BJS Open, 2023, zrac160
https://doi.org/10.1093/bjsopen/zrac160
Protocol

Single-stapling technique versus hand-sewn anastomosis in inter-sphincteric resection with transanal total mesorectal excision (Super SST): protocol for a multicentre randomized clinical trial

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Abstract

Background: Currently, hand-sewn anastomosis is the standard procedure for inter-sphincteric resection (ISR); however, distal purse-string suturing during transanal total mesorectal excision (TaTME) has allowed a single-stapling technique (SST). Although it was originally intended for cases requiring anastomosis of 2 cm or more above the anorectal junction (ARJ), SST could be safely performed in ISR. The aim of this trial is to determine the superiority of SST over hand-sewn anastomosis in ISR with TaTME.

Methods: The Super SST trial is a multicentre randomized clinical trial comparing stapled and hand-sewn anastomoses in ISR with TaTME. The trial will recruit patients scheduled for TaTME with anastomosis below the ARJ, who will be allocated 1:1 to receive either hand-sewn or stapled anastomosis. The primary endpoint is anastomosis-related complications within 30 postoperative days. Secondary endpoints include all early and late complications, operating time, reoperation, mortality rate, length of postoperative hospital stay, readmission, incidence of anal pain and rectal mucosal prolapse, length of temporary stoma retention, the proportion of patients with a temporary stoma at 1 year after surgery, and anorectal function at 1 year after surgery.

Conclusion: This trial will provide important clinical insights for new and promising anastomotic options for patients with very low rectal cancer.

Registration number: UMIN000047818 (https://www.umin.ac.jp/ctr/index-j.htme).

Introduction

Colorectal cancer is the third most common cancer worldwide, accounting for more than 1.8 million new cases and more than 0.9 million deaths annually[1]. Approximately one-third of all colorectal cancers are localized in the rectum, and total mesorectal excision (TME) is the standard surgical treatment[2]; however, conventional transabdominal TME is associated with specific technical hurdles in difficult cases, particularly those with bulky tumours, narrow male pelvis, or obesity. Transanal TME (TaTME) was recently developed to overcome these difficulties through enhanced visualization of the dissection plane and manoeuvrability in the deep pelvis[3]. In addition, anastomotic techniques after TaTME, known as double purse-string circular stapled anastomosis or single-stapling technique (SST), are expected to reduce anastomotic failure[4] as multiple stapler firing[5–7] or dog ear formation[8,9] does not occur, whereas this is more common in other approaches for tumours involving the lower third of the rectum, within 5–6 cm from the anal verge (AV)[10]. Although abdominoperineal resection is conventionally performed in low rectal cancer cases[11], permanent colostomy could result in poor quality of life (QoL). Inter-sphincteric resection (ISR) was first proposed by Schiessel in 1994 for more distal locations and combines rectal removal with partial or complete internal anal sphincter excision, followed by restoration with hand-sewn coloanal anastomosis[12]. While ISR has allowed many patients to preserve their anus, conventional transabdominal ISR still has several challenges, including anastomosis-related complications, oncological outcomes, and decreased postoperative anorectal function[13].

Along with the expanding indications for TaTME, anastomotic techniques in TaTME are currently being established; notably, the distal purse-string suture technique allows SST to be safely performed, even in cases of ISR with coloanal anastomosis[14]. While SST was originally proposed as an anastomotic technique for cases requiring anastomosis of 2 cm or more above the anorectal junction (ARJ), in "Super SST" the anastomotic line is located near or below the ARJ[4]. Currently, the standard method for

Received: July 13, 2022. **Revised:** October 26, 2022. **Accepted:** October 28, 2022

anastomotic surgery in ISR is the hand-sewn technique[13]; however, the superiority of SST over hand-sewn anastomosis in ISR with TaTME has not yet been comprehensively evaluated. Therefore, the Super SST trial is a multicentre randomized clinical trial (RCT) designed to compare short-term postoperative outcomes and long-term anorectal functional outcomes between stapled and hand-sewn anastomoses in ISR with TaTME.

Methods

Study design

The Super SST trial is a Japanese multicentre RCT with 1:1 randomization between stapled anastomosis and hand-sewn anastomosis in ISR with TaTME. This study protocol was prepared according to the reporting guidelines of the Standard Protocol Items Recommendations for Interventional Trials[15].

Participants, interventions, and outcomes

Study setting and recruitment

This is a hospital-based study to be conducted in Japan. Eligible candidates will be identified from patients referred to a colorectal surgeon or the colorectal cancer multidisciplinary team based on the findings of colonoscopy, CT, or MRI, and eligibility will be confirmed after review of the criteria.

Eligibility criteria

Consecutive patients between 20 and 80 years of age, who are scheduled to undergo ISR with TaTME for a rectal tumour located within 6 cm from the AV will be included in the Super SST trial. As long-term outcomes are not included in the endpoints, patients with any clinical stage, histopathological type, and type of neoadjuvant therapy will be eligible. Emergent surgery, two or more anastomoses resulting from the same surgery, poorly controlled diabetes mellitus, and cases deemed unsuitable by the doctor in charge will be excluded. The trial flow diagram is shown in *Fig. 1*.

Surgical interventions

The surgical procedure for TaTME and the anastomotic technique after TaTME are as described in previous reports[4,16]. In the stapled anastomosis group, either abdominal double purse-string circular stapled anastomosis or transanal pull-through circular stapled anastomosis is selected at the discretion of the primary surgeon.

For the abdominal double purse-string circular stapled anastomosis, before the anastomotic procedure, purse-string suturing is circumferentially performed on the rectal cuff with a 2-0 monofilament non-absorbable suture (*Fig. 2*). A catheter is inserted transanally into the pelvis, and the rectal cuff is then manually ligated and closed. The centre shaft of the circular stapler is then connected to the catheter and the abdominal team retracts the catheter and guides the centre shaft into the pelvis. Next, the anvil is connected to the centre shaft from the abdominal side and the circular stapler is fired.

For the transanal pull-through circular stapled anastomosis, the purse-string suturing is performed on the rectal cuff with a 2-0 monofilament non-absorbable suture (*Fig. 3*). Before manual ligation, the anvil is pulled out from the perineal side and connected to the centre shaft of the circular stapler. After connection, the suture is ligated manually, and the circular stapler is fired.

For hand-sewn anastomosis, eight knotted sutures are applied circumferentially with a 3-0 monofilament absorbable suture, then mosquito forceps are used to grasp the sutures and spread the anastomotic site widely and evenly. Next, either one or two knotted sutures are applied between each circumferential suture and the anastomosis is completed, resulting in a total of 16 or 24 knotted sutures.

Primary outcome

The primary outcome of this trial is the occurrence of anastomosis-related complications within 30 days after surgery. Anastomosis-related complications include anastomotic leakage, anastomotic stricture, anastomotic bleeding, and perianastomotic abscess. All severity grades will be included in the analysis because even postoperative anastomosis-related complications without clinical symptoms can affect the indications and timing of temporary stoma closure and postoperative anorectal function. Severity grades will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE), the Clavien–Dindo classification, and the definition and grading of anastomotic leakage by the International Study Group of Rectal Cancer.[17]

Secondary outcomes

Secondary outcomes include late anastomosis-related complications within 1 year after surgery, operating time, reoperation, mortality rate, length of postoperative hospital stay, readmission, incidence of anal pain requiring analgesics, rectal mucosal prolapse, length of temporary stoma retention, proportion of patients with a temporary stoma at 1 year after surgery, and anorectal function at 1 year after surgery. All severity grades according to the three abovementioned grading systems will also be included in the late anastomosis-related complications. In addition, all early complications within 30 days after surgery and their severity grades according to CTCAE and the Clavien–Dindo classification, as well as all late complications within 1 year after surgery and their severity grades according to CTCAE and the Clavien–Dindo classification will be collected as secondary outcomes. Postoperative anorectal function will be evaluated using the low anterior resection syndrome (LARS) score[18] and the Wexner incontinence score[19].

Participant timelines and follow-up schedules

Before surgery, written informed consent will be obtained from all patients; patients will be allocated to their respective groups via the electronic data capture (EDC) system; and a preoperative report, including patient and disease background information, will be provided using case report forms (CRFs). After surgery, an intraoperative report on surgical information will be provided using CRFs. At 1 and 12 months after surgery, postoperative course and outcome reports, including postoperative complications, date of discharge, and date of temporary stoma closure will be provided using CRFs. At 12 months after surgery, a postoperative anorectal functional report will be provided using CRFs. The study schedule is shown in *Table 1*. The study's design will not regulate modalities of examinations or intervals between examinations for each participating institution and will not intervene in each institution's routine clinical practice; however, it is assumed that anastomosis-related complications will be strictly evaluated in patients scheduled for temporary stoma closure.

Sample size

Including all severity grades, the incidences of anastomosis-related complications within 30 days after ISR with TaTME, followed by either hand-sewn anastomosis or stapled

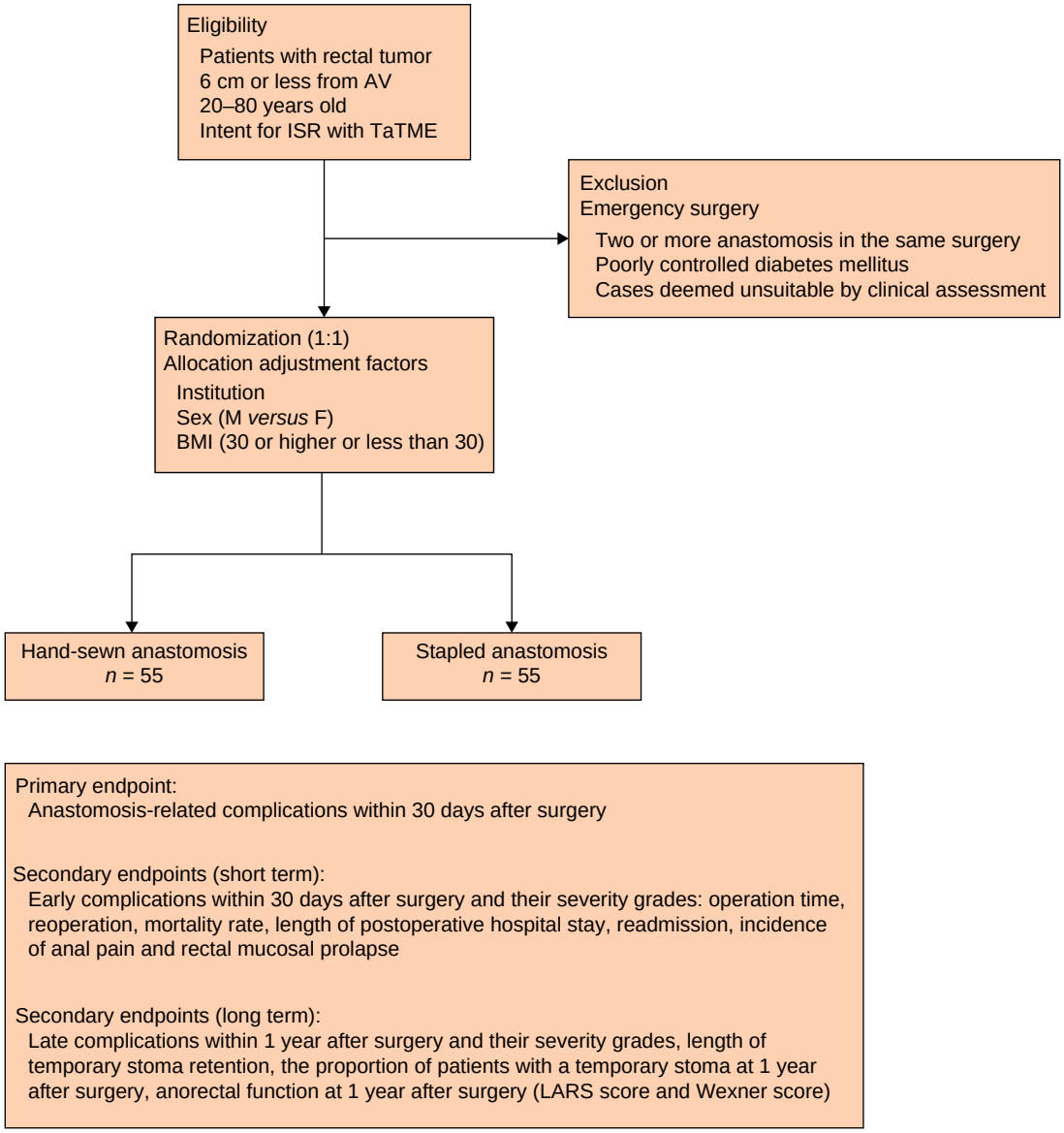

Fig. 1 Trial flow diagram

AV, anal verge; ISR, inter-sphincteric resection; TaTME, transanal total mesorectal excision; M, male; F, female; LARS, low anterior resection syndrome.

anastomosis, are estimated to be 20 per cent and 4 per cent respectively, based on previous reports[14,20,21]. For a 16 per cent decrease in early postoperative anastomosis-related complications to be demonstrated in the stapled anastomosis group compared with the rate of complications in the hand-sewn anastomosis group at a randomization ratio of 1:1 and α-error of 0.05, 50 patients in each group (100 patients in total) would be required to generate a power of 80 per cent for this RCT. Twenty additional patients will be included, in consideration of dropouts and ineligibilities, resulting in a target sample size of 110 patients.

Assignment of interventions

Once eligibility is established, patients will be centrally allocated to either the stapled or hand-sewn anastomosis groups. Randomization, performed by computers through the internet (https://www2.epoc-ncc.net/), will be adjusted by the minimization method with a random component to balance the groups, concerning the participating institution, sex (male *versus* female), and BMI (less than 30 kg/m^2 *versus* 30 kg/m^2 or higher). Patients will be randomized in a 1:1 ratio. Data will be analysed on an 'intention-to-treat' basis in cases where patients are not subject to the randomized treatment modality.

Data collection, management, and analysis

Data collection will be carried out using CRFs and validated anorectal function questionnaires, including the LARS score and the Wexner incontinence score. All data will be entered into an EDC system. Regular data quality checks will be performed as per the Quality Management Plan once a year in principle. All data will be handled in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. Data backups will be stored in secure fireproof locations, and test restorations will be performed on a regular basis. After completion of the trial, all essential trial documentation and

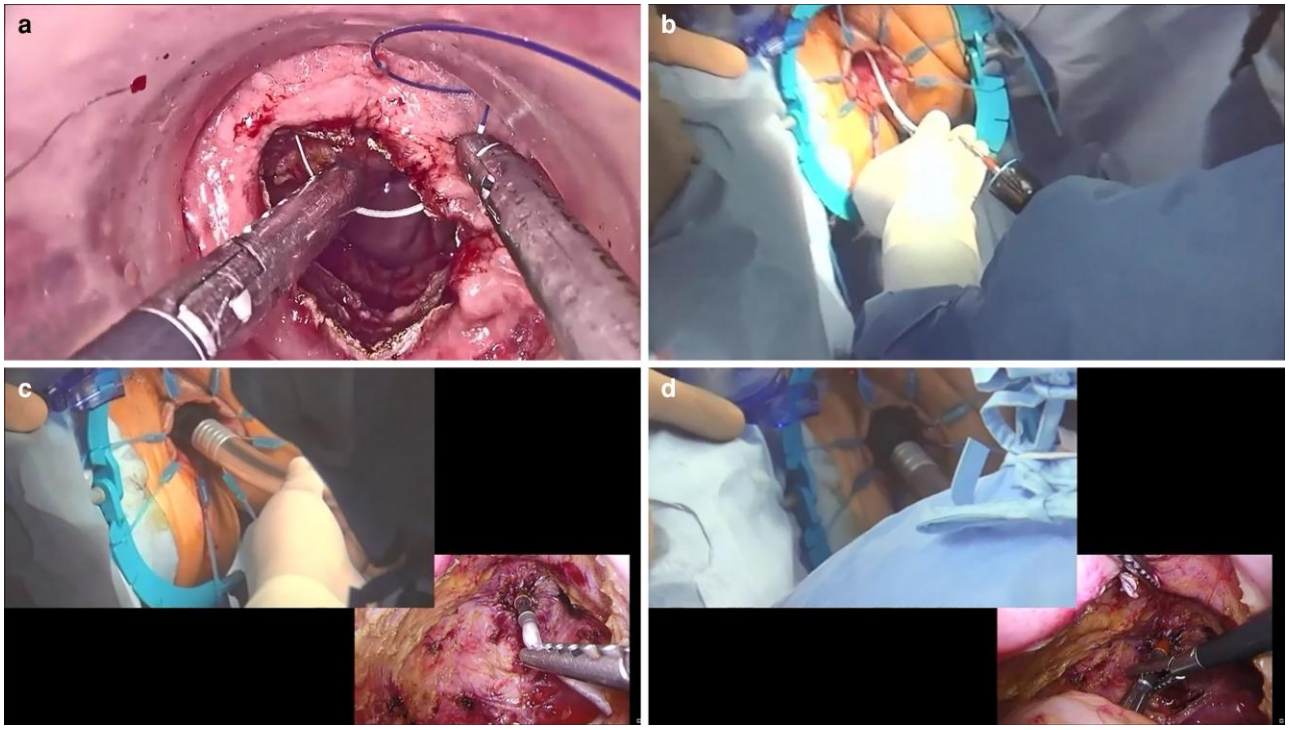

Fig. 2 Procedure of abdominal double purse-string circular stapled anastomosis

a A purse-string suture is circumferentially performed on the rectal cuff. **b** A catheter is inserted transanally into the pelvis, and the rectal cuff is then manually ligated and closed. The center shaft of the circular stapler is connected to the catheter. **c** The abdominal team retracts the catheter and guides the center shaft into the pelvis. **d** The anvil is connected to the center shaft from the abdominal side, and the circular stapler is fired.

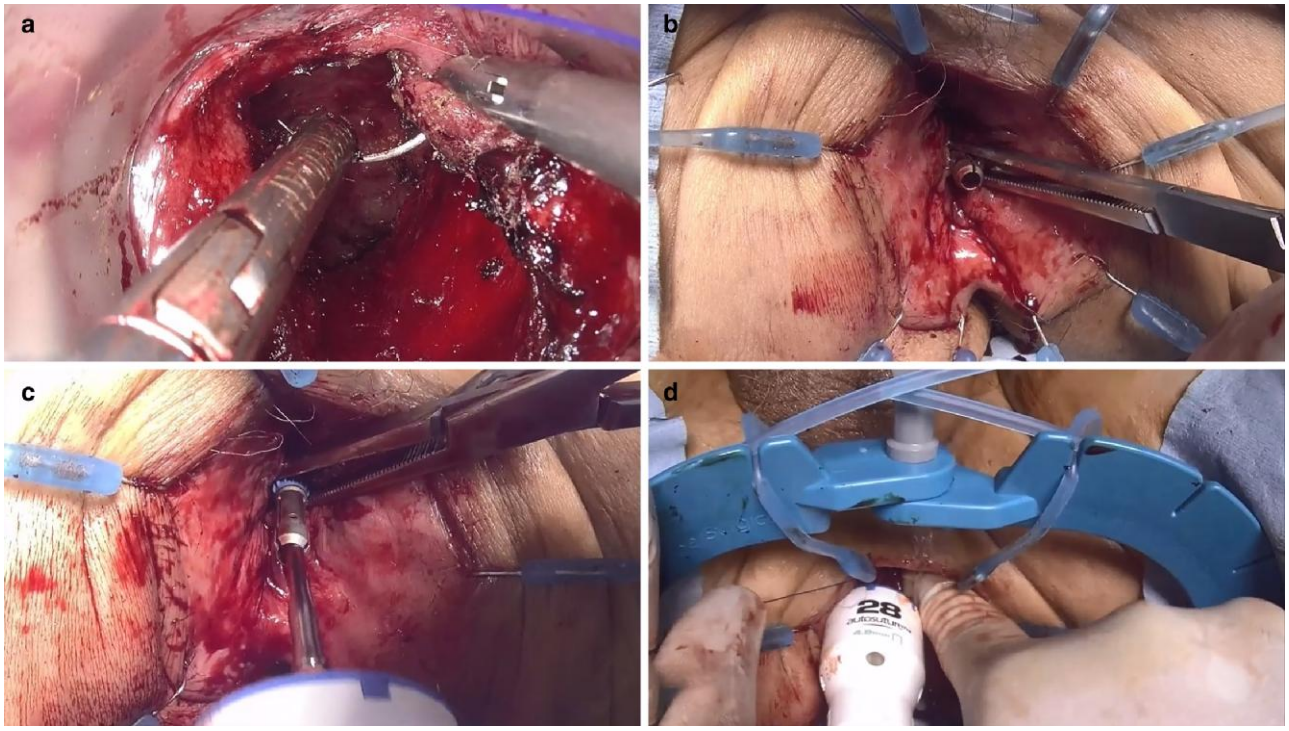

Fig. 3 Procedure of transanal pull-through circular stapled anastomosis

a A purse-string suture is circumferentially performed on the rectal cuff. **b** Before manual ligation, the anvil is pulled out from the perineal side. **c** The anvil is connected to the center shaft of the circular stapler. **d** After connection, the suture is ligated manually and the rectal cuff is closed, and finally, the circular stapler is fired.

Table 1 Study schedule

	Preoperative	Postoperative	Postoperative (1 month)	Postoperative (12 months)
Informed consent allocation preoperative report	X			
Patient background				
Disease background				
Postoperative report		X		
Surgical information				
Postoperative course and outcome report			X	X
Morbidiy rate				
Date of discharge				
Date of stoma closure				
Anorectal functional report				X

source documents, including signed informed consent forms and copies of CRFs, will be securely retained for at least 5 years.

Statistical methods

Baseline numerical data will be described as mean(s.d), or median (range). Baseline categorical data will be displayed as percentages. All comparative analyses will be conducted on an 'intention-to-treat' basis (patients who are randomized to the stapled anastomosis group and intraoperatively converted to the hand-sewn group will be analysed as part of the stapled anastomosis group). Apart from the 'intention-to-treat' analysis, per-protocol and as-treated analyses will be also applied as sensitivity analyses. Primary outcomes will be compared using Pearson's chi-squared test. Secondary outcomes will be compared using Pearson's chi-squared test, or the Wilcoxon signed rank test if necessary.

Monitoring

Regular data quality checks will be performed as per the Quality Management Plan once a year, in principle. Central monitoring will be conducted by the data centre based on the CRF data collected via the EDC system. The monitoring staff will prepare a monitoring report after the central monitoring and will report it to the principal investigator.

Ethics and dissemination

Participating institutions will be three high-volume centres with sufficient TaTME caseloads (more than 20 cases per year), including one national cancer centre and two university hospitals in Japan. The protocol for this RCT has been reviewed and approved by the ethics committees of each participating institution, and the trial has been registered at UMIN-CTR (https://www.umin.ac.jp/ctr/index-j.htme) under trial ID UMIN000047818. Written informed consent will be obtained from all patients after a thorough oral explanation by the doctor in charge at each centre participating in the Super SST trial.

Discussion

TaTME is a relatively modern method that has emerged as a conjunction of two minimally invasive techniques, namely transabdominal laparoscopy and transanal minimally invasive surgery. While it can offer a better operating approach in cases of narrow pelvis and thus support radical TME both technically and oncologically, results in terms of local recurrence remain controversial[22]. Two randomized studies (COLOR III and ETAP-GRECCAR 11) are currently in progress and might soon clarify the position of TaTME in clinical practice[23,24].

The formation of anastomosis is a critical step following TaTME and has commonly been performed using both hand-sewn and stapling techniques. In the original report about the anastomotic technique in TaTME, the hand-sewn approach seemed to be more suitable for coloanal anastomosis because a distal purse-string suture was unlikely to be suitable due to the insufficient stump length[4]; however, in practical settings, a distal purse-string suture is technically possible, even in cases of coloanal anastomosis. In this regard, several reports of outcomes of stapled anastomosis in TaTME also included ISR-indicated cases with tumours less than 5–6 cm from the AV[14,21].

One of the most common anastomosis-related complications after rectal resection is anastomotic leakage. Anastomotic leakage after rectal cancer surgery must be avoided because it can lead to life-threatening diffuse peritonitis. Even mild symptoms of anastomotic leakage could cause postoperative anorectal dysfunction, sexual inactivity, chronic pelvic pain, high local recurrence, and poor survival[25–27].

Several RCTs on early stoma closure after proctectomy and TME have been published[28–30]. Most of these concluded that early stoma closure could be safely implemented in selected patients after TME and sphincter-saving surgery for rectal cancer. Early closure has a significant benefit, because the stoma may be associated with deterioration of the patient's QoL. Additionally, early closure has been reported to shorten hospital stays and reduce stoma-related complications[31,32]. However, rectal anastomosis must be confirmed as intact before early stoma closure. Even minor anastomosis-related complications could have a major impact on the determination of the indication for stoma closure.

While SST has been considered technically feasible in ISR with TaTME in some institutes, the standard method for coloanal anastomosis is still hand-sewn. Before the adaptation of Super SST as a standard anastomotic method in ISR with TaTME, a well designed study is required to demonstrate its efficacy and safety in a multicentre randomized setting, such as that in this trial. As such, this trial will provide important clinical insights about new and promising anastomotic options for patients with very low rectal cancer.

Funding

The authors have no funding to declare.

Acknowledgements

This RCT has been registered at UMIN-CTR (https://www.umin.ac.jp/ctr/index-j.htme) under the trial ID UMIN000047818. The protocol for this RCT has been reviewed and approved by the ethics committees of each participating institution.

Disclosure

The authors declare no conflict of interest.

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