs for greater than 10 days following surgery or that requires intervention including nasogastric tube, surgery, medication, etc. Secondary ileus will be defined as bowel dysfunction that occurs in a patient that had been taking enteral nutrition, but that subsequently requires NPO status.

5) Uroschesis will be defined as the condition of urinary dysfunction that occurs for greater than 5 days following surgery or that requires intervention, including replacement of Foley catheter, surgery, etc.

6) Lymphatic leakage was confirmed with a chyle test when abdominal drainage fluid exceeded 200 mL daily for 5 continuous days after postoperative day 3.

7) Deep vein thrombosis is manifestations of venous thromboembolism, and develops most often in the legs, the deep veins of the arms, and the splanchnic veins. Clinical manifestations of deep vein thrombosis include swelling or pitting oedema, redness, tenderness, and presence of collateral superficial veins. The diagnostic work-up of suspected deep vein thrombosis includes the sequential application of a clinical decision rule and D-dimer testing. All suspected deep vein thrombosis should be confirmed by compression ultrasonography or CT venography.

8) Pulmonary embolism is manifestations of venous thromboembolism. Signs and symptoms of pulmonary embolism comprise sudden onset of dyspnoea or deterioration of existing dyspnoea, chest pain, syncope or dizziness due to hypotension or shock, haemoptysis, tachycardia, or tachypnoea. All suspected pulmonary embolism should be confirmed by CT pulmonary angiography, or MRI or single-photon emission CT.

9) Postoperative cerebral infarction was defined as a diffusion-weighted imaging high-intensity lesion with or without symptoms. Any cerebral infarction should be confirmed

by CT, MRI, MR angiography (MRA), or by carotid and cardiac ultrasonography.

10) Other sequelae as reported by clinicians.

9.2.3 Mortality

Mortality will be calculated as the ratio between the number of patients who died as numerator and number of all patients undergoing surgical treatment as the denominator. All deaths (no matter if causally related to surgery) within 30 days after the end of surgery (including 30 days); or during a longer period of time after 31 days after end of surgery if there is conclusive evidence that there is a direct causal relationship between the patient's death and the first surgery.

9.2.4 Overall Survival

The Overall survival (OS) is defined as the time from intervention to the date of death of any cause or last follow-up. In case of inability to follow-up, the last date of survival should be confirmed.

9.3 Determination of Surgical Results

9.3.1 Postoperative Rehabilitation Indicators

9.3.1.1 **Time to start bowel function, to restore liquid food and semi-liquid food**

1) Starting from the postoperative 1 day to the first postoperative discharge, within the initial recognition of the earliest time for bowel function (flatulence/bowel movement), to restoration of fluid/semi-fluid diet; records are made hourly.
2) Flatulence/bowel movement on the day of surgery is excluded.

3) In case of no flatulence/bowel movement/restoration of liquid/semi-liquid diet before the first postoperative discharge, the discharge time should be recorded as the time of flatulence/bowel movement/restoration of liquid/semi-liquid diet.
4) The initial time of flatulence/bowel movement/restoration of liquid/semi-liquid diet is per patient report.

9.3.1.2 Highest Body Temperature

The highest body temperature starting from postoperative day 1 up to 7 days should be measured at least three times a day.

9.3.2 Percentage of Transanal Surgeries Completed

Ratio expressed as percentage for completion of transanal surgeries will be calculated with number of patients failing to convert to transabdominal as the numerator, and number of all patients undergoing surgical treatment (transanal surgery/transabdominal) as the denominator.

9.3.3 Ratio of Conversion to Open Surgery

Conversion to open surgery is defined as a change in operative approach to an open procedure. Conversion to a celiotomy will be at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, inability to complete the planned procedure for sphincter sparing, or associated conditions requiring treatment. Conversion will be defined as a fascial incision that is longer than 10 cm, utilized to achieve anything other than specimen extraction. Utilizing the extraction site for transverse stapler insertion to accomplish the distal anastomosis will not be considered a conversion. Identification of any grossly visible positive margins or extensions into adjacent organs will mandate conversion to an open procedure. Completion of the

pelvic dissection through the extraction site also will be considered a conversion.

9.3.4 Ratio of Conversion to Transanal Surgery

Conversion to transanal surgery is defined as a change in operative approach to a transanal procedure. Conversion to a celiotomy will be at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, inability to complete the planned procedure for sphincter sparing, or associated conditions requiring treatment. Conversion is defined as transanal mesorectal excision. Utilizing the transanal procedure to accomplish the distal anastomosis will not be considered a conversion. Identification of any grossly visible positive margins or extensions into adjacent organs will mandate conversion to a transanal procedure. Completion of the pelvic dissection through the extraction site also will be considered a conversion.

10. Statistical Analysis

10.1 Definition of Population Set for Statistical Analysis

1) Intent-to-treat Population: cases that expressed intention to participate in the study and signed an informed consent form.

2) Modified Intent-to-treat Population: cases that underwent randomization and taTME or laTME, with records of data of at least one valid efficacy evaluation after intervention.

3) Per-protocol Population: cases complying with the study protocol, with good compliance and completed CRF, allowing statistical analysis of efficacy. The main analytical results are consistent with those of the mITT analysis.

4) Safety Analysis Population (SAP): all cases that underwent randomization and taTME or laTME, with records of data for safety evaluation after intervention constitute a safety analysis population of this study, allowing a statistical description and analysis of safety indicators and incidence of adverse reactions.

10.2 Statistical Analysis Plan

1) Statistical software: A database will be established, and data will be entered into it using Excel. Statistical analyses will be performed using SAS 9.3 software (SAS Institute, Cary, NC).

2) Primary endpoint analysis: The noninferiority analysis for the primary endpoint of 3-year disease-free survival rate and 5-year overall survival rate will be conducted by comparing 95% confidence intervals (calculated by Newcombe method with adjustment for randomisation strata as recommended by the FDA and NCCLS) of survival rates between the test and control groups on a modified intent-to-treat population basis and using a noninferiority margin for 3-year tumor-free survival rate and 5-year overall survival rate of 10% was chosen for this study.

3) Statistical Analysis Populations: Analyses of baseline data and validity analyses will be conducted on a modified intent-to-treat basis, and the primary endpoints will also be analyzed on a per-protocol basis when appropriate. Two interim analyses will be conducted and reported for morbidity and mortality rates, as well as pathologic outcomes, when about half and all the projected study patient population has been enrolled.

4) Descriptive Statistics for endpoints: Normally distributed continuous variables will be presented as mean and standard deviation and compared using the t-test if normally distributed, or as median and interquartile range and compared using the Wilcoxon

rank-sum test if non-normally distributed; while categorical variables were expressed as numbers (percentages), and were analyzed by Fisher's exact test or χ^2 test as appropriate. Survival data (time and rate) will be analyzed using the Kaplan-Meier method and log rank test. General linear model for quantitative indicators, logistic regression for qualitative indicators and Cox's proportional hazards model for survival data will be used to assess the effects of baseline, treatment, center, and treatment-by-center interactions. The numbers of loss to follow-up participants will be compared using the Fisher's exact test. A two-sided $P < 0.05$ will be considered statistically significant.

5) Attrition Analysis: Comparison of total attrition rates and attrition rates due to adverse events between the two groups will be conducted using Fisher's exact test or χ^2 test as appropriate.

6) Method for Determination of Outliers: Any observed value that is thrice lower or higher than the lowest (P25) or highest (P75) interquartile range will be considered an outlier. The effect of retention and elimination of outliers will be analyzed by sensitivity analysis; in the case of no contradiction, the data shall be retained; in the case of any contradictory, a decision shall be made on individual cases.

7) Subgroup analysis: Analyses of the possible impact of prognostic factors on results is not excluded if possible.

8) Interim analysis: Two interim analyses on a modified intent-to-treat basis will be conducted and reported for morbidity and mortality rates when about 50% and 100% of the patients has been enrolled.

11. Data Management

11.1 Case Report Form (CRF)

11.1.1 CRF Types and Submission Deadline

1) Case Screening: 7 days prior surgery.
2) Enrolling: submitted to the CTESC Data Center at 1 day prior to surgery.
3) Surgery: within 1 day after surgery.
4) Postoperative discharge: within 3 days after the first discharge.
5) Follow-up: within 7days after each planned follow-up time point.

11.1.2 CRF Transmittal Methods

Including the paper CRF and ECRF form.

11.1.3 CRF Amendment

After the start of the study, if the CRF is found to lack items that are then deemed pertinent, under the premises of ensuring the amendment of the CRF does not cause medical and economic burden and increased risks to the selected patients, the CRF can be modified after the CTESC Research Committee adopt it through discussion at the meeting. If the amendment of the CRF requires no changes to this study protocol, the latter will not be modified. Submission of a report or application to each research participating hospital's IRB for the CRF amendment should follow the provisions of the various hospitals.

11.2 Monitoring and Supervision

1) To assess whether study implementation follows protocol and data are being collected properly, monitoring should be conducted at each participating site monthly during the enrollment period and every two months during the follow-up period. The CTESC Data Center was responsible for study inspection.

2) The data center should periodically submit the monitoring reports to the Research Committee, the Research Responsible Person, and Efficacy and Safety Evaluation Committee for discussion and analysis in accordance with relevant monitoring provisions. Regular monitoring is aimed at providing feedback for improving the scientific and ethical nature of the study rather than trying to expose study or hospital issues. The Research Committee, the Research Responsible Person and the person in charge of research at the participating hospital should strive to improve and to avoid the problems pointed out in the regular monitoring reports.

11.2.1 Monitoring Items

1) Data Collection Completion Status: By selected registration numbers (cumulative and for each time, overall and each center).

2) Eligibility: Not eligible patients/potentially ineligible patients (different centers).

3) Different end of treatment, the reasons for suspension/end (different centers) of the study protocol.

4) Background factors, pre-treatment report factors, post-treatment report factors when selected for registration.

5) Severe adverse events (different centers).

6) Adverse events/adverse reactions (different centers).

7) Laparoscopic surgery and transanal surgery completion percentage (different centers).

8) Proportion of conversion (different centers).

9) Protocol deviation (different centers).

10) Disease-free survival /overall survival (all patients selected for registration).

11) Progress and safety of the study, other issues.

11.2.2 Acceptable Range of Adverse Events

Treatment-related death and life-threatening complications caused by surgeries occur relatively rarely and partly are dependent on the qualifications of the research participating hospitals and their staff; a rate of over 3% is considered unacceptable. If treatment-related death is suspected or non-hematologic Grade 4 toxicity has a causal relationship with the surgery is determined, adverse events should be reported to the CTESC Efficacy and Safety Evaluation Committee. If the number of treatment-related deaths or the number of patients with determined non-hematologic Grade 4 toxicity having a causal relationship with the surgery reached 17, the final incidence proportion of adverse events would be expected to exceed 3%, and therefore the inclusion of patients must be immediately suspended. Whether the study can continue should be determined by the CTESC Efficacy and Safety Evaluation Committee.

11.2.3 Deviation/Violation of Study Protocol

Surgical resection, clinical examinations, or toxicity and efficacy evaluation that are not conducted in accordance with the study protocol are considered study protocol deviations. Deviations prespecified by the Data Center and Research Committee (allowed up to after the start of the study in special circumstances) that are found during monitoring to exceed acceptable ranges as specified for each study center should be included in the monitoring report under “possible cases of deviation,” and listed under the following categories after discussion with the Research Committee:

11.2.3.1 Violation

A violation is a clinically inappropriate deviation involving at least one of the following: endpoint evaluation affecting the study; doctor in charge/center, intentional or systematic; poses significant risk to patient. Violation must be recorded in detail.

11.2.3.2 Acceptable Deviation

Deviation within the acceptable range set by the Research Committee and the Data Center for each item before the beginning of the study or after the beginning of the study. They do not need to be recorded in the monitoring report.

11.2.3.3 Deviation

1) Items that do comply with 11.2.3.1 nor with 11.2.3.2 are deviation items.
2) Specific deviations that occur several times should be highlighted as red flags.
3) When the monitoring report is discussed, the following cases should be classified: deviated from undesired results: should be reduced; deviation (inevitable): not to be actively reduced; deviation (clinically appropriate): positive affirmation of the judgment of the chief physician/ hospital.

12. Relevant Provisions on Adverse Events

The adverse events are evaluated by the CTCAE v3.0 and the accordion severity grading system.

12.1 Expected Adverse Events

12.1.1 Surgery-related Adverse Events

The surgery-related adverse events are defined in 9.2 Definition of the study endpoints.

12.1.2 Adverse Events Caused by Worsening Primary Diseases

Adverse events relating to various forms of deterioration in primary diseases should be recorded according to Short Name of CTCAEv3.0, including:

1) Adverse events caused by the deterioration of the primary lesions and peritoneal disseminated lesions: gastrointestinal adverse events: loss of appetite, constipation, dehydration, abdominal fullness, heartburn, nausea, gastrointestinal occlusion-[stomach, duodenum, ileum, colorectum, small intestine - cannot be broken down], gastrointestinal perforation-[stomach, duodenum, jejunum, ileum, colorectum], digestive tract stenosis-[stomach, duodenum, jejunum, ileum, colorectum], vomiting, hyponatremia, gastrointestinal bleeding-[stomach, duodenum, jejunum, ileum, colorectum]

2) Adverse events caused by deterioration of liver metastases: abnormal metabolism/laboratory test values: AST, ALT, bilirubin, alkaline phosphatase.

3) Adverse events caused by deterioration of lung metastases: lung/Upper Respiratory Tract: atelectasis, dyspnea, hypoxemia, airway occlusion-[bronchial].

4) Adverse events caused by deterioration of other focus metastases: pain: pain-[metastasis sites], hypercalcemia.

5) Adverse events caused by deterioration of systemic status: systemic status: fatigue, weight loss, cachexia quality; blood /bone marrow: hemoglobin, platelet; cardiovascular system: hypotension; lymphatic system: edema: head and neck, limbs, trunk/ genitalia, viscera; metabolic/clinical laboratory values: low albumin, AST, ALT, acidosis, creatinine, hyperglycemia, hypoglycemia, hypernatremia, hyponatremia,

hyperkalemia, hypokalemia, other electrolyte disturbances; lung/upper Respiratory Tract: pleural effusion (non-malignant), dyspnea, hypoxemia, pulmonary infections; renal/genitourinary system: cystitis, renal failure, oliguria/anuria.

12.2 Evaluation of Adverse Events

1) Evaluation of adverse event/adverse reaction are based on [Accordion Severity Grading System] and [CTCAE v3.0]; for more comprehensive detail, refer to the latter sources.

2) Adverse events will be graded 0 ~ 4 as per definition. For treatment-related death, fatal adverse events are classified as Grade 5 in the original CTCAE.

3) Toxicity items specified in the [surgery-related adverse events], Grade and the discovery date of Grade should be recorded in the treatment process report. For other toxicity items observed, observed Grade 3 toxicity items are only recorded in the freedom registration column of the treatment process report, as well as Grade and the discovery date of Grade. Grade recorded in the treatment process report should be recorded in the case report form.

4) CTCAE v3.0, the so-called “Adverse Event”, “all observed, unexpected bad signs, symptoms and diseases (abnormal value of clinical examination are also included) in the treatment or disposal, regardless of a causal relationship with the treatment or handling, including determining whether there is a causal relationship or not”. Thus, even if events were “obviously caused by primary disease (cancer)” or caused by supportive therapy or combination therapy rather than the study regimen treatment (protocol treatment), they are “adverse events”.

5) For adverse event data collection strategy, the following principles should be complied with in this study: a) Adverse events within 30 days from the last treatment day of the study regimen treatment (protocol treatment), regardless of the presence or absence of a causal relationship should be completely collected. (When adverse events are reported, the causality and classification of adverse events are separately discussed);

b) For adverse events within 31 days from the last treatment day of the study regimen treatment (protocol treatment), only those determined (adverse reactions, adverse drug reactions) to have a causal relationship (any of definite, probable, possible) with the protocol treatment will be collected.

12.3 Reporting of Adverse Events

1) Once “severe adverse events” or “unexpected adverse events” occur, the Research Responsible Person of each research participating unit should report them to the CTESC Research Committee/Research Responsible Person (Liang Kang). The CTESC Research Committee should send the report style to each research participating unit before the study is started.

2) Based on the relevant laws and regulations, adverse events should be reported to the province (city) Health Department at the location of each research center. Severe adverse events based on clinical research-related ethical guidelines should be reported to the person in overall charge of the medical institution. The appropriate reporting procedures should be completed in accordance with the relevant provisions of all medical institutions at the same time. The person in charge of research of each research participating unit should hold accountability and responsibility for the emergency treatment of patients with any degree of adverse events to ensure patient safety.

12.3.1 Adverse Events with Reporting Obligations

12.3.1.1 Adverse Events with Emergency Reporting Obligations

The following adverse events must be reported on an emergent programmer:

1) All patients who die during the treatment or within 30 days from the last treatment day, regardless of the presence or absence of a causal relationship with the study regimen treatment. Also, cases of discontinuation of treatment, even if within 30 days

from the last treatment day, those patients are also emergent reporting objects. (“30 days” refers to day 0, the final treatment day, 30 days starting from the next day).

2) Those patients with unexpected Grade 4 non-hematologic toxicity (CTCAE v3.0 adverse events other than the blood/bone marrow group), having a causality of treatment (any of definite, probable, possible) who are emergent reporting objects.

12.3.1.2 Adverse Events with Regular Reporting Obligations

The following adverse events are regular reporting objects: a) After 31 days from the last treatment day, deaths for which a causal relationship with treatment cannot be denied, including suspected treatment-related death; death due to obvious primary disease is included; b) Expected Grade 4 non-hematologic toxicity (CTCAE v3.0 adverse events other than the blood/bone marrow group; c) Unexpected Grade 3adverse events: Grade 3 adverse events are not recorded in the 12.1 expected adverse events; d) other significant medical events: adverse events that the study group deems cause important and potentially permanent, significant impact on their offspring (MDS myelodysplastic syndrome, except for secondary cancer); Adverse events among b-d, determined to have a causal relationship (any of definite, probable, possible) with the study regimen are regular reporting objects.

12.3.2 Reporting Procedure

12.3.2.1 Emergency Reporting

1) In case of any adverse event on emergency study reporting objects, the doctor in charge will quickly report it to the Research Responsible Person of the research participating hospitals. When the Research Responsible Person of the hospital cannot be contacted, the coordinator or the doctor in charge of the hospital must assume the responsibility on behalf of the Research Responsible Person of the hospital.

2) First Reporting: Within 72 hours after the occurrence of adverse events, the Research Responsible Person of the hospital should complete the “AE/AR/ADR first emergency report” and send it to the CTESC Research Committee by fax and telephone.
3) Second Reporting: The Research Responsible Person of each research participating hospital completes the “AE/AR/ADR Report” and a more detailed case information report, and then faxes the two reports to the CTESC Research Committee within 15 days after the occurrence of adverse events. If any autopsy examination, the autopsy result report should be submitted to the CTESC Research Committee.

12.3.2.2 General Reports

The Research Responsible Person of each research participating hospital completes the “AE/AR/ADR report”, and then faxes it to the CTESC Research Committee within 15 days after the occurrence of adverse events.

12.4 Responsibilities and Obligations of Research Responsible Person/Research Committee

12.4.1 Judgment of Study Discontinuation and Necessity for Sending an Emergency Notice to the Hospital

After the receipt of the report from the Research Responsible Person of the research participating hospital, the CTESC Research Committee replies to the Research Responsible Person of the unit for confirmation and negotiation, and then they jointly determine the urgency and importance of reporting events; if necessary, they can temporarily stop the study, and contact all research participating hospitals to take emergency notification countermeasures. According to the urgency degree, the data center should contact the research participating hospitals by telephone or by fax as soon as possible after the initial contact by phone.

12.4.2 Report to CTESC Efficacy and Safety Evaluation Committee

1) After the CTESC Research Group reports adverse events in line with 11.3.1 adverse events with reporting obligations in the emergency reports or regular reports to the Research Responsible Person of research participating units and discusses and clarifies the adverse events, the CTESC Research Group should submit a report in writing to the Efficacy and Safety Evaluation Committee within 3 days after the occurrence of adverse events and request a review of the Research Responsible Person as to the suitability of analysis of the cause of the adverse events and handling of the adverse events.

2) At that time, “AE/AR/ADR First Emergency Report” and “AE/AR/ADR Report” submitted by the research participating center should include the discussion results and countermeasures of the CTESC Research Group/Research Responsible Person (including judgment on research continuation/discontinuation). For death within 30 days, treatment-related death among death after 31 days and expected Grade 4 non-hematologic toxicity, not only the course of the individual patient should be included but also whether the frequency of occurrence falls within the expected range. If the frequency of occurrence falls outside the expected range, it should be faithfully recorded in the “II classification of adverse events-others” of “AE/AR/ADR Report”.

12.4.3 Notice to the Research Participating Hospitals

1) After submitting the report to the CTESC Efficacy and Safety Evaluation Committee, the CTESC Research Group/Research Responsible person need report the review, proposal content of the CTESC Efficacy and Safety Evaluation Committee in writing to all research participating centers.

2) If failing to submit the report to the CTESC Efficacy and Safety Evaluation Committee, the CTESC Research Group/Research Responsible Person should report their judgement in writing to the Research Responsible Person of a research

participating hospital that submitted the report.

12.4.4 Discussion of Adverse Events Under Regularly Monitoring

During regular monitoring, the CTESC Research Group/Research Responsible Person should carefully discuss study adverse events in the monitoring report submitted by the research data center to confirm whether there is under-reporting of adverse events for each research participating hospital. The presence or absence of under-reporting adverse events should be clearly documented in the discussion results of [regularly monitoring report] of the CTESC Research Group.

12.5 Review of CTESC Efficacy and Safety Evaluation Committee

The CTESC Efficacy and Safety Evaluation Committee reviews and discusses the report comply with the procedures recorded in the Clinical Safety Information Management Guideline and provides recommendations in writing for the Research Responsible Person, including whether to continue to include study objects or to revise the study protocol.

13. Ethical Considerations

13.1 Responsibilities of Investigators

Responsible for the establishment of this study at their centers. Each investigator will ensure the implementation of this study comply with the study protocol and in accordance with the Declaration of Helsinki, as well as domestic and international ethical guiding principles and applicable regulatory requirements. It is especially noted that the investigators should ensure the enrolled subjects, in this study, must provide

signed informed consent form.

13.2 Information and Informed Consent of Subjects

1) An unconditional prerequisite for subjects to participate in this study is their written informed consent. The written informed consent of subjects participating in this study must be given before study-related activities are conducted.

2) The investigators should provide the information pages to subjects, and the information must in accordance with the applicable regulatory requirements. While providing written information, the investigators will orally inform the subjects of all the relevant circumstances of this study. In this process, the information must be fully and easily understood by non-professionals, so that subjects can sign the informed consent form according to their own will since their full understanding of this study.

3) The informed consent form must be signed and dated personally by the subjects and investigators. All subjects will be asked to sign the informed consent form to prove that they agree to participate in this study. The signed informed consent form should be kept at the research center where the investigator is located and must be properly safe kept for future review at any time during audit and inspection throughout the inspection period. Before participating in the study, the subjects should provide a copy of signed and dated informed consent form.

4) If important new information becomes available that may be related to the consent of the subjects at any time, the investigators will revise the information pages and any other written information which must be submitted to the Independent Ethics Committee/Institutional Review Board for review and approve. The revised information approval will be provided to each subject participating this study. The researchers will explain the changes made to the previous version of informed consent form to the subjects.

13.3 Identity and Privacy of Subjects

1) After obtaining an informed consent form, each enrolled case is assigned a unique number (ID). This number will represent the identity of the subject during the entire study and for the clinical research database of this study. The collected data of subject in this study will be stored in the ID.

2) In the entire study, several measures will be taken to minimize any breaches of personal information, including: 1) only the investigators will be able to link to the research data of the subjects to themselves through the identify table kept at the research center after authorization; 2) during onsite auditing of raw data by the supervisors of this study, as well as relevant inspection and inspection visits by the supervision departments, the personnel engaging in the above activities may view the original medical information of subjects that will be kept strictly confidential.

3) Collection, transmission, handling, and storage of data on study subjects will comply with the data protection and privacy regulations. This information will be provided to the study subjects when their informed consent is being obtained for treatment procedures in accordance with national regulations.

13.4 Independent Ethics Committee or Institutional Review Committee

1) Before beginning the study, the Research Center will be responsible for submitting the study protocol and relevant documents (informed consent form, subject information page, CRF, and other documents that may be required) to the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) to obtain their favorable opinion/approval. The favorable opinions/approval documents of the IEC/IRB will be archived in the research center folders of the investigators.

2) Before beginning the study at the center, the investigators must obtain written proof of favorable opinions/approval by the IEC/IRB, and should provide written proof of the date of the favorable opinions/approval meeting, written proof of the members

presenting at the meeting and voting members, written proof of recording the reviewed study, protocol version and Informed Consent Form version, and if possible, a copy of the minutes.

3) In case of major revisions to this study, the amendment of the study protocol should be submitted to the IEC/ IRB prior to performing the study. In the course of the study, the relevant safety information will be submitted to the IEC/IRB in accordance with national regulations and requirements

13.5 Regulatory Authority

The study protocol and all relevant documents, such as the informed consent form, will be submitted based on the Ethical Review Approach of Biomedical Research Involving Human Beings (Trial) (2007) and applicable regulatory requirements of our country or will announce the ethical review guidance counseling organization of the provincial health administrative departments at the location of each research center.

14. Organizations and Responsibilities of Study

14.1 CTESC Research Committee

1) Responsible for developing study protocol, auditing eligibility for inclusion and guiding the interpretation of informed consent; also responsible for the collection of adverse event reports, guiding the clinical diagnosis and treatment of such events and the emergency intervention of serious adverse events.

2) Person in charges of CTESC Group: Liang Kang (Colorectal surgery, The Sixth Affiliated Hospital, Sun Yat-sen University)

3) Address: 20B, No.1 Building, No.26, Yuan Cun Er Heng Road, Guangzhou, Guangdong, China, postcose: 510655; Tel: 020-38455369; Mobile Phone:

+8613602886833; E-mail: kangl@mail.sysu.edu.cn

4) Principal Investigator: Liang Kang (Colorectal surgery, The Sixth Affiliated Hospital, Sun Yat-sen University)

5) Address: 20B, No.1 Building, No.26, Yuan Cun Er Heng Road, Guangzhou, Guangdong, China, postcose: 510655; Tel: 020-38455369; Mobile Phone: +8613602886833; E-mail: kangl@mail.sysu.edu.cn

6) Center invited by the CTESC group to participate in this study:

Num.	Enrollment sites	investigator	Location
1	Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University	Liang Kang	Guangzhou, Guangdong
		Jianping Wang	Guangzhou, Guangdong
2	Department of Colorectal Surgery, Shengjing Hospital of China Medical University	Hong Zhang	Shenyang, Liaoning
3	Department of Gastrointestinal Surgery, The Second People's Hospital of Yibin	Miao Wu	Yibin, Sichuan
4	Department of Gastrointestinal Surgery, The Affiliated Nanchong Central Hospital of North Sichuan Medical College	Mingyang Ren	Nanchong, Sichuan
5	Department of General Surgery, Daping Hospital, Army Medical university	Weidong Tong	Chongqing
6	Department of General Surgery, Xinqiao Hospital, Army Medical university	Dan Ma	Chongqing
7	Department of Gastrointestinal Surgery, The First Hospital of Jilin University	Quan Wang	Changcun, Jilin
8	Department of Gastrointestinal Surgery, Affiliated Hospital of Zunyi Medical University	Ming Xie	Zunyi, Guizhou
9	Department of Gastrointestinal Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University	Qing Xu	Shanghai
10	Department of Gastrointestinal Surgery, The First Affiliated	Jun Ouyang	Hengyang, Hunan

	Hospital of University of South China		
11	Department of General Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences	Yi Xiao	Beijing
12	Department of Gastrointestinal Surgery, The First Affiliated Hospital of Xi'an Jiaotong University	Yongchun Song	Xian, Shaanxi
13	Department of Gastrointestinal Surgery, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University	Bo Feng	Shanghai
14	Department of Gastrointestinal Surgery, The Affiliated Hospital of Guangdong Medical University	Qingwen Xu	Zhanjiang,Guangdong
15	Department of Gastrointestinal Surgery, Nanfang Hospital, Southern Medical University	Yanan Wang	Guangzhou, Guangdong
16	Department of Gastrointestinal Surgery, The Third Xiangya Hospital of Central South University	Yi Zhang	Changsha, Hunan

Chief statistical expert of CTESC group: Yuantao Hao (Sun Yat-sen Global Health Institute, Sun Yat-sen University).

7) CTESC Group office

Contact persons: Huashan Liu, Ziwei Zeng, Shuangling Luo, and Liang Kang

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14.2 CTESC Efficacy and Safety Evaluation Committee

Responsible for the supervision of treatment safety and efficacy of this study.

14.3 CTESC Data Center

1) Participates in the design of this study protocol, being responsible for data analyses and statistical explanations and issuing of statistical reports.
2) Responsible for the formulation and provision of CRFs and eCRF (web-based electronic case reports forms, www.cntatme.com) and management, storage of research data and maintenance of database.
3) Person in charge of CETSC Data Center: Professor Yuantao Hao (Sun Yat-sen Global Health Institute, Sun Yat-sen University)

14.4 Data and Safety Monitoring Board

Responsible for the supervision of efficacy, safety of this study, supervising all aspects of study performance, validation, and approval before release of study results.

14.5 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

1) Responsible for evaluating this study to determine if risks to which subjects are exposed have been duly minimized and whether these risks are reasonable compared to expected benefits
2) The independent Ethics Committee/Institutional Review Board (IEC/IRB) at the location of each research participating center is responsible for the ethics review of all research participating units.

15. Special Matters

None.

16. Publication of Research Results

1) The publication of research results need be done on a timely manner in keeping with the principles stated in this study protocol.
2) Results and conclusions originated from the main statistical analysis and from the other statistical analyses can be published in journals after obtaining approval from the CTESC Efficacy and Safety Evaluation Committee. Manuscripts that do not contain data of patients from the trial, such as a protocol of the trial, only need consent from the person in charge of the CTESC Data Center.
3) Regarding the authorship of the main published paper related to the trial results: the main authorship belongs to the CTESC Group, followed by the research representative, and the person at the Data Center in charge of statistical analysis for the target of publication. The remaining authorship will be allocated according to contribution rules. In the order of respective sample size registration, the Research Responsible Investigator of all research participating hospitals are listed as co-authors. All co-authors must review the paper and agree to publish it before the paper is submitted to the journal. Every investigator reserves the right that choose not to be listed as co-author in particular publications.
4) If an investigator plans to conduct secondary analyses or analyses for other research aims based on the overall collected data in this study, the investigator must acquire approval from the CTESC Group. An investigator is willing to use data from this study in presentation or other conditions should mention the data resource and inform the CTESC Group.
5) The publication of assumption-related research results aiming at the main research

purpose should be completed by the person in charge of research. The publication of assumption-related research results aimed at the secondary research purpose or secondary analytic research results of control data may be negotiated by the person in charge of research participating units of this research organization but must obtain the permission of the person in charge of research.

6) The persons managing the research units are the custodians of their own single-center data and should obey privacy rules: the relevant responsibilities for the results, form and content of published single-center data should be self-borne by the person managing the publication center. Nonetheless, the CTESC Group does not assume any responsibility; the used of single-center data must be informed to the CTESC data center who has to provide approval of accuracy; the statistical analysis of single-center data should be marked as from this study of CTESC in order to avoid repeat inclusion at the time of system analysis.

7) Without the consent of both the CTESC Group and the CTESC Data Center, investigators beyond those in the CTESC Group cannot directly obtain the overall data and results of statistical analysis of this study from the data center.

17. Annex

17.1 Informed Consent Form

Title: Surgical Safety and Efficacy of Transanal Versus Laparoscopic Total Mesorectal Excision for Rectal Cancer: A Randomised, Open-label, Phase 3, Non-inferiority Trial

(TaLaR Trial)

Statistical Analysis Plan

Authors: Yuantao Hao, Huashan Liu, Ziwei Zeng, Liang Kang

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Primary Rationale for Amendment:

There was no amendment for the statistical analysis plan in TaLaR Trial.

Abstract

Background: The prospective randomized controlled multicenter clinical trial (TaLaR Trial) is a large-scale investigation of the surgical efficacy and safety of transanal versus laparoscopic total mesorectal excision for rectal cancer.

Objective: To outline in detail and make public the pre-determined statistical analysis plan (SAP) for the main analyses of TaLaR for the primary report of the trial results, and outline subsequent key publications. The SAP was finalized before completion of data collection and is what investigators will adhere to in analyzing data.

Methods: All data collected by participating researchers will be reviewed and formally assessed. Information pertaining to the baseline characteristics of patients will be selected and for each item statistically relevant descriptive elements are described. Information relevant to the transanal and laparoscopic total mesorectal excision groups is classified and, for each item, descriptive statistical analyses are planned for comparisons between the randomised two groups. Finally, for the trial outcomes that are classified as primary, secondary, the most appropriate statistical comparisons to be made between groups are described.

Results: A SAP has been developed for the results of the TaLaR study. This plan will allow a comprehensive description of baseline characteristics, features of the trial treatments, along with pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before completion of data collection.

Conclusions: We have developed a pre-determined SAP for the TaLaR study which is to be followed, once data are complete, to avoid analysis bias arising from prior knowledge of the study findings.

Trial registration: NCT02966483

Table of Contents

1. Background

About 704,000 patients per year are diagnosed with rectal cancer globally [CA Cancer J Clin. 2015;65(2):87-108]. Total mesorectal excision (TME) was first highlighted in the 1980s by Heald and Ryall [Br J Surg. 1982; 69(10):613-6; Lancet. 1986; 1(8496):1479-82] due to its significant contribution to reducing local recurrence. The procedure has been considered the standard surgical technique for rectal cancer since then.

Along with the development of minimally invasive techniques, laparoscopy has become common practice in colorectal surgery for decades. Even though controversy still exists, laparoscopic TME (lapTME) has been proven to achieve similar resection quality and oncological outcomes compared with open TME (opTME) in several clinical trials. Laparoscopic surgery proved feasible and safe in the COREAN trial; moreover, this procedure has some short-term benefits for patients compared with open surgery, especially those with middle or low rectal cancer who have been treated with neoadjuvant chemoradiotherapy [Lancet Oncol. 2010; 11(7):637-45]. In addition, the COLOR II trial reported no statistically significant differences for treating high- or middle-rectal-cancer patients with either lapTME or opTME, but lapTME had advantages for low-rectal-cancer patients [Lancet Oncol. 2013; 14(3):210-8]. It is also worth noting that, when comparing lapTME with opTME, the former can reduce the operative wound, enhance patient recovery, and reduce wound-related complications [N Engl J Med. 2015; 373(2):194]. As a result, lapTME has become common over the past few decades.

However, it remains difficult to acquire complete TME with a safe surgical margin by conventional transabdominal methods in obese male patients with low rectal cancer have undergone neoadjuvant treatment and have a narrow pelvic floor, etc. [Lancet Oncol. 2010; 11(7):637-45; N Engl J Med. 2015; 373(2):194; Br J Surg. 2009; 96(9):982-9]. In order to tackle these issues, transanal total mesorectal excision (taTME) was introduced by Sylla et al. [Surg

Endosc. 2010; 24(5):1205-10]. The feasibility, safety, and advantages of this method have been verified by more recent studies, and it has become a hot topic for rectal cancer both in the literature and at conferences [Surg Endosc. 2010; 24(5):1205-10; Tech Coloproctol 2015; 19:57–61; J Am Coll Surg 2015; 221:415–23]. Theoretically, taTME could achieve better pathological outcomes than lapTME, as it provides better vision to mobilize the distal rectum. Thus, taTME may result in a better oncological outcome for patients [Ann Surg 2015;261:234–6]. However, taTME is still in the early stages of development and the desired or expected oncological outcomes have yet to be achieved before it can become the standard technique for rectal-cancer treatment.

The Chinese Transanal Endoscopic Surgery Collaborative (CTESC) group performed a series of retrospective investigations regarding the feasibility, learning curve, safety, and oncologic outcomes of taTME for rectal cancer. These studies suggested that taTME could be considered by skilled surgeons and achieve satisfactory oncologic radicality. To further determine the suitability of taTME for patients with rectal cancer, a phase 3, open-labelled, multicentre, noninferiority RCT was launched by the CTESC group in April 2016. The trial (transanal versus conventional laparoscopic TME for rectal cancer [TaLaR]) aimed to assess the surgical safety and oncological outcomes of taTME versus laTME in patients with rectal cancer (NCT 02966483).

2. Study design

2.1 Overview

The TaLaR study is a prospective, multicentre, randomised, parallel positive control, open labelled clinical trial that compares the long-term outcomes between taTME and laTME in patients with clinical stage I-III rectal cancer below peritoneal reflection. The study is registered (ClinicalTrials.gov, NCT02966483) and the first patient was randomised on April 13, 2016.

The primary aim of the TaLaR study is to compare the 3-year disease-free survival (DFS) and 5-year overall survival (OS) of taTME versus laTME. The treatment according to pre-defined treatment protocols. The null hypothesis is that the taTME is non-inferiority against the laTME for the patients with clinical stage I-III rectal cancer below peritoneal reflection in the 3-year DFS and 5-year OS.

2.2 Patient population

The inclusion/exclusion criteria are kept simple and broad to allow the inclusion of patients with a wide range of characteristics. This not only facilitates recruitment and data collection in a large number of patients as part of routine care, but it also improves the external validity of the results.

2.2.1 Inclusion criteria

Patients are eligible for inclusion in the study if all of the following criteria are met.

1) Age older than 18 and younger than 75 years

2) Patient eligible for surgery, with American Society of Anesthesiologists class I-III

3) Primary rectal cancer below peritoneal reflection, with clinical stage I-III based on the 7th edition of the American Joint Committee on Cancer staging system

4) Pathologically confirmed rectal adenocarcinoma before surgery

5) Patients are suitable for a sphincter-sparing procedure

6) Expected curative resection via TME

7) Written informed consent

2.2.2 Exclusion criteria

Patients are excluded from the study if one or more of the following criteria are present.

1) T1 tumors that can be locally resected

2) Involvement of the circumferential resection margin as indicated by MRI or CT scan

3) Tumors with ingrowth in the internal sphincter or levator ani

4) Previous rectal surgery or pregnancy

5) Absolute contraindications to general anesthesia or prolonged pneumoperitoneum

6) Signs of acute intestinal obstruction or synchronous abdominal surgery

7) Having a medical history of FAP, active IBD, or other carcinomas within 5 years

8) Any psychological, familial, sociological, or geographical conditions that could hamper compliance with the study protocol or the follow-up schedule

2.3 Randomization

The study will use a central, dynamic, and stratified randomization method. Randomization is stratified by centers. Upon receipt by research participating centers of an [eligibility confirmation notice], the designated person is responsible for immediately sending the selected patient information (institution) to the randomized

enforcement department of the data center. The central randomization department will determine the enrollment of cases after analyzing the case information and will immediately inform the research center. All the patients are blinded to the surgical approach that they are going to receive and will be required to sign the informed consent before being enrolled in the study.

Central randomization is achieved via a password-protected web-based program operated from the Sixth Affiliated Hospital of Sun Yat-sen University in Guangzhou China.

Seventeen surgical teams at 16 institutions (as follows) in China are included.

1) Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China (Liang Kang MD, Huashan Liu MD, Ziwei Zeng MD, Jianping Wang MD, Xingwei Zhang MD, Shuangling Luo MD, Liang Huang MD, Xiaobin Zheng MD, Yanping Liu, Zijun Huang, YuJie Hou MD, Zhanzhen Liu MD, Yonghua Cai MD, Sicong Lai MD, Huanxin Hu MD, Ping Lan MD, Zuli Yang MD, Junsheng Peng MD, Xiaojian Wu MD, Donglin Ren MD, Meijin Huang MD)

2) Department of Colorectal Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China (Hong Zhang MD, Dingsheng Liu MD, Jinchun Cong MD)

3) Department of Gastrointestinal Surgery, The Second People's Hospital of Yibin, Yibin, Sichuan, China (Miao Wu MD, Mengyin Peng MD, Xian Liu MD)

4) Department of Gastrointestinal Surgery, The Affiliated Nanchong Central Hospital of North Sichuan Medical College, Nanchong, Sichuan, China (Mingyang Ren MD, Xuanhua Yang MD, Dongbing Zhou MD)

5) Department of General Surgery, Daping Hospital, Army Medical university, Chongqing, China (Weidong Tong MD, Yue Tian MD, Jingwang Ye MD)

6) Department of General Surgery, Xinqiao Hospital, Army Medical university, Chongqing, China (Dan Ma MD, Guoqing Chen MD, Jianghong Chen MD)

7) Department of Gastrointestinal Surgery, The First Hospital of Jilin University,

Changchun, Jilin, China (Quan Wang MD, Meng Li MD, Jiaxin Zhang MD)

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10) Department of Gastrointestinal Surgery, The First Affiliated Hospital of University of South China, Hengyang, Hunan, China (Jun Ouyang MD, Ling Zhan MD)

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16) Department of Gastrointestinal Surgery, The Third Xiangya Hospital of Central South University, Changsha, Hunan, China (Yi Zhang MD, Kai Gao MD)

2.4 taTME and laTME groups

taTME group: Patients allocated to the taTME group are commenced on a transanal surgery according to the TME principles. In patients undergoing taTME, the transanal endoscopic device was used for rectal mobilization, and the rectum and mesorectum resection in a “bottom-to-up” fashion. The taTME procedures were

permitted to be done by one team (the transabdominal phase followed by the transanal phase was performed by one surgical team) or two teams (with separate transabdominal and transanal teams operating at the same time).

laTME group: Patients allocated to the laTME group are commenced on a conventional laparoscopic TME procedure according to the TME principles. In patients undergoing taTME, the procedures of vascular ligation, colonic mobilization, and anterograde total mesorectal excision with a nerve-sparing dissection were performed in a ‘‘up-to-down’’ manner.

2.5 Baseline and follow-up assessments

All responsible investigators receive training in the data collection systems and Good Clinical Practice (GCP), and training in the assessment scales if they have had no certification prior to participation. Each collaborating site is required to complete the online screening log, for a randomly assigned calendar month in each participating year, of all patients presenting with a diagnosis of clinical stage I-III rectal cancer below peritoneal reflection who are considered for the study but are subsequently excluded. The screening log records each patient’s initials and date of admission together with a brief description of the main reason as to why he or she was not randomised. The log is used to monitor recruitment and identify specific barriers to randomisation of eligible patients.

A detailed list of the assessment schedule is contained in the TaLaR protocol and clinical site manuals. Briefly, once informed consent has been obtained, the responsible registered clinician is able to randomize a patient through the secure web-based system after eligibility is confirmed and data are entered for admitting hospital. Socio-demographic and clinical history are then recorded on a baseline form. All data on clinical status, treatment and care are recorded prospectively on special prepared

worksheets, and subsequently transferred to electronic data capture (EDC) system on the database. All patients are followed every 3 months for the first year, every 6 months for the second year, and annually thereafter, unless death occurs earlier.

The hospital coordinator at each collaborating site ensures that all data are completed in a timely manner. Patients who do not receive the allocated randomised treatment or do not follow the protocol are still followed up and analyzed by the 'modified intention to treat' (mITT) principle. Data collection is kept to a minimum to ensure rapid enrolment and follow-up of patients within the context of routine clinical practice.

2.6 Sample size estimation

The sample size was calculated using PASS software. Sample-size calculation of this trial was on the basis of three-year disease-free survival (DFS) and five-year overall survival (OS); but the sample size according to five-year OS was larger than that based on three-year DFS. The three-year DFS and five-year OS among patients with clinical stage I-III rectal cancer treated with laTME were assumed to be 74·6% and 77·4%, respectively. According to a log-rank test with an α error of 2·5% (in a two-sided test), power of 80%, and a non-inferiority margin of 10%, at least 610 and 910 patients would be required to sufficiently declare taTME noninferior to laTME in three-year DFS and five-year OS, respectively. Assuming a dropout rate of 20%, a total of 1114 patients were planned to enroll for this trial.

2.7 Unblinding

Treatment allocations are open labelled in this study.

2.8 Definitions of the outcomes

2.8.1 Primary outcome

The primary outcomes were 3-year DFS and 5-year OS.

Disease-free survival (DFS) is defined as the time from intervention to disease or death of any cause, and it is censored at the last day when the patient is alive without any evidence of disease. If there is no follow-up data on death or a tumor recurrence event, the final date of no relapse should be confirmed (eventually relapse-free survival confirmation date: the outpatient day or the last date to accept the inspection) as the termination point.

The Overall survival (OS) is defined as the time from intervention to the date of death of any cause or last follow-up. In case of inability to follow-up, the last date of survival should be confirmed.

As loss to follow-up is expected to be minimal, missing values will not be imputed for the primary analysis. And we will undertake a secondary analysis for the primary outcomes using survival data methods. A sensitivity analysis will also be undertaken of the primary outcomes adjusted by key prognostic covariates. Where appropriate, data will be summarized by an odds ratio (OR) and 95% confidence intervals (CI), and for secondary analysis hazard ratio (HR) will be used.

2.8.2 Secondary outcomes

Secondary outcomes will include the following.

1) Morbidity and mortality rates within 30 days after the treatments.

Morbidity was defined as intraoperative or postoperative surgical complications. Postoperative complications will be stratified according to the Clavien-Dindo

classification. Mortality was defined as death from any cause within 30 days after surgery. The morbidity and mortality rates were calculated by dividing the number of affected patients by the total number of recruited patients based on the modified intention-to-treat principle.

2) Pathologic outcomes

The resected specimen must be inspected fresh in the pathology department or operating room of each participating institution. The pathologist should not be informed of the patient's treatment assignment. Surgeons will measure fresh, unstretched proximal and distal margins in the operating room. The completeness of the TME resection will be evaluated by the pathologist. Pathologists should make every effort to identify at least 12 lymph nodes in the surgical specimen. Efforts to locate lymph nodes (e.g., defatting) should be included in the pathology report. The mesorectal specimen must be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs will be submitted for review by the CTESC Research Committee as part of the pathology review that is required for all registered patients. The CTESC Research Committee will review pathologic case report forms, pathology reports and photographic images of the TME specimen for all registered patients. Reports of pathologic outcomes will include the total mesorectal excision quality, circumferential resection margin, distal resection margin, number of harvested lymph nodes and number positive, length from the inferior of tumor to distal resection margin, length of resected sample, lymphovascular invasion, and nerve invasion, pathology stage, tumor differentiation and tumor types. The CTESC Research Committee will evaluate the reports and provide education for failure to meet minimal standards of the pathology evaluation with potential site closure if minimal standards cannot be met.

A complete TME is defined as a rectal resection specimen that has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transection with no coning in of the mesorectum above the point of transection. The

surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat. A nearly complete TME is defined as a rectal resection specimen where the mesentery is all present, without coning or missing fat. A < 5 mm deep defect may be present in the envelope covering the mesenteric fat caused either by a wayward incision or traction injury during extraction of the TME specimen through a small extraction site.

The involvement of the circumferential resection margin (CRM) was considered if the distance was ≤1 mm from the tumor to the mesorectal fascia.

A positive distal resection margin (DRM) was defined if the distance between the closest tumor to the cut edge of the tissue was ≤1 mm.

A successful resection for the trial was the adequacy of the surgical approach determined by three oncological parameters: negative distal resection margins (DRM, >1 mm between the closest tumor to the cut edge of the tissue), negative circumferential resection margins (CRM, >1 mm between the deepest extent of tumor invasion into the mesorectal fat and the inked surface of the specimen), and “complete” TME specimen or “nearly complete”. A patient will be considered to have a successful resection on either arm if and only if the 3 parameters (distal margin, circumferential radial margin, and total mesorectal excision quality [complete or nearly complete]) are satisfied.

3) Delayed Complications

Delayed Complications are defined as complications occurring >30 days after surgery. Any delayed complications such as bowel obstruction will be monitored and reported on data forms. Details of hospital admissions will be recorded in the patient ‘s records, including dates, location, and admitting physician’s name. The reason for admission‖ will provide guidance as to whether the hospitalization was related to the

cancer diagnosis and surgery or for other reasons.

4) 3-year OS

The 3-year OS is defined as the time from intervention to the date of death of any cause or last follow-up.

5) 3-year recurrence pattern

The appearance of rectal carcinoma in the primary site, nodal basin or distant organ sites during follow-up will be classified as recurrent cancer. Recurrence will be classified into three categories at the time of first diagnosis: local, distant, and mixed type. Suspected tumor recurrence within the surgical field should be documented histologically or cytologically. Pathological documentation of suspected distant metastasis is also recommended. The summary of local recurrence-free survival, disease-free survival and overall survival will be summarized graphically. Appropriate imaging should be used to document extent of disease (PET/CT, CT, MRI).

6) Postoperative recovery course

Time to first flatus, time to first intake, time to ambulation and duration of hospital stay are used to assess the postoperative recovery course, and the amount of drainage and blood transfusion are also recorded.

7) Functional surgery outcome and quality of life

Postoperative quality of life was tested by EORTC QLQ-CR38 and EORTC QLQ-C30 questionnaires, and anal function was assessed by LARS and Wexner questionnaires. Functional surgery outcome and quality of life will be evaluated at 3-, 6-, 12-, and 24-months post operation.

2.8.3 Safety variables

Intra- and post-operative complications are the main adverse event and safety issue. The morbidity and mortality were examined in the first 30 days after surgery. Any documented medical or anesthetic complications that result in patient disability or that requires intervention will be recorded. Intraoperative complications were defined as unexpected surgical adverse events occurring during surgery (eg, iatrogenic injury of the blood vessels, bowel, or other organs; haemorrhage; CO_2 embolism; or Subcutaneous emphysema). Correction of preoperative anemia will not be included as a complication. The decision to transfuse will be made at the surgeon's discretion. Vascular injury was defined as laceration or break of the presacral vessels. Intraoperative haemorrhage was defined as blood loss of more than 200 mL in the absence of vascular injury. CO_2 embolism was defined as an abrupt decrease in end-tidal CO_2 and oxygen saturation in the setting of venous bleeding. Any diagnosis on intraoperative complications will be made by the surgeons based on the intraoperative situation and our trial protocol, and reviewed and confirmed by the CTESC Research Committee according to the unedited surgical videos.

Post-operative complications were recorded as follows: Anastomotic leakage; Anastomotic bleeding; Intestinal obstruction; Uroschesis; Incisional infection; Abdominal/pelvic infection; Deep vein thrombosis; Pulmonary embolism; Cerebral infarction; Lymphatic leakage; and Others. Diagnosis on any specific postoperative complication was established according to the specific image-based physical examinations, laboratory evaluations, or significant clinical manifestations. Once a specific complication was diagnosed, the severity was assessed according to the Clavien-Dindo classification. The diagnosis on any post-operative complications will be reviewed and confirmed by the CTESC Research Committee according to the available evidence (including specific image-based physical examinations, laboratory evaluations, or significant clinical manifestations).

1) Anastomosis-related complications (leakage, stenosis, or bleeding) were confirmed

by intestinal X-ray imaging, endoscopy, or angiography. Anastomotic leakage was defined as clinical evidence of a defect of the integrity of the intestinal wall at the anastomotic site. 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 for anastomotic leakage were confirmed by digital rectal examination, computed tomography (CT) scan, or surgery when necessary. Anastomotic bleeding was defined as clinically significant rectal bleeding, active and continuous fresh blood from the drain with a drop in hemoglobin for which no other cause was established.

2) Postoperative intraperitoneal hemorrhage was defined as an amount of hemorrhage exceeding 200 mL.

3) Abdominal/pelvic/incisional or other organ infections will be defined by the need for antibiotic treatment and/or drainage. Abdominal/pelvic infection was proven by ultrasonography or computed tomography examination and resulted in a systemic inflammatory response for at least 24 hours. Incisional infection is defined as an infection that occurs within 30 days after the operation and involves the skin/subcutaneous tissue and deep soft-tissue infection of the incision. The criteria for diagnosis of incisional infection include at least one of the following signs or symptoms: redness, heat, pain or tenderness, localized swelling and purulent drainage.

4) Intestinal obstruction will include primary ileus and secondary ileus. Primary ileus will be defined as the condition of bowel dysfunction (NPO status) that occurs for greater than 10 days following surgery or that requires intervention including nasogastric tube, surgery, medication, etc. Secondary ileus will be defined as bowel dysfunction that occurs in a patient that had been taking enteral nutrition, but that subsequently requires NPO status.

5) Uroschesis will be defined as the condition of urinary dysfunction that occurs for greater than 5 days following surgery or that requires intervention, including replacement of Foley catheter, surgery, etc.

6) Lymphatic leakage was confirmed with a chyle test when abdominal drainage fluid exceeded 200 mL daily for 5 continuous days after postoperative day 3.

7) Deep vein thrombosis is manifestations of venous thromboembolism, and develops most often in the legs, the deep veins of the arms, and the splanchnic veins. Clinical manifestations of deep vein thrombosis include swelling or pitting oedema, redness, tenderness, and presence of collateral superficial veins. The diagnostic work-up of suspected deep vein thrombosis includes the sequential application of a clinical decision rule and D-dimer testing. All suspected deep vein thrombosis should be confirmed by compression ultrasonography or CT venography.

8) Pulmonary embolism is manifestations of venous thromboembolism. Signs and symptoms of pulmonary embolism comprise sudden onset of dyspnoea or deterioration of existing dyspnoea, chest pain, syncope or dizziness due to hypotension or shock, haemoptysis, tachycardia, or tachypnoea. All suspected pulmonary embolism should be confirmed by CT pulmonary angiography, or MRI or single-photon emission CT.

9) Postoperative cerebral infarction was defined as a diffusion-weighted imaging high-intensity lesion with or without symptoms. Any cerebral infarction should be confirmed by CT, MRI, MR angiography (MRA), or by carotid and cardiac ultrasonography.

10) Other sequelae as reported by clinicians.

2.8.4 Quality of Life

The impact of the disease and surgery on patient quality of life (QOL) will be evaluated after randomization, and before surgery. These data will serve as our baseline data. Subsequent assessments will be collected post-operatively at 3-, 6-, 12-, and 24-months. We will gain information about long term impact on QOL. Not only will we be able to compare these different impacts on QOL between these two treatments, we will be able to gain knowledge about potential interventions to improve QOL for patients in this population. Postoperative quality of life was tested by EORTC QLQ-CR38 and C30 questionnaires. QOL questionnaires for all patients should be completed as required in the Study Calendar, regardless of surgical outcome and/or conversion to open laparotomy. Questionnaires may be completed at any time during the day in the clinic, or they may be taken home by the patient for completion and then returned.

2.8.5 Postoperative anal function

The impact of the disease and surgery on anal function will be evaluated after randomization, and before surgery. These data will serve as our baseline data. Subsequent assessments will be collected post-operatively at 3-, 6-, 12-, and 24-months. We will gain information about long term impact on anal function. Not only will we be able to compare these different impacts on anal function between these two treatments, we will be able to gain knowledge about potential interventions to improve anal function for patients in this population. P Postoperative anal function was tested by LARS and Wexner questionnaires. LARS and Wexner questionnaires for all patients should be completed as required in the Study Calendar, regardless of surgical outcome and/or conversion to open laparotomy. Questionnaires may be completed at any time during the day in the clinic, or they may be taken home by the patient for completion and then returned.

3. Funding

This study was supported by grants from the Sun Yat-sen University Clinical Research 5010 Program (2016005).

4. Statistical analysis

4.1 Analysis principles

1) Analyses will be conducted on an intention-to-treat (ITT) analysis. If applicable, a per-protocol analysis will be carried out.
2) All tests are two-sided; the nominal level of type I error will be 5% and the confidence level for all confidence intervals will be 95%.
3) The primary analysis of the primary outcomes will be unadjusted except for centre variable. All other statistical analyses will be unadjusted, except where indicated.
4) Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcomes.
5) There will be no imputing of missing values, unless specified. The number of observations used in an analysis will be reported. Last observations will not be carried forward and multiple imputation will not be used.
6) Data were coded and entered using electronic data capture (EDC) system on the database.
7) Analyses will be conducted primarily using SAS 9.3 software (SAS Institute, Cary, NC).

4.2 Data sets analyzed

The intent-to-treat data set (ITT set) will be constituted of all patients randomized

in the study without exclusion and the analysis conducted according to the ITT principle. The modified intent-to-treat set (mITT set) will be constituted of the subset of ITT set with at least one available primary or secondary outcome after the treatments. This will be used to assess the morbidity, mortality, and pathologic outcomes of taTME vs laTME. If applicable, the per-protocol data set (PP set) will be constituted of all randomized patients who fulfil the protocol in terms of the eligibility, interventions, and outcome assessment.

4.3 Interim analyses

There were no planned interim analyses for 3-year DFS and 5-year OS. The first formal interim analyse was planned when approximately 50% of the patients were enrolled and followed up for 30 days were planned for the secondary outcome of morbidity and mortality rates, as well as pathologic outcomes. The second formal interim analyse was planned when 100% of the patients were enrolled and followed up for 30 days were planned for the secondary outcome of morbidity and mortality rates, as well as pathologic outcomes.

Because the present study is open labelled, the independent Data and Safety Monitoring Board (DSMB) were not organized to keep the data unblinded during interim analyses conduct. Besides the interim analyses weren't designed for the primary outcomes, so the type I error were not adjusted in the samples size estimation and for the final analysis. The study was not terminated early.

4.4 Dates, vital status, elimination criteria and consent-related issues

The study is conducted at sites with experienced clinicians. Regionally-based experienced clinical research monitors performed online and on-site data verification. Site monitoring was undertaken, initially after the first few patients were randomized

at a site, and thereafter according to number of patients recruited during the course of the trial. As this is an open trial of differing management strategies in a critical illness, monitoring serves to confirm that investigators are adhering to the protocol and Good Clinical Practice (GCP) Guidelines, and should improve the accuracy of the data obtained. Site monitoring aims to confirm: (i) eligibility; (ii) demographic and consent details on all randomised patients; (iii) details of all SAEs against source documents; (iv) collect/correct any outstanding/missing data; and (v) check selected variables against source medical documents in a 10% random selection of patients.

Inconsistencies in key data points, vital status at final follow-up, dates and details of any deaths are queried by the DSMB to limit the number of errors and missing values. Due to the specific circumstances surrounding emergency care research it may not always be possible to obtain consent from either the patient or next of kin without delaying the initiation of treatment. In the situation where a patient is unable to give consent and a next of kin or other person responsible is not available or cannot be contacted, and with approval of the local ethics committee, clinicians may enroll eligible patients and inform the patient or their person responsible for the patient as soon as possible so that delayed consent can be requested. The reasons for being unable to obtain prior consent will be documented, dated, and signed in the patient's file. If the patient should die or continue to be unable to give informed consent at the end of the follow up period, the next of kin or person responsible should be approached to obtain delayed consent. In the case of a patient's death, the site Principal Investigator will use discretion on a case-by-case basis before contacting the next of kin or surrogate, in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or person responsible consent will be documented in the patient's file.

Some important situations can lead to cessation of the study treatment:

1) Intra- or postoperative examine reveals metastasis (M1) and / or cytology positive

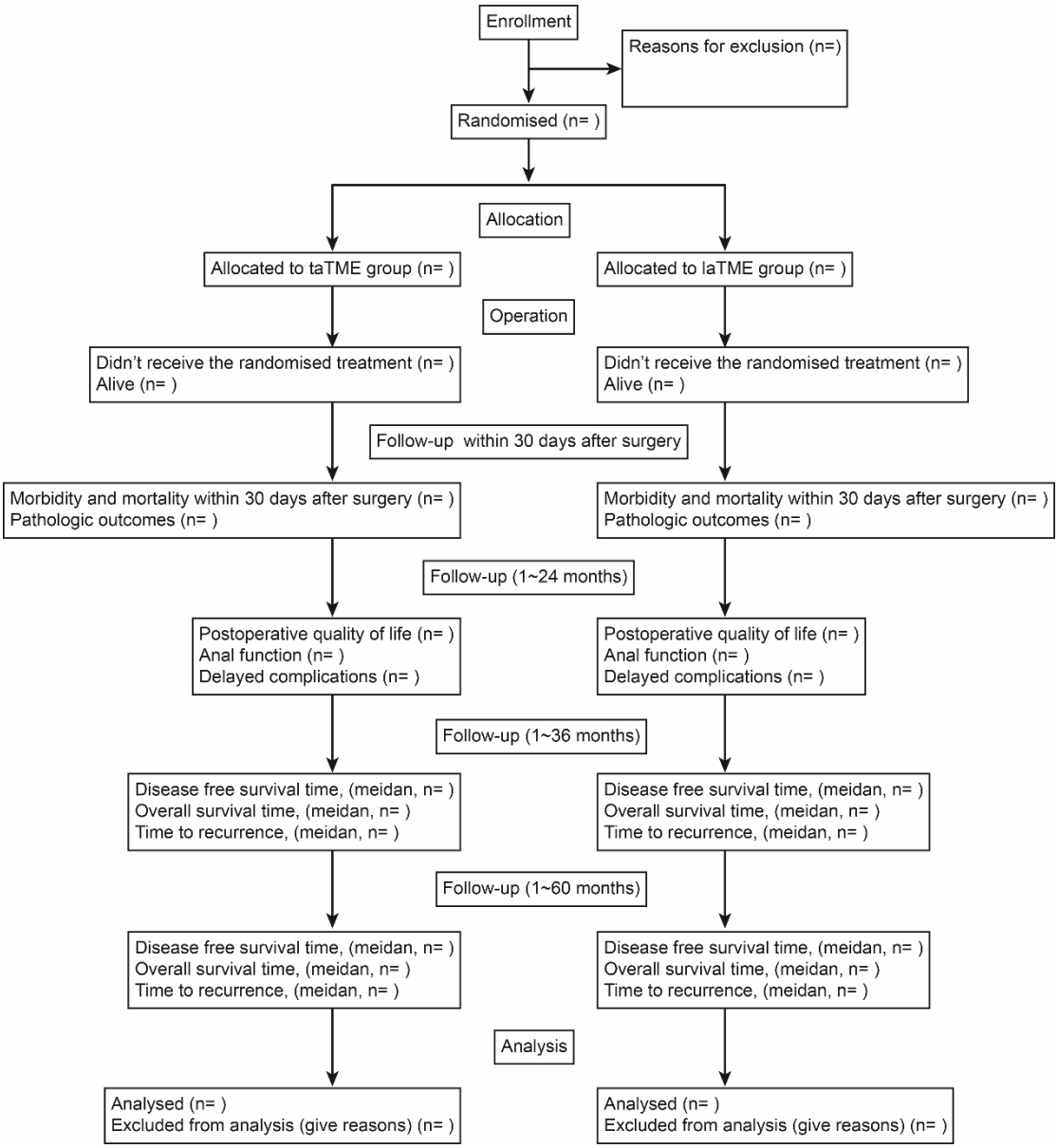
2) Any situation that could result in impossibility of R0 resection
3) A sphincter-sparing procedure cannot be done
4) Emergency situation (intolerance to surgery or anesthesia) after enrollment
5) Requirement of performing emergency surgery after enrolment
6) Withdrawing the study due to patient's personal reasons after enrollment
7) Proved to have violated the protocol

In all cases, the study treatment will cease, and the patient will receive appropriate treatment as determined by the attending clinician. The information sheet provided to the patient and/or the next of kin or surrogate clearly states that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal is documented in the patient's file. If withdrawal of consent relates to the treatments alone, data collection can continue on documentation of this fact in the patient's files. If consent for use of all data is withheld, the patient's data will be removed from the analysis, except for data related to consent. If consent for future study inclusion is withdrawn, the patient's data will be included up to the date the consent was withdrawn. Censoring dates will be used only in case of 'real' loss to follow-up, such that the date of censoring will be the last day of contact, or the date of hospital discharge if no other information is available.

4.5 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram (See the Figure below). The report will include the number of screened patients who met the inclusion criteria and the number included, and reasons for exclusion of non-included patients. In addition, the number of patients randomised outside the time window and other significant protocol deviations will be provided.

Figure: TaLaR Flow Diagram based on CONSORT 2010


Enrollment
Reasons for exclusion (n=)
Randomised (n=)
Allocation
Allocated to taTME group (n=)
Allocated to laTME group (n=)
Operation
Didn't receive the randomised treatment (n=)
Alive (n=)
Didn't receive the randomised treatment (n=)
Alive (n=)
Follow-up within 30 days after surgery
Morbidity and mortality within 30 days after surgery (n=)
Pathologic outcomes (n=)
Morbidity and mortality within 30 days after surgery (n=)
Pathologic outcomes (n=)
Follow-up (1~24 months)
Postoperative quality of life (n=)
Anal function (n=)
Delayed complications (n=)
Postoperative quality of life (n=)
Anal function (n=)
Delayed complications (n=)
Follow-up (1~36 months)
Disease free survival time, (meidan, n=)
Overall survival time, (meidan, n=)
Time to recurrence, (meidan, n=)
Disease free survival time, (meidan, n=)
Overall survival time, (meidan, n=)
Time to recurrence, (meidan, n=)
Follow-up (1~60 months)
Disease free survival time, (meidan, n=)
Overall survival time, (meidan, n=)
Time to recurrence, (meidan, n=)
Disease free survival time, (meidan, n=)
Overall survival time, (meidan, n=)
Time to recurrence, (meidan, n=)
Analysis
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)

4.6 Patients characteristics and baseline comparisons

Description and statistical inference of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data is available. If missing values are ≥5%, the denominator will be added in a footnote in the corresponding summary table. In some instances, frequencies and percentage of patients in the category will be reported as further indicated in the tables. Continuous variables will be summarized by use of standard measures of central tendency and dispersion, either mean and standard deviation [Mean ± SD], or median and 25%, 75% quartiles [Median (IQR). Durations will also be summarized by medians and IQR.

Statistical inference of normally distributed continuous variables was performed using t-tests; non-normally distributed continuous variables were analyzed using Wilcoxon rank-sum tests. Categorical variables were expressed as numbers (percentages), and were analyzed by Fisher's exact test or χ^2 test as appropriate. Baseline measures for all patients will be tabulated for the following variables: demographics and pathological characteristics.

4.7 Operation details and postoperative recovery course

Operation details will be summarized by treatment arm. Counts and percentages will be displayed for all categorical items. Continuous outcomes will be summarized by either means (SD) or medians (IQR).

4.8 Primary outcomes

The non-inferiority test for the primary outcomes, 3-year DFS and 5-year OS, in

two groups was conducted by 95% confidence interval (CI) of two rates which was compared with the non-inferiority limit of 10%. The 95%CI was calculated by the Newcombe method with adjustment for randomisation strata recommended by FDA and NCCLS. Frequencies and percentages per arm, and an OR measuring the treatment effect and its 95% CI will be reported. We will undertake a secondary analysis for the primary outcomes using log-rank test. Median disease-free survival time per arm, and an HR measuring the treatment effect and its 95% CI will also be reported. Cox's proportional hazards model will also be used to for the adjusted analysis.

4.9 Missing values in the primary endpoint

The missing data for the 3-year DFS and 5-year OS is expected to be small and will not be imputed. Instead, a secondary analysis based on survival methods will be performed and the missing data will be treated as censored data.

4.10 Secondary outcomes

Categorical variables were expressed as numbers (percentages), and were analyzed by Fisher's exact test or χ^2 test as appropriate. These data will be summarized by an OR and its 95% CI. The effect of treatment on survival time or any time-to-event type of outcome will be tested by a log-rank test. Skewed continuous endpoints will all be summarized by medians (IQR). The effect of treatment will be tested by a Wilcoxon test. A difference between medians and its 95% CI will be imputed if deemed useful. Rates of death and recurrence by treatment group will also be presented as Kaplan-Meier curves.

4.11 Safety endpoints

Counts and percentages per treatment arm will generally summarize all specific

pre-defined SAE categories. They generally represent the number of patients experiencing a specific SAE (at least once), the fatal ones, and the breakdown by subcategory (when appropriate). This includes morbidity and mortality. The exact definitions based on MedDRA codes have been established prior to interim analysis and are available upon request. Fisher's exact test or χ^2 test as appropriate of a treatment effect will be carried out and its p value reported. A measure of treatment effect (i.e. a relative risk and its 95% CI) might be reported if its computation is possible. None of the above analyses will be adjusted.

4.12 Proposed content of primary and subsequent publications

An outline of the publication plan for the TaLaR trial is provided, alone and when combined with data from TaLaR.

	Content / overview of analytic approach
1	Interim analysis 1: when approximately 50% of the patients were enrolled and followed up for 30 days were planned for the secondary outcome of morbidity and mortality rates, as well as pathologic outcomes.
2	Interim analysis 2: when 100% of the patients were enrolled and followed up for 30 days were planned for the secondary outcome of morbidity and mortality rates, as well as pathologic outcomes.
3	Main results paper 1: when all of the patients were followed up for 3 years after operation, 3-year disease-free survival will be compared between the two groups.
4	Main results paper 2: when all of the patients were followed up for 5 years after operation, 5-year overall survival will be compared between the two groups.

4.13 Statement of contribution of the authors

Yuantao Hao, Huashan Liu, Ziwei Zeng, and Liang Kang participated in writing the first draft and all revisions of the SAP. All the members of the TaLaR group participated in critical reviews of the SAP. Finally, the SAP was approved by the TaLaR Executive Committee. The SAP was prepared without knowledge of the data. The study statisticians prepared tabulations of the baseline characteristic as grouped data for reports during the course of the study, which were used to inform the authors in selection of cut-points to define subgroups and aspects of the overall analysis plan. The SAP was prepared independent of the key funding agency for the trial.