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The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

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ABSTRACT

Introduction: Gastric cancer is the fifth most common cancer worldwide and the detection rate of proximal gastric cancer has since been increasing. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. With the widespread popularity of laparoscopic total gastrectomy (LTG), surgeons increasingly perform the procedure on adenocarcinoma of the esophagogastric junction. However, totally laparoscopic total gastrectomy (TLTG) is only performed by a few surgeons due to difficulty associated with esophagojejunostomy (EJ), in which there is no consensus on a standardized anastomosis technique. We propose a randomized trial to compare functional end-to-end anastomosis (FETE) and a side-to-side anastomosis (Overlap) for esophagojejunostomy.

Methods and analysis: A prospective, randomized, open-label, single-center, interventional trial is designed to evaluate the quality of life (QoL) and safety of FETE and Overlap, with a 1-year follow-up as the primary endpoint. The trial began in 2020 and is scheduled to enroll 96 patients according to a prior sample size calculation. Patients were randomly allocated to the FETE or Overlap group with a follow-up of one year to assess QoL after the procedure. All relevant clinical data, including biological markers were collected. The primary indicator is the D-value between the postoperative and preoperative QoL. Student's t tests will be used to compare continuous variables, while Chi square tests or Fisher's tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software. A *p*-value of less than 0.05 will be considered statistically significant.

Ethics and dissemination: This study has been approved by the Hospital Institutional Review Board (HIRB) of Huashan Hospital, Fudan University (2020-1055). The results will be submitted for publication in peer-reviewed journals.

Trial registration number: ChiCTR2000035583.

Strengths and limitations of this study

- The current study is one of few randomized clinical trials aimed at comparing functional end-to-end anastomosis with a side-to-side anastomosis for esophagojejunostomy in totally laparoscopic total gastrectomy.
- The trial aims to evaluate procedural safety and quality of life during a one-year

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4 postoperative follow-up.

- 5 ● The study result is limited to a single center study. Future multicenter study may be
6 warranted to further validate study results.
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INTRODUCTION

Gastric cancer is the fifth most common cancer, after breast cancer (11.7%), lung cancer (11.4%), colorectal cancer (10%), and prostate cancer (7.3%)[1]. In 2020, estimated new cases of gastric cancer is 1,089,103 worldwide (5.6% of all incident cancer cases), with new deaths of 768,793 (7.7% of all sites). The highest incidence rates are in Japan (male population) and Mongolia (female population). Gastric cancer is the fourth leading cause of cancer death in both genders worldwide, with an estimated gastric cancer death of 769,000 in 2020 (equivalent to one in every 13 deaths globally). In recent years, the detection rate of proximal gastric cancer has been increasing [2]. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) has been performed since 1999[3]. Evidence from several have demonstrated that totally laparoscopic total gastrectomy (TLTG) has the benefits of minimal blood loss, less postoperative pain, faster bowel function recovery, shorter hospital stay and lower postoperative morbidity, at the price of longer operative time compared with open total gastrectomy (OTG) [4-6]. TLTG have not been popularized due to difficulty associated with esophagojejunostomy (EJ). When performing OTG, EJ with a circular stapling device is generally accepted as a substitute for hand sutured anastomosis. However, there are two disadvantages in this technique: first, purse-string suturing is a mandatory step; second, it can be difficult to introduce the anvil of the circular stapler into the esophagus. These disadvantages become more complicated in laparoscopic surgery than in open surgery. However, purse-string suturing and anvil introduction are not necessary when performing EJ with linear staplers. Two types of EJ have been reported using linear staplers, including the functional end-to-end anastomosis [7] and the side-to-side anastomosis (or the overlap method) [8]. The functional end-to-end procedure is performed by inserting the linear stapler into the esophagus through a small hole on the left side of the esophageal stump, while simultaneously lifting the jejunum to insert the stapler through a small hole on the opposite side of the jejunum mesenterium. The entry holes are closed using the linear stapler, usually one at a time. By contrast, the overlap method is performed by creating holes on the left side of the esophageal stump and 6–7 cm from the jejunal stump. After stapling, the entry hole is closed using hand-sewn sutures. Based on our retrospective study, the FETE group showed lower QoL compared

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4 with the Overlap group shortly after surgery, and the rates of postoperative complications were
5 similar between the two groups. However, there is no agreement on the standard anastomosis
6 technique for EJ [6, 9-11]. A retrospective study in South Korea, showed that laparoscopic EJ
7 with the Overlap method is associated with less postoperative pain and anastomotic
8 complications compared to FETE [12]. To date, there is no prospective study to compare which
9 method is more reasonable based on the QoL and surgical safety of patients undergoing TLTG.
10 We hypothesize that gastric cancer patients undergoing TLTG with either FETE or Overlap
11 intracorporeal EJ experience different QoL and surgical safety after the procedure.
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19 **Institutional data**

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21 Our institution is one of the leading institutions Shanghai, China affiliated to Fudan
22 University. Our surgeons perform over 500 gastrectomy annually, with over 200 cases
23 performed via laparoscopy. We have previously reported several novel reconstruction methods
24 in performing totally laparoscopic proximal gastrectomy, distal gastrectomy, and total
25 gastrectomy [13-15]. Self-pulling and latter transected (SPLT) reconstruction is one of our novel
26 and routine method in performing laparoscopic total gastrectomy. The operational procedure
27 and difficulty of anastomosis have been simplified, which effectively resolved problems
28 associated with traditional EJ, such as esophageal retraction after transection, difficulty in
29 opening the esophagus, difficulty in closing entry holes, complex technical requirements, higher
30 cost (cheaper than traditional linear anastomosis), and difficulty in promotion. The results of a
31 retrospective study of 100 TLTG+SPLT cases demonstrate SPLT is a safe and feasible
32 procedure [16]. Our surgeons have surpassed the learning curve for this procedure and have
33 successfully performed over 150 SPLT surgeries.
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46 **METHODS AND ANALYSIS**

47 **Patient and Public Involvement**

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49 Laparoscopic surgery has become a leading trend for the treatment of various malignant
50 diseases, including gastric cancer. Different methods of total laparoscopic total gastrectomy,
51 including functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap)
52 for esophagojejunostomy (EJ) are both accepted methods in clinical practice. However, there
53 is currently no consensus comparing the two techniques in terms of procedural safety and long-
54 term quality of life. Based on our retrospective study, the SPLT technique is easier, cheaper
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4 and a more feasible method compared to traditional EJ. Patients did not participate in the
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6 design of the study. However, prior to enrollment, each patient will be thoroughly informed on
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8 the purpose of the study and the different interventional methods. Should the patient prefer one
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10 method over another, he or she will no longer participate in the present trial. We predict that
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12 the study results will help distinguish the different impacts on quality of life between the two
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14 anastomosis techniques, which will provide scientific evidence for future decision making.

15 **Trial design**

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17 The current study is a prospective, randomized, open-label, single-center, interventional
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19 trial using a parallel-arm design which would commence from October 1, 2020, through
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21 September 30, 2022. Subjects will be randomized to receive one of two interventions: the FETE
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23 group or the Overlap group. Figure 1 shows an overview of the trial design, and each aspect of
24
25 the trial is introduced in detail below.

26
27 **Inclusion criteria:** 1. Patient between 18 to 75 years old; 2. Primary gastric adenocarcinoma
28
29 confirmed pathologically by endoscopic biopsy; 3. Locally advanced tumor in the upper- or
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31 middle-third stomach, or locally advanced adenocarcinoma of the esophagogastric junction
32
33 (AEG) with Siewert type II or III (cT1-4a, N-/+, M0); 4. No distant metastasis, no direct invasion
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35 of the pancreas, spleen or other neighboring organs found on preoperative examinations; 5.
36
37 Performance status of 0 or 1 on the ECOG (Eastern Cooperative Oncology Group) scale; 6.
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39 ASA (American Society of Anesthesiology) class I to III; 7. Written informed consent.

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41 **Exclusion Criteria:** 1. Pregnant and lactating women; 2. Suffering from severe mental
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43 disorder; 3. History of previous upper abdominal surgery (except for laparoscopic
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45 cholecystectomy); 4. Enlarged or bulky regional lymph node (diameter over 3cm) found on
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47 preoperative imaging including enlarged or bulky No.10 lymph node; 5. History of other
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49 malignant disease within the past 5 years; 6. History of unstable angina or myocardial
50
51 infarction within the past 6 months. 7. History of cerebrovascular accident within the past 6
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53 months; 8. Emergency surgery (bleeding, obstruction, perforation) caused by gastric cancer.

54 **Contrast and grouping**

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56 Patients are enrolled by the clinical research coordinator (CRC) on the team.

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58 Patients who fulfilled the eligibility criteria are randomized to receive either laparoscopic
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60 EJ with FETE-SPLT or Overlap-SPLT on a 1:1 ratio. SPSS software is used to generate the

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4 random sequence, and the subjects are coded according to the order of entering the group.
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6 The random sequence number corresponded to the coding sequence of patients, whom will be
7
8 randomly divided into two groups (odd number into SPLT-FETE group and even number into
9
10 SPLT Overlap Group). While blinding surgeons or participants is not feasible in this study.

11 **Treatment**

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13 **Lymphadenectomy:** A D2 lymph nodes (LNs) dissection will be regularly conducted
14
15 according to the Japanese gastric cancer treatment guidelines 2014 (ver. 4)[17].

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17 **Reconstruction of anastomosis:** After completing lymphadenectomy, the abdominal
18
19 esophagus will be routinely mobilized. The subsequent conventional transection will be
20
21 substituted by ligation of the cardia (or esophagus above the upper margin of the tumor) using
22
23 a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm
24
25 endoscopic linear stapler per usual.

26
27 **FETE group (Figure 2):** Throughout the course of reconstruction, the ligature rope will be
28
29 held to drag down the esophagus to allow easier detachment from the posterior mediastinum.
30
31 Next, a hole will be made on the posterior wall of the esophagus, 2–3cm above the ligature
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33 rope. Then, another hole will be made at the anti-mesenteric border of the jejunum 25cm
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35 distal to the ligament of Treitz, serving as an entrance for the second stapler. Then, a side-to-
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37 side E-J will be performed through two holes, forming an entry hole. The following FETE will
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39 be modified in a “latter transected” fashion.

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41 **Overlap group (Figure 3):** The jejunum will be intracorporeally transected 20cm distal to the
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43 ligament of Treitz using a linear stapler. The distal side of the jejunum will be additionally
44
45 removed to avoid excessive tension at the anastomosis of the EJ. A small enterotomy will be
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47 made at 7cm distal to the stapler line on the antimesenteric side of the jejunal limb. Another
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49 small hole will be made on the left wall of the esophagus, 2–3cm above the ligature rope. After
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51 one fork of the stapler is being inserted into the opening to form a jejunal limb toward the oral
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53 side of the lumen, the jejunal limb will be dragged up and positioned at the left side of the
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55 abdominal esophagus. Another fork of the linear stapler will be inserted carefully into the hole
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57 of the esophagus. After each fork has been completely inserted into each lumen, the firing of
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59 the stapler will convert the two openings into a single-entry hole to create an end-to-side EJ.
60
The entry hole will be simultaneously closed together with the esophagus being transected with

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4 a stapler.

5 6 **Outcomes**

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8 The primary purpose of the present study is to compare the QoL between FETE and
9
10 Overlap groups (1, 3, 6, 9,12 months after surgery)[18] with EORTC QLQ-C30 and QLQ-
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12 STO22[19, 20]. The EORTC QLQ-C30 is designed as a multidimensional assessment of QoL
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14 including 5 scales on functional assessment, 3 symptom scales, a global health status, and 6
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16 single items. Higher score indicates a better status in functioning domains, but a worse status
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18 in symptom domains. The EORTC STO22 is designed specifically for examining QoL of gastric
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20 cancer patients. It contains 22 questions including 5 symptom scales and 4 single items. Higher
21
22 scores indicate a worse status. Early postoperative complications (anastomotic leakage,
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24 pulmonary complication, bleeding, pancreatic fistula) between FETE and Overlap groups will
25
26 also be compared. Early postoperative complication is defined as an event observed within 30
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28 days after surgery.

29 30 **Adverse events**

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32 Adverse events (AEs) are any disadvantageous or uncertain event that affect the subject,
33
34 regardless of its association to the treatment procedure. All AEs are recorded on the case report
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36 form (CRF) in detail, such as occurrence, duration, prognosis, severity, relevance to the
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38 treatment, and such. If events are defined as serious adverse events (SAEs), which results in
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40 death, disability, dysfunction, teratogenesis, or prolonged hospitalization. The occurrence of
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42 SAEs will be reported to the Huashan Hospital Committee within 24 hours.

43 44 **Sample size**

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46 In the present study, postoperative quality of life of patients is the main evaluation index,
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48 which is set as a non-inferiority study. According to the data of the retrospective study in China,
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50 the QoL scores of the EJ Overlap group and FETE group are increased by 17 points relative to
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52 the preoperative baseline, with a standard deviation of D-value of 6.5 points and a non-
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54 inferiority margin of 4 points. According to $\alpha = 0.025$, $\beta = 0.20$, the sample size of 86 (43 per
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56 group) is calculated by the PASS 2020 software. The final sample size is 96 (48 per group)
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58 after considering a 10% dropout rate in each group. Our team is capable of performing 150
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60 TLTG operations annually, therefore the planned recruitment period is 2 years, with a 1-year
follow-up period.

Data collection

Trained professionals collect data via paper-form datasheets from patient hospitalization and outpatient records until 1 year after the surgery.

Preoperative records

Initial staging and diagnosis include endoscopy, endoscopic ultrasound, non-contrast enhanced CT scan of the chest, and contrast-enhanced CT scan of the abdomen, and endoscopic pathology. The patient's age, sex, weight, ASA classification, Eastern Cooperative Oncology Group (ECOG) score, hemoglobin, C-reactive protein (CRP), comorbidities, history of abdominal surgery, QoL, and tumor markers were recorded.

Intraoperative records

The type of EJ, operation time, blood loss (and blood transfusion), anastomosis time, intra-abdominal adhesion, specimen measurement (margin), and relevant complications were recorded.

Postoperative records

Pathological diagnosis, postoperative complications (anastomotic leakage, anastomotic bleeding, abdominal bleeding, abdominal infection, and intestinal obstruction), postoperative mortality, postoperative hospitalization days, postoperative first aerofluxus time, postoperative time to liquid diet, postoperative time to soft food diet, postoperative C-reactive protein, and evaluation of postoperative biological markers were recorded.

Follow-up records

The follow-up medical history and physical examination, questionnaire results, blood tests, adjuvant therapy and completion, imaging examination results and endoscopic results were recorded.

Patient follow-up in the outpatient clinics abided by postoperative standards. Table 1 summarized the follow-up period and parameters.

Data analysis

Data processing of QoL scale

1. Raw Score (RS) = $(Q1 + Q2 + Q?) / n$, (Q: score of each item; n: number of all items)
2. Functional field: standard score (SS) = $[1 - (RS - 1) / R(\text{Range})] \times 100$
3. Symptom field and general health field: SS = $[(RS - 1) / R(\text{Range})] \times 100$

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4 Continuous data are expressed as mean \pm standard deviation ($\bar{x}\pm S$), while categorical data
5 are shown as percentage (%). The D-value between the standard score of postoperative and
6 preoperative QoL is the comparative indicator. Student's t tests will be used to compare
7 continuous variables, while Chi square tests or Fisher's tests will be used to compare
8 categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software.
9 A *p*-value of less than 0.05 will be considered statistically significant.

15 **Patient informed consent**

17 All participants should sufficiently understand the instructions detailed in the written
18 informed consent. All patients will be given the opportunity to ask questions and provided with
19 a comprehensive response. Patients may choose not to participate in the research, or withdraw
20 at any time after notifying the researchers, to ensure patient rights to treatment will not be
21 affected. All participants are required to provide a written informed consent before participating
22 in the trial.

29 **Expectation**

31 Upon completion of the study, the results of the primary study will be published in a peer-
32 reviewed journal. We hope to provide a more scientific and reasonable theoretical basis for
33 total laparoscopic gastrointestinal anastomosis, establish treatment standards, and further
34 advertise the advantages of SPLT, which is safe, effective, and easy to promote. We anticipate
35 a multicenter clinical trial for esophagojejunostomy with TLTG-SPLT in the near future to further
36 validate the advances of the procedure. Study results will allow more AEG patients to benefit
37 from the TLTG-SPLT technique.
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FIGURE LEGENDS**Figure 1. Study Flowchart****Figure 2. TLTG FETE SPLT**

A. The esophagus is pulled right and a hole is made on the posterior wall of the esophagus, 2–3cm above the ligature rope. B. The mesentery of the jejunum 25cm distal to the ligament of Treitz is mobilized to ensure blood supply. C. Another hole is made at the anti-mesenteric border of the jejunum. D. The lateral posterior wall of esophagus is anastomosed with the jejunum. E. The jejunum is checked for injury. F. The entry hole is closed. G. The jejunojejunostomy is performed at the jejunum, 40–45cm distal to EJ. H. The entry hole is closed. I. A drainage tube is placed posteriorly to EJ.

Figure 3. TLTG Overlap SPLT

Step 1 and step 2 of the Overlap method is consistent with the FETE method, followed by: A. The jejunum 20cm distal to the ligament of Treitz is transected using a linear stapler. B. A small enterotomy will be made 6 cm distal to the stapler line on the antimesenteric side of the jejunal limb. C. The lateral posterior wall of esophagus is anastomosed with the distal jejunum. D. The entry hole is closed. E. A small hole is made in the proximal jejunum. F. The jejunojejunostomy is performed at the jejunum 40–45cm distal to EJ. G. The entry hole is closed. H. A drainage tube is placed posteriorly to EJ.

Table 1. Follow-up arrangements

	Observation Period					
	Preoperative	Postoperative	Postoperative	Postoperative	Postoperative	Postoperative
	1 week	1 month	3 months	6 months	9 months	12 months
Patient Informed Consent	✓	✓	✗	✗	✗	✗
Previous Surgery	✓	✓	✗	✗	✗	✗
ASA Class	✓	✓	✗	✗	✗	✗
ECOG Scale	✓	✓	✗	✗	✗	✗
Weight	✓	✓	✓	✓	✓	✓
Blood routine test	✓	✓	✓	✓	✓	✓
CRP	✓	✓	✗	✗	✗	✗
Tumor markers	✓	✗	✓	✓	✓	✓
CT Scan	✓	✗	✗	✓	✗	✓
Endoscopy	✓	✗	✓	✗	✗	✓
EORTC QLQ-C30	✓	✓	✓	✓	✓	✓
QLQ-STO22	✓	✓	✓	✓	✓	✓

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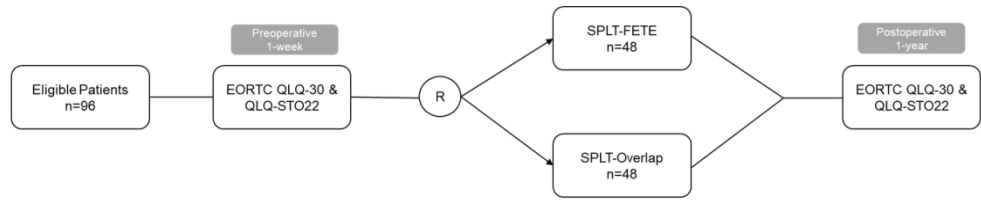
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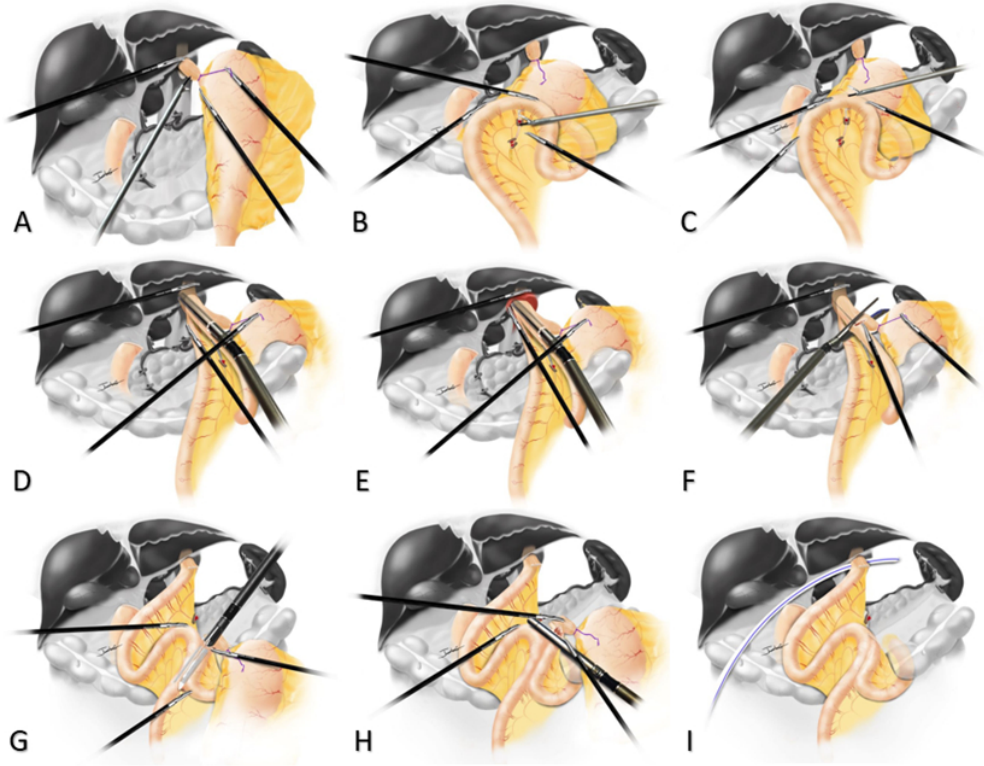
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Study Flowchart

313x68mm (150 x 150 DPI)

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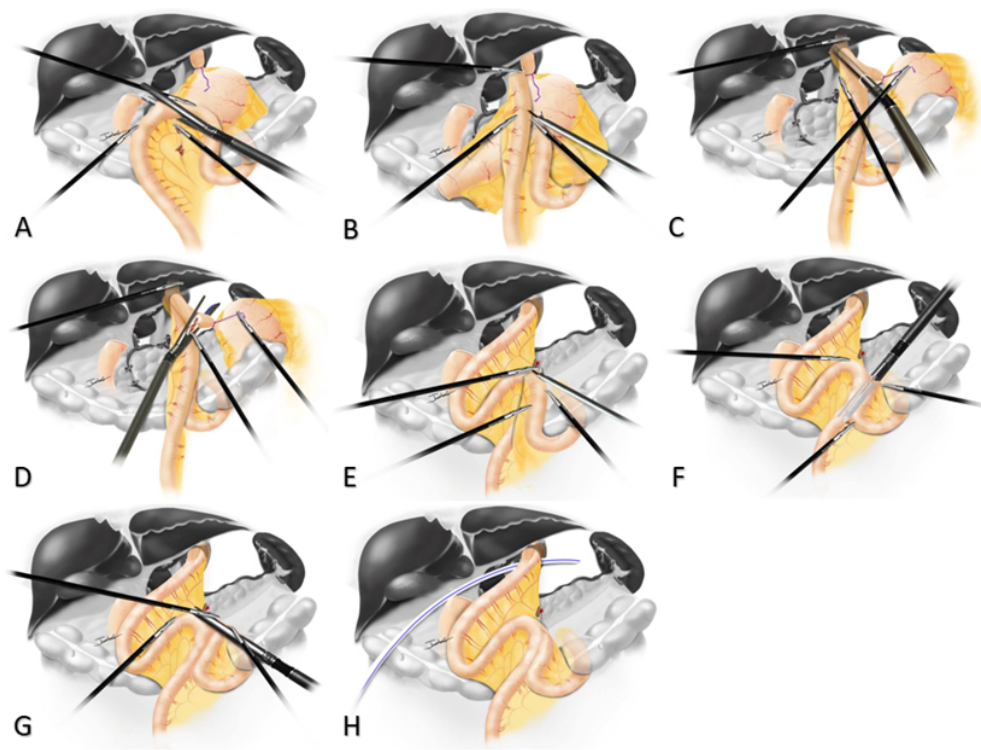


TLGT FETE SPLT

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TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

BMJ Open

The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

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Secondary Subject Heading:	Research methods
Keywords:	SURGERY, Gastrointestinal tumours < GASTROENTEROLOGY, Clinical trials < THERAPEUTICS

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Title Page

Title: The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

Running Title: study protocol for comparing different esophagojejunostomy methods

Type of Manuscript: Protocol

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ABSTRACT

Introduction: Gastric cancer is the fifth most common cancer worldwide and the detection rate of proximal gastric cancer has since been increasing. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. With the widespread popularity of laparoscopic total gastrectomy (LTG), surgeons increasingly perform the procedure on adenocarcinoma of the esophagogastric junction. However, totally laparoscopic total gastrectomy (TLTG) is only performed by a few surgeons due to difficulty associated with esophagojejunostomy (EJ), in which there is no consensus on a standardized anastomosis technique. We propose a randomized trial to compare functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) for esophagojejunostomy.

Methods and analysis: A prospective, randomized, open-label, single-center, interventional trial is designed to evaluate the quality of life (QoL) and safety of FETE and Overlap, with a 1-year follow-up as the primary endpoint. The trial began in 2020 and is scheduled to enroll 96 patients according to a prior sample size calculation. Patients were randomly allocated to the FETE or Overlap group with a follow-up of one year to assess QoL after the procedure. All relevant clinical data, including biological markers were collected. The primary indicator is the D-value between the postoperative and preoperative QoL. Student's t-tests will be used to compare continuous variables, while Chi-square tests or Fisher's tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software. A *p*-value of less than 0.05 will be considered statistically significant.

Ethics and dissemination: This study has been approved by the Hospital Institutional Review Board (HIRB) of Huashan Hospital, Fudan University (2020-1055). The results will be submitted for publication in peer-reviewed journals.

Trial registration number: ChiCTR2000035583.

Strengths and limitations of this study

- The current study is one of few randomized clinical trials aimed at comparing functional end-to-end anastomosis with side-to-side anastomosis for esophagojejunostomy in totally laparoscopic total gastrectomy.
- The present study is primarily focused on comparing the quality of life of patients with a

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4 one-year follow-up period.

- 5
6 ● The study result is limited to a single-center study.
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8 ● Future multicenter study may be warranted to further validate study results.
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INTRODUCTION

Gastric cancer is the fifth most common cancer, following breast cancer (11.7%), lung cancer (11.4%), colorectal cancer (10%), and prostate cancer (7.3%)^[1]. In 2020, the estimated number of new cases of gastric cancer is 1,089,103 worldwide (5.6% of all incident cancer cases), with new deaths of 768,793 (7.7% of all sites). The highest incidence rates are in Japan (male population) and Mongolia (female population). Gastric cancer is the fourth leading cause of cancer death in both genders worldwide, with an estimated gastric cancer death of 769,000 in 2020 (equivalent to one in every 13 deaths globally). In recent years, the detection rate of proximal gastric cancer has been increasing^[2]. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) has been performed since 1999^[3]. Evidence from several studies have demonstrated that totally laparoscopic total gastrectomy (TLTG) has the benefits of minimal blood loss, less postoperative pain, faster bowel function recovery, shorter hospital stay and lower postoperative morbidity, at the price of longer operative time compared with open total gastrectomy (OTG)^[4-6]. TLTG has not been popularized due to difficulty associated with esophagojejunostomy (EJ). When performing OTG, EJ with a circular stapling device is generally accepted as a substitute for hand-sutured anastomosis. However, there are two disadvantages to this technique: first, purse-string suturing is a mandatory step; second, it can be difficult to introduce the anvil of the circular stapler into the esophagus. These disadvantages become more complicated in laparoscopic surgery than in open surgery. However, purse-string suturing and anvil introduction are not necessary when performing EJ with linear staplers. Two types of EJ have been reported using linear staplers, including the functional end-to-end anastomosis^[7] and the side-to-side anastomosis (or the overlap method)^[8]. The functional end-to-end procedure is performed by inserting the linear stapler into the esophagus through a small hole on the left side of the esophageal stump, while simultaneously lifting the jejunum to insert the stapler through a small hole on the opposite side of the jejunal mesentery. The entry holes are closed using the linear stapler, usually one at a time. By contrast, the overlap method is performed by creating holes on the left side of the esophageal stump and 6 to 7 cm from the jejunal stump. After stapling, the entry hole is closed using hand-sewn sutures. Based on our retrospective study, the FETE

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4 group showed lower QoL compared with the Overlap group shortly after surgery, while the rates
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6 of postoperative complications were similar between the two groups. However, there is no
7
8 agreement on the standard anastomosis technique for EJ [6, 9-11]. A retrospective study in South
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10 Korea showed that laparoscopic EJ with the Overlap method is associated with less
11
12 postoperative pain and anastomotic complications compared to FETE [12]. To date, there is no
13
14 prospective study to compare which method is more reasonable based on the QoL and surgical
15
16 safety of patients undergoing TLTG. We hypothesize that gastric cancer patients undergoing
17
18 TLTG with either FETE or Overlap intracorporeal EJ experience different QoL and surgical
19
20 safety after the procedure.

21 22 **Institutional data**

23
24 Our institution is one of the leading institutions in Shanghai, China affiliated to Fudan
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26 University. Our surgeons perform over 500 gastrectomies annually, with over 200 cases
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28 performed via laparoscopy. We have previously reported several novel reconstruction methods
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30 in performing totally laparoscopic proximal gastrectomy, distal gastrectomy, and total
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32 gastrectomy [13-15]. Self-pulling and latter transected (SPLT) reconstruction is one of our novel
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34 and routine method in performing laparoscopic total gastrectomy. The operational procedure
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36 and difficulty of anastomosis have been simplified, which effectively resolved problems
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38 associated with traditional EJ, such as esophageal retraction after transection, difficulty in
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40 opening the esophagus, difficulty in closing entry holes, complex technical requirements, higher
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42 cost (cheaper than traditional linear anastomosis), and difficulty in promotion. The results of a
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44 retrospective study of 100 TLTG+SPLT cases demonstrate SPLT is a safe and feasible
45
46 procedure [16]. Our surgeons have surpassed the learning curve for this procedure and have
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48 successfully performed over 150 SPLT surgeries.

49 50 **METHODS AND ANALYSIS**

51 52 **Patient and Public Involvement**

53
54 Laparoscopic surgery has become a leading trend for the treatment of various malignant
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56 diseases, including gastric cancer. Different methods of total laparoscopic total gastrectomy,
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58 including functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap)
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60 for esophagojejunostomy (EJ) are both accepted methods in clinical practice. Based on our
retrospective study, the SPLT technique is easier, cheaper and a more feasible method

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4 compared to traditional EJ. The present study design was concocted based on previous clinical
5 experience and patients' feedback. Prior to enrollment, each patient will be thoroughly informed
6 on the purpose of the study and the different interventional methods. Should the patient prefer
7 one method over another, he or she will no longer participate in the present trial. The primary
8 study outcome quality of life (QoL) will be assessed by the EORTC QLQ-C30 and QLQ-STO22
9 questionnaires, which mainly include patient self-reported symptoms and functional assessment.
10 The results of the study will be disseminated through a peer-reviewed journal. Study
11 participants will not be individually informed of study results.
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19 **Trial design**

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21 The current study is a prospective, randomized, open-label, single-center, interventional
22 trial using a parallel-arm design which would commence from October 1, 2020, through
23 September 30, 2022. Subjects will be randomized to receive one of two interventions: the FETE
24 group or the Overlap group. Figure 1 shows an overview of the trial design and each aspect of
25 the trial is introduced in detail below. Clinical trial registration is completed in the Chinese
26 Clinical Trial Registry, ChiCTR2000035583.
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33 **Inclusion criteria:** 1. Patients between 18 to 75 years old; 2. Primary gastric adenocarcinoma
34 confirmed pathologically by endoscopic biopsy; 3. Locally advanced tumor in the upper or
35 middle-third stomach, or locally advanced adenocarcinoma of the esophagogastric junction
36 (AEG) with Siewert type II or III (cT1-4a, N-/+, M0); 4. No distant metastasis, no direct invasion
37 of the pancreas, spleen, or other neighboring organs found on preoperative examinations; 5.
38 Performance status of 0 or 1 on the ECOG (Eastern Cooperative Oncology Group) scale; 6.
39 ASA (American Society of Anesthesiology) class I to III; 7. Written informed consent.
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46 **Exclusion Criteria:** 1. Pregnant and lactating women; 2. Suffering from severe mental
47 disorders; 3. History of previous upper abdominal surgery (except for laparoscopic
48 cholecystectomy); 4. Enlarged or bulky regional lymph node (diameter over 3 cm) found on
49 preoperative imaging including enlarged or bulky No.10 lymph node; 5. History of other
50 malignant diseases within the past 5 years; 6. History of unstable angina or myocardial
51 infarction within the past 6 months. 7. History of cerebrovascular accident within the past 6
52 months; 8. Emergency surgery (bleeding, obstruction, perforation) caused by gastric cancer.
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Contrast and grouping

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4 Patients are enrolled by the clinical research coordinator (CRC) on the team.

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6 Patients who fulfilled the eligibility criteria are randomized to receive either laparoscopic
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8 EJ with FETE-SPLT or Overlap-SPLT on a 1:1 ratio. SPSS software is used to generate the
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10 random sequence, and the subjects are coded according to the order of entering the group.
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12 The random sequence number corresponded to the coding sequence of patients, who will be
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14 randomly divided into two groups (odd number into SPLT-FETE group and even number into
15
16 SPLT Overlap Group). Blinding surgeons or participants is not feasible in this study.

17 Treatment

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19 **Lymphadenectomy:** A D2 lymph nodes (LNs) dissection will be regularly conducted
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21 according to the Japanese gastric cancer treatment guidelines 2014 (ver. 4)^[17].

22
23 **Reconstruction of anastomosis:** After completing lymphadenectomy, the abdominal
24
25 esophagus will be routinely mobilized. The subsequent conventional transection will be
26
27 substituted by ligation of the cardia (or esophagus above the upper margin of the tumor) using
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29 a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm
30
31 endoscopic linear stapler per usual.

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33 **FETE group (Figure 2):** Throughout the course of reconstruction, the ligature rope will be
34
35 held to drag down the esophagus to allow easier detachment from the posterior mediastinum.
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37 Next, a hole will be made on the posterior wall of the esophagus, 2 to 3 cm above the ligature
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39 rope. Then, another hole will be made at the anti-mesenteric border of the jejunum, 25 cm
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41 distal to the ligament of Treitz, serving as an entrance for the second stapler. Then, a side-to-
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43 side EJ will be performed through two holes, creating an entry hole. The following FETE will
44
45 be modified in a “latter transected” fashion.

46
47 **Overlap group (Figure 3):** The jejunum will be intracorporeally transected 20 cm distal to the
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49 ligament of Treitz using a linear stapler. The distal side of the jejunum will be additionally
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51 removed to avoid excessive tension on the anastomosis of the EJ. A small enterotomy will be
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53 created at 7cm distal to the stapler line on the antimesenteric side of the jejunal limb. Another
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55 small hole will be made on the left wall of the esophagus, 2 to 3 cm above the ligature rope.
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57 After one fork of the stapler is being inserted into the opening to form a jejunal limb towards the
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59 oral side of the lumen, the jejunal limb will be dragged up and positioned at the left side of the
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abdominal esophagus. Another fork of the linear stapler will be inserted carefully into the hole

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4 of the esophagus. After each fork has been completely inserted into each lumen, the firing of
5 the stapler will convert the two openings into a single-entry hole to create an end-to-side EJ.
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7 The entry hole will be simultaneously closed together as the esophagus is being transected
8
9 with the stapler.
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11 **Outcomes**

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13 The primary purpose of the present study is to compare the QoL between FETE and
14 Overlap groups (1, 3, 6, 9, 12 months after surgery)^[18] using the EORTC QLQ-C30 and QLQ-
15 STO22 questionnaires^[19, 20]. The EORTC QLQ-C30 is designed as a multidimensional
16 assessment of QoL, including 5 scales on functional assessment, 3 symptom scales, a global
17 health status, and 6 single items. A higher score indicates a better status in functioning domains,
18 but a worse status in symptom domains. The EORTC STO22 is designed specifically for
19 examining QoL of gastric cancer patients. It contains 22 questions including 5 symptom scales
20 and 4 single items. Higher scores indicate a worse status. Early postoperative complications
21 (anastomotic leakage, pulmonary complication, bleeding, pancreatic fistula) between FETE and
22 Overlap groups will also be compared. Early postoperative complication is defined as an event
23 observed within 30 days after surgery.
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35 **Adverse events**

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37 Adverse events (AEs) are any disadvantageous or uncertain events that affect the subject,
38 regardless of its association to the treatment procedure. All AEs are recorded on the case report
39 form (CRF) in detail, including occurrence, duration, prognosis, severity, and relevance to the
40 treatment. If such events result in death, disability, dysfunction, teratogenesis, or prolonged
41 hospitalization, it is defined as serious adverse events (SAEs). The occurrence of SAEs will be
42 reported to the Huashan Hospital Committee within 24 hours.
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49 **Sample size**

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51 In the present study, the postoperative quality of life of patients is the main evaluation index,
52 which is set as a non-inferiority study. According to the data of the retrospective study in China,
53 the QoL scores of the EJ Overlap group and FETE group are increased by 17 points relative to
54 the preoperative baseline^[19], with a standard deviation of D-value of 6.5 points and a non-
55 inferiority margin of 4 points. According to $\alpha = 0.025$, $\beta = 0.20$, the sample size of 86 (43 per
56 group) is calculated by the PASS 2020 software. The final sample size is 96 (48 per group)
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4 after considering a 10% dropout rate in each group. Our team is capable of performing 150
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6 TLTG procedures annually, therefore the planned recruitment period is 2 years, with a 1-year
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8 follow-up period.

9 10 **Data collection**

11 Data collection will be performed by trained professionals via paper-form datasheets from
12
13 inpatient and outpatient records until 1 year after the surgery. All relevant data will remain
14
15 anonymous and will only be accessible to relevant researchers and statisticians.

16 17 **Preoperative records**

18 Initial staging and diagnosis include endoscopy, endoscopic pathology, endoscopic
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20 ultrasound, non-contrast enhanced CT scan of the chest, and contrast-enhanced CT scan of
21
22 the abdomen. The patient's age, sex, weight, ASA classification, Eastern Cooperative
23
24 Oncology Group (ECOG) score, hemoglobin, C-reactive protein (CRP), comorbidities, history
25
26 of abdominal surgery, QoL, and tumor markers were recorded.

27 28 **Intraoperative records**

29 The type of EJ, operation time, blood loss (and blood transfusion), anastomosis time, intra-
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31 abdominal adhesion, specimen measurement (margin), and relevant complications were
32
33 recorded.

34 35 **Postoperative records**

36 Pathological diagnosis, postoperative complications (anastomotic leakage, anastomotic
37
38 bleeding, abdominal bleeding, abdominal infection, and intestinal obstruction), postoperative
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40 mortality, postoperative hospital stay, postoperative time to first aerofluxus, postoperative time
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42 to liquid diet, postoperative time to soft food diet, postoperative C-reactive protein, and
43
44 evaluation of postoperative biological markers were recorded.

45 46 **Follow-up records**

47 The follow-up medical history and physical examination, adjuvant therapy and completion,
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49 questionnaire results, laboratory results, imaging and endoscopic examination results were
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51 recorded.

52 Patient follow-up in the outpatient clinic abided by postoperative standards. The follow-up
53
54 period and parameters were summarized in Table 1.

55 56 **Data analysis**

Data processing of QoL scale

1. Raw Score (RS)=(Q1+Q2+Q?)/n, (Q: score of each item; n: number of all items)
2. Functional field: standard score (SS)=[1-(RS-1)/R(Range)] ×100
3. Symptom field and general health field: SS=[(RS-1)/R(Range)] ×100

Continuous data are expressed as mean ± standard deviation ($\bar{x}\pm S$), while categorical data are shown as percentage (%). The D-value between the standard score of postoperative and preoperative QoL is the comparative indicator. Student's t-tests will be used to compare continuous variables, while Chi-square tests or Fisher's tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software. A *p*-value of less than 0.05 will be considered statistically significant.

Patient informed consent

All participants should sufficiently understand the instructions detailed in the written informed consent (Appendix 1). All patients will be allowed to ask questions and be provided with a comprehensive response. Patients may choose not to participate in the research, or withdraw at any time after notifying the researchers to ensure that patient rights to treatment will not be affected. All participants are required to provide written informed consent before participating in the trial.

Data monitoring and interim analysis

Data monitoring and interim analysis will be conducted annually by a specialist committee organized by the funding organization (Shanghai ShenKang Hospital Development Center). An independent statistician will be invited to evaluate study outcomes after enrollment of over 60% participants. If a significant difference is noticed between the two intervention methods, the institution HIRB will be notified to determine whether early termination is necessary.

Ethics and dissemination

This study has been approved by the Hospital Institutional Review Board (HIRB) of Huashan Hospital, Fudan University (2020-1055). Upon completion of the study, the results of the primary study will be published in a peer-reviewed journal. We hope to provide a more scientific and reasonable theoretical basis for total laparoscopic gastrointestinal anastomosis, establish treatment standards, and further advertise the advantages of SPLT, which is safe, effective, and easy to promote. We anticipate a multicenter clinical trial for

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4 esophagojejunostomy with TLTG-SPLT in the near future to further validate the advantages of
5 the procedure. Study results will allow more AEG patients to benefit from the TLTG-SPLT
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7 technique.
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FIGURE LEGENDS**Figure 1. Study Flowchart****Figure 2. TLTG FETE SPLT**

A. The esophagus is pulled right and a hole is made on the posterior wall of the esophagus, 2 to 3 cm above the ligature rope. B. The mesentery of the jejunum 25 cm distal to the ligament of Treitz is mobilized to ensure blood supply. C. Another hole is made at the anti-mesenteric border of the jejunum. D. The lateral posterior wall of the esophagus is anastomosed with the jejunum. E. The jejunum is checked for injury. F. The entry hole is closed. G. The jejunojejunostomy is performed at the jejunum, 40 to 45 cm distal to EJ. H. The entry hole is closed. I. A drainage tube is placed posteriorly to EJ.

Figure 3. TLTG Overlap SPLT

Step 1 and step 2 of the Overlap method are consistent with the FETE method, followed by: A. The jejunum 20 cm distal to the ligament of Treitz is transected using a linear stapler. B. A small enterotomy will be made 6 cm distal to the stapler line on the anti-mesenteric side of the jejunal limb. C. The lateral posterior wall of the esophagus is anastomosed with the distal jejunum. D. The entry hole is closed. E. A small hole is made in the proximal jejunum. F. The jejunojejunostomy is performed at the jejunum 40 to 45 cm distal to EJ. G. The entry hole is closed. H. A drainage tube is placed posteriorly to EJ.

Table 1. Follow-up arrangements

	Observation Period					
	Preoperative 1 week	Postoperative 1 month	Postoperative 3 months	Postoperative 6 months	Postoperative 9 months	Postoperative 12 months
Patient Informed Consent	✓	✓	X	X	X	X
Previous Surgery	✓	✓	X	X	X	X
ASA Class	✓	✓	X	X	X	X
ECOG Scale	✓	✓	X	X	X	X
Weight	✓	✓	✓	✓	✓	✓
Blood routine test	✓	✓	✓	✓	✓	✓
CRP	✓	✓	X	X	X	X
Tumor markers	✓	X	✓	✓	✓	✓
CT Scan	✓	X	X	✓	X	✓
Endoscopy	✓	X	✓	X	X	✓
EORTC QLQ- C30	✓	✓	✓	✓	✓	✓
QLQ-STO22	✓	✓	✓	✓	✓	✓

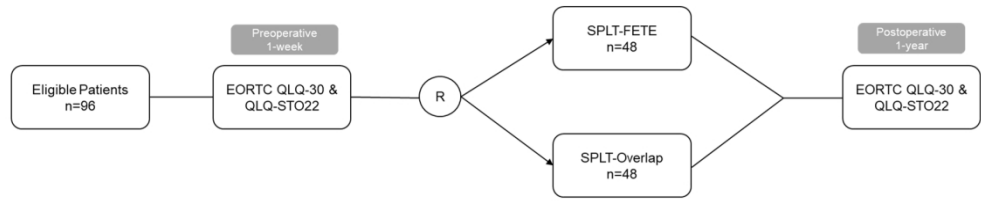
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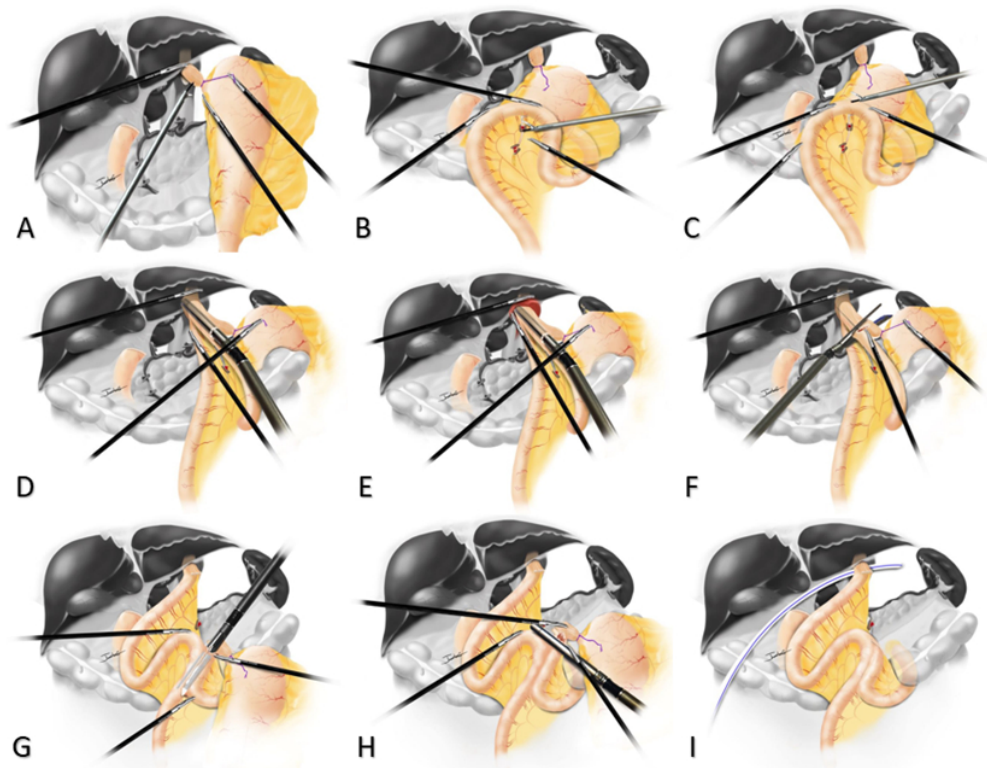
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Study Flowchart

313x68mm (150 x 150 DPI)

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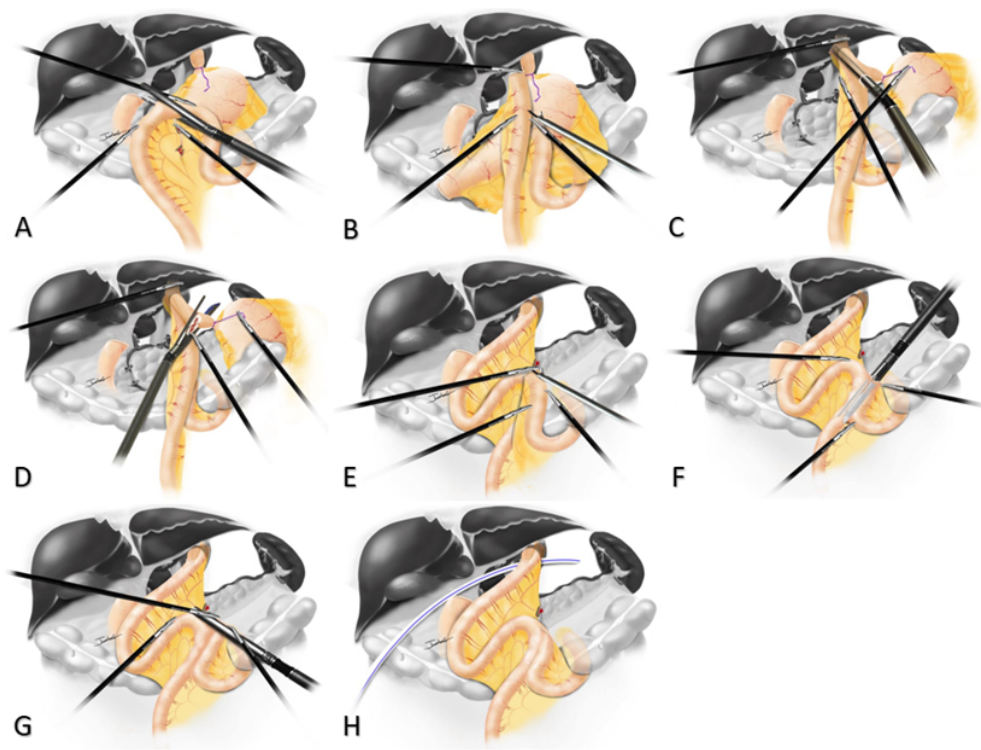


TLTG FETE SPLT

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TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

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Informed consent

(Translated version for reference)

Project Title: The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

Project Number: KY2021-496

Version: 01, March 30, 2021

Version of Informed consent: 02, May 15, 2021

Research Institution: Department of General Surgery, Huashan Hospital, Fudan University

Principal Investigator: Hankun Hao, Yaping Wang

You will be invited to participate in a clinical trial. You can decide whether to participate in this trial with the information provided. If you have any question about the trial, please contact the researcher.

You volunteer to participate in this study. This study has been reviewed by the ethics committee of this research institution.

Background and Objective

Gastric cancer is one of the most common cancers in China, while surgery is the most effective treatment for locally advanced gastric cancer. Prof. Kitano first reported laparoscopic assisted radical gastrectomy for distal gastric cancer in 1994. Laparoscopic surgery has since been recognized and widely promoted in the surgical treatment of gastric cancer. Compared with open surgery, laparoscopic surgery is less invasive with faster recovery. Laparoscopic gastrectomy can be divided into laparoscopic-assisted gastrectomy (extracorporeal anastomosis) and totally laparoscopic total gastrectomy (intracorporeal anastomosis) according to different anastomosis techniques. Laparoscopic total gastrectomy has been performed since 1999 by Prof. Uyama. Compared with open total gastrectomy, totally laparoscopic total gastrectomy developed more slowly due to difficulty associated with esophagojejunostomy. However, totally laparoscopic total gastrectomy can avoid disadvantages of laparoscopic assisted total gastrectomy, such as open incision and difficulty in exposure of the surgical field. Therefore, totally laparoscopic total gastrectomy is more commonly used in clinical practice. Roux-en-Y is the most common esophagojejunostomy

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4 method in total gastrectomy. Totally laparoscopic total gastrectomy can be divided into circular
5 stapler anastomosis and linear stapler anastomosis according to the type of stapler used.
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7 Compared with circular stapler anastomosis, linear stapler anastomosis has the advantages of
8 no purse-string suturing, no anvil placement, and better vision. There are two methods in linear
9 esophagojejunostomy for totally laparoscopic total gastrectomy: the functional end-to-end
10 (FETE) method and the Overlap method. The advantage of FETE esophagojejunostomy is that
11 closing entry hole does not result in stenosis of the lumen. The disadvantage is that retrograde
12 anastomosis requires a larger esophageal hiatal space, which in theory may cause evacuation
13 obstruction. Overlap has the advantages of a smaller space requirement, lower mesenteric
14 tension, and unobstructed jejunal evacuation. The disadvantage of this method is that the
15 closing of entry holes may cause jejunum stenosis, and hand-sewn anastomosis is often
16 required. The procedure is difficult and requires a longer operation time, which makes it difficult
17 to promote in clinical practice.

18
19 The Self-pulling and latter transected (SPLT) technique was first created by Prof. Hankun
20 Hao and has effectively resolved the shortcomings of traditional esophagojejunostomy, such
21 as esophageal retraction after transection, difficulty in opening the esophagus, difficulty in
22 closing entry holes, complex technical requirements, higher cost (cheaper than traditional linear
23 anastomosis), and difficulty in promotion. Our surgeons have surpassed the learning curve for
24 this procedure and have successfully performed over 150 SPLT surgeries, which confirmed
25 that SPLT is a simple, safe, feasible and economical procedure. The results of research have
26 been published in Surg Endoscopy and Chinese Journal of Gastrointestinal Surgery. The
27 evaluation of postoperative quality of life is an important standard of surgical quality in addition
28 to the postoperative survival of patients with gastric cancer. High quality of life should be
29 preferred in the case of similar postoperative survival. The difference in alimentary canal
30 reconstruction is the main factor affecting the postoperative quality of life, especially the diet of
31 patients with gastric cancer. There is no prospective research on the quality of life comparing
32 different laparoscopic esophagojejunostomy methods (Overlap and FETE). EORTC QLQ-C30
33 and QLQ-STO22 scales are the most common questionnaires used to evaluate the quality of
34 life after radical gastrectomy. The current study is a prospective, randomized, open-label,
35 single-center, interventional trial. We hypothesize that gastric cancer patients undergoing TLTG

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4 with either FETE or Overlap intracorporeal esophagojejunostomy experience different quality
5 of life and surgical safety after the procedure.
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7 Methods

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9 According to the data of a retrospective study conducted in China, the final sample size is
10 96 (48 Overlap group and 48 FETE group).
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13 Randomization principle: If you agree to participate in this study, a designated medical
14 profile will be established at the time you enter this study. The SPSS software will be used to
15 generate random sequences, which will correspond to your coding sequence, which will
16 randomly allocate you into the Overlap or FETE group.
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20 Your basic information will be collected and recorded by a dedicated physician. Records
21 include your name, age, sex, weight, ASA classification, Eastern Cooperative Oncology Group
22 (ECOG) score, hemoglobin, C-reactive protein (CRP), comorbidities, history of abdominal
23 surgery, tumor markers, intraoperative conditions, TNM staging, postoperative conditions,
24 regular questionnaire survey, and follow-up.
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28 After entering the study, you will receive liquid diet for preoperative bowel preparation on
29 one day before the procedure and prophylactic antibiotics (a single dose of second-generation
30 cephalosporin) will be given half an hour before the procedure. We will perform D2 / D2 + lymph
31 node dissection according to the location of the tumor, and complete esophagojejunostomy
32 with SPLT-Overlap or SPLT-FETE. The procedure requires a linear cutting stapler, several
33 reloads, and a negative pressure drainage. During the course of the treatment, it is necessary
34 to record your relevant data (anastomosis method, operation duration, time of reconstruction,
35 blood loss), postoperative complications (anastomotic leakage, anastomotic bleeding, infection,
36 etc.), postoperative hospital stay, postoperative quality of life, and postoperative follow-up
37 (medical history, physical examination, tumor markers, chest and abdominal CT). We hope that
38 you will follow-up at the designated outpatient clinic according to follow-up instructions of
39 postoperative gastric cancer, which includes one visit every 3 months within 2 years after the
40 procedure, one visit every 6 months starting from the 3rd year after the procedures. Gastroscopy
41 should be repeated annually for a consecutive 3 years after the procedure.
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58 Risk: All your personal information will remain confidential. Your treatment procedure will
59 be in strict accordance with current clinical guidelines. The relatively new anastomosis methods
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4 may increase the incidence of postoperative complications, such as anastomotic leakage,
5 anastomotic bleeding, intestinal obstruction, and infection. Very few patients require a second
6 surgical procedure.
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9 Benefit: You will receive advanced laparoscopic gastrectomy techniques for the treatment
10 of your condition, with relevant perioperative management, records, and evaluation. We will
11 provide necessary suggestions for your treatment and recommendations to improve your
12 postoperative quality of life.
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17 Expense: No additional expenditure is required for participating in this study. You will not
18 receive additional compensation.
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21 Compensation: Two anastomosis methods in this study are proven effective techniques. If
22 harm (except surgical complications and adverse drug reactions) occurs, the medical team will
23 try their best to reverse any damage. There is no additional compensation for participating in
24 this study.
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29 Your responsibilities: Provide authentic information about your medical history and current
30 physical condition. Inform the researchers about any discomfort during the study. Inform
31 researchers whether you have participated in other studies or are participating in other studies.
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35 Privacy issues: If you decide to participate in the study, your personal data will remain
36 confidential. Your medical information will be identified with the coding number rather than your
37 name. Information that can identify you will not be disclosed, other than to members of the
38 research team, unless permission is granted. All researchers are required to keep your identity
39 confidential. Your files will be stored in a locked filing cabinet for research purposes only. To
40 ensure that the research is carried out in accordance with these provisions, if necessary, the
41 members of government authorities or the ethics review committee can consult your personal
42 data within the research institute. When the results of this study are published, no personal
43 information will be disclosed.
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52 You can decide not to participate in the study or notify the researchers at any time to
53 withdraw from the study. Your data will not be included in the research results, and your medical
54 treatment and rights will not be affected. You can also discuss your treatment plan with your
55 attending physician.
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60 If you require other treatments or do not comply with the research plan or suffer from

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4 research-related harm, the researcher can terminate your participation in this study.

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6 You can always request information about the research progress. If new security
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8 information related to this study occurs, you will be notified. If you have any questions or
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10 concerns related to this study or experience any discomfort during the course of the study,
11
12 please contact Dr. Yaping Wang, Tel: 86-18917760598.

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14 If you have any questions or concerns about your rights and health, please contact Cuiyun
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16 Wu, member of Ethics Committee, Tel: 021-52888045.

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Signature Page

I have read this informed consent.

I have had the opportunity to ask questions and received adequate response.

I understand that participating in this study is voluntary.

I can choose not to participate in this study or decide to withdraw from the study at any time, without discrimination and my medical treatment and rights will not be affected.

If I require other treatments or do not comply with the research plan or suffer from research-related harm, the researcher can terminate my participation in this study.

I will receive a copy of the informed consent.

Name of Participant:

Signature of Participant:

Date:

I have accurately informed the participant. He/she has read and understood the informed consent and was given the opportunity to ask questions.

Name of researcher:

Researchers' signature:

Date:

(Ps: Witness signature is required if the participant is not literate and proxy signature is required if the participant is incapacitated.)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3, 7)
	2b	All items from the World Health Organization Trial Registration Data Set (n/a)
Protocol version	3	Date and version identifier (Appendix 1)
Funding	4	Sources and types of financial, material, and other support (Page 2)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Page 1)
	5b	Name and contact information for the trial sponsor (Page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 11)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 11)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Page 5-6)
	6b	Explanation for choice of comparators (Page 5-6)
Objectives	7	Specific objectives or hypotheses (Page 9)

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) **(Page 7-9)**
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8 **Methods: Participants, interventions, and outcomes**
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10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained **(Page 6)**
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) **(Page 7)**
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19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered **(Page 8-9)**
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) **(Page 6, 9)**
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) **(Page 9-10)**
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial **(Page 10)**
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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended **(Page 9-10)**
40
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42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended **(Page 7, Figure 1)**
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives
47 and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations **(Page 7-8)**
49

50 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
51 target sample size **(Page 9-10)**
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54 **Methods: Assignment of interventions (for controlled trials)**
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56 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Page 9-10)
8			
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Page 9-10)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (Page 7-10)
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how (n/a)
21			
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23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (n/a)
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page 9-10)
36			
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38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 9-10)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page 9-
46			10)
47			
48			
49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 10-11)
52			
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54		20b	Methods for any additional analyses (eg, subgroup and adjusted
55			analyses) (n/a)
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (n/a)
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Methods: Monitoring

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4 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role
5 and reporting structure; statement of whether it is independent from
6 the sponsor and competing interests; and reference to where further
7 details about its charter can be found, if not in the protocol.
8 Alternatively, an explanation of why a DMC is not needed (**Page 11**)
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10
11 21b Description of any interim analyses and stopping guidelines, including
12 who will have access to these interim results and make the final
13 decision to terminate the trial (**Page 11**)
14
15 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
16 spontaneously reported adverse events and other unintended effects
17 of trial interventions or trial conduct (**Page 9**)
18
19 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
20 whether the process will be independent from investigators and the
21 sponsor (**Page 11**)
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Ethics and dissemination

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25
26 Research ethics 24 Plans for seeking research ethics committee/institutional review board
27 approval (REC/IRB) approval (**Page 3 and 11**)
28
29 Protocol 25 Plans for communicating important protocol modifications (eg,
30 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
31 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
32 regulators) (**Page 11**)
33
34
35 Consent or assent 26a Who will obtain informed consent or assent from potential trial
36 participants or authorised surrogates, and how (see Item 32) (**Page**
37 **11**)
38
39 26b Additional consent provisions for collection and use of participant data
40 and biological specimens in ancillary studies, if applicable (**n/a**)
41
42
43 Confidentiality 27 How personal information about potential and enrolled participants will
44 be collected, shared, and maintained in order to protect confidentiality
45 before, during, and after the trial (**Page 10**)
46
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48 Declaration of 28 Financial and other competing interests for principal investigators for
49 interests the overall trial and each study site (**Page 1**)
50
51 Access to data 29 Statement of who will have access to the final trial dataset, and
52 disclosure of contractual agreements that limit such access for
53 investigators (**Page 10**)
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55 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for
56 post-trial care compensation to those who suffer harm from trial participation (**n/a**)
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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 11-12) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (n/a) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (n/a) |

16 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Page 11, Appendix 1) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (n/a) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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ABSTRACT

Introduction: Gastric cancer is the fifth most common cancer worldwide and the detection rate of proximal gastric cancer has been increasing. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) is increasingly performed for adenocarcinoma of the esophagogastric junction. However, totally laparoscopic total gastrectomy (TLTG) is only performed by a few surgeons due to difficulty associated with oesophagojejunostomy (OJ), in which there is no consensus on a standardised anastomosis technique. We propose a randomized trial to compare functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) for oesophagojejunostomy.

Methods and analysis: A prospective, randomized, open-label, single-centre, interventional trial has been designed to evaluate the quality of life (QoL) outcomes and safety of FETE and Overlap, with a 1-year follow-up as the primary endpoint. The trial began in 2020 and is scheduled to enrol 96 patients according to a previous sample size calculation. Patients were randomly allocated to the FETE or Overlap groups with a follow-up of one year to assess QoL after the procedure. All relevant clinical data including biological markers were collected. The primary indicator is the D-value between the postoperative and preoperative QoL. Student's t-tests will be used to compare continuous variables, while Chi-square tests or Fisher's tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software. A *p*-value of less than 0.05 will be considered statistically significant.

Ethics and dissemination: This study has been approved by the Hospital Institutional Review Board (HIRB) of Huashan Hospital, Fudan University (2020-1055). The results will be submitted for publication in peer-reviewed journals.

Trial registration number: ChiCTR2000035583.

Strengths and limitations of this study

- The current study is one of few randomised clinical trials aimed at comparing functional end-to-end anastomosis with side-to-side anastomosis for oesophagojejunostomy in totally laparoscopic total gastrectomy.
- The quality of life of patients and procedural safety of two different oesophagojejunostomy techniques will be compared, with a one-year follow-up period.

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- 4 ● The study result is limited to a single-centre study.
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- 6 ● Future multicentre studies may be warranted to further validate study results.
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INTRODUCTION

Gastric cancer is the fifth most common cancer, following breast cancer (11.7%), lung cancer (11.4%), colorectal cancer (10%), and prostate cancer (7.3%)^[1]. In 2020, the estimated number of new cases of gastric cancer is 1,089,103 worldwide (5.6% of all incident cancer cases), with new deaths of 768,793 (7.7% of all sites). The highest incidence rates are in Japan (male population) and Mongolia (female population). Gastric cancer is the fourth leading cause of cancer death in both sexes worldwide, with an estimated gastric cancer death of 769,000 in 2020 (equivalent to one in every 13 deaths globally). In recent years, the detection rate of proximal gastric cancer has been increasing ^[2]. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) has been performed since 1999^[3]. Evidence from several studies have demonstrated that totally laparoscopic total gastrectomy (TLTG) has the benefits of minimal blood loss, less postoperative pain, faster bowel function recovery, shorter duration of hospitalisation, and lower postoperative morbidity, at the cost of longer operative time compared with open total gastrectomy (OTG) ^[4-6]. TLTG has not been widely adapted due to difficulties associated with oesophagojejunostomy (OJ). When performing OTG, OJ with a circular stapling device is generally accepted as a substitute for hand-sutured anastomosis. However, there are two disadvantages to this technique: first, purse-string suturing is a mandatory step; second, it can be difficult to introduce the anvil of the circular stapler into the oesophagus. These disadvantages become more complicated in laparoscopic surgery than in open surgery. However, purse-string suturing and anvil introduction are not necessary when performing OJ with linear staplers. Two types of OJ have been reported using linear staplers, including the functional end-to-end anastomosis ^[7] and the side-to-side anastomosis (or the overlap method) ^[8]. The functional end-to-end procedure is performed by inserting the linear stapler into the oesophagus through a small hole on the left side of the oesophageal stump, while simultaneously lifting the jejunum to insert the stapler through a small hole on the opposite side of the jejunal mesentery. The entry holes are closed using the linear stapler, usually one at a time. In contrast, the overlap method is performed by creating holes on the left side of the oesophageal stump and 6 to 7 cm from the jejunal stump. After stapling, the entry hole is closed using hand-sewn sutures. Based on our retrospective

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4 study, the FETE group had poorer QoL outcomes compared with the Overlap group shortly
5 after surgery, while the rates of postoperative complications were similar between the two
6 groups. However, there is no agreement on the standard anastomosis technique for OJ [6, 9-11].
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8 A retrospective study in South Korea showed that laparoscopic OJ with the Overlap method is
9 associated with less postoperative pain and anastomotic complications compared to FETE [12].
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11 To date, there is no prospective study to compare which method is more reasonable based on
12 QoL outcomes and procedural safety of patients undergoing TLTG. We hypothesise that gastric
13 cancer patients undergoing TLTG with either FETE or Overlap intracorporeal OJ experience
14 different QoL and surgical sequelae after the procedure.
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20 21 **Institutional data**

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23 Our institution is one of the leading institutions in Shanghai, China affiliated to Fudan
24 University. Our surgeons perform over 500 gastrectomies annually, with over 200 cases
25 performed via laparoscopy. We have previously reported several novel reconstruction methods
26 in performing totally laparoscopic proximal gastrectomy, distal gastrectomy, and total
27 gastrectomy [13-15]. Self-pulling and latter transected (SPLT) reconstruction is one of our novel
28 and routine method in performing laparoscopic total gastrectomy. The operational procedure
29 and difficulty of anastomosis have been simplified, which effectively resolved problems
30 associated with traditional OJ, such as oesophageal retraction after transection, difficulty in
31 opening the oesophagus, difficulty in closing entry holes, complex technical requirements,
32 higher cost (cheaper than traditional linear anastomosis), and difficulty in promotion. The results
33 of a retrospective study of 100 TLTG+SPLT cases suggest that SPLT is a safe and feasible
34 procedure [16]. Our surgeons have surpassed the learning curve for this procedure and have
35 successfully performed over 150 SPLT surgeries.
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48 **METHODS AND ANALYSIS**

49 **Patient and Public Involvement**

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51 The present study design was concocted based on previous clinical experience and patient
52 feedback. Prior to enrolment, each patient will be thoroughly informed on the purpose of the
53 study and the different interventional methods. Should the patient prefer one method over
54 another, he or she will no longer participate in the present trial. Quality of life (QoL), will be
55 assessed by the EORTC QLQ-C30 and QLQ-STO22 questionnaires, which primarily include
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4 patient self-reported symptoms and functional assessment. The results of the study will be
5 disseminated through a peer-reviewed journal. Study participants will not be individually
6 informed of study results.
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9 **Trial design**

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11 The current study is a prospective, randomized, open-label, single-centre, interventional
12 trial using a parallel-arm design which would commence from October 1, 2020 through
13 September 30, 2022. Subjects will be randomised to receive one of two interventions: FETE or
14 Overlap. Figure 1 shows an overview of the trial design and each aspect of the trial is introduced
15 in detail below. Clinical trial registration is completed in the Chinese Clinical Trial Registry,
16 ChiCTR2000035583.
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20 **Inclusion criteria:** 1. Patients between 18 to 75 years old; 2. Primary gastric adenocarcinoma
21 confirmed pathologically by endoscopic biopsy; 3. Locally advanced tumour in the upper or
22 middle-third of the stomach, or locally advanced adenocarcinoma of the oesophagogastric
23 junction (AEG) with Siewert type II or III (cT1-4a, N-/+ , M0); 4. No distant metastasis, no direct
24 invasion of the pancreas, spleen, or other neighbouring organs found on preoperative
25 examinations; 5. Performance status of 0 or 1 on the ECOG (Eastern Cooperative Oncology
26 Group) scale; 6. ASA (American Society of Anesthesiology) class I to III; 7. Written informed
27 consent.
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31 **Exclusion Criteria:** 1. Pregnant or breastfeeding women; 2. Suffering from severe mental
32 disorders; 3. History of previous upper abdominal surgery (except for laparoscopic
33 cholecystectomy); 4. Enlarged or bulky regional lymph node (diameter over 3 cm) found on
34 preoperative imaging including enlarged or bulky No.10 lymph node; 5. History of other
35 malignant diseases within the past 5 years; 6. History of unstable angina or myocardial
36 infarction within the past 6 months. 7. History of cerebrovascular accident within the past 6
37 months; 8. Emergency surgery (bleeding, obstruction, perforation) caused by gastric cancer.
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40 **Contrast and grouping**

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42 Patients are enrolled by the clinical research coordinator (CRC) on the team.
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46 Patients who meet the eligibility criteria are randomized to receive either laparoscopic OJ
47 with FETE-SPLT or Overlap-SPLT on a 1:1 ratio. SPSS software is used to generate the
48 random sequence, and the subjects are coded according to the order of entering the group.
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4 The random sequence number corresponding to the coding sequence of patients will be
5 randomly divided into two groups (odd numbers into the SPLT-FETE group and even numbers
6 into the SPLT Overlap Group). Blinding surgeons or participants is not feasible in this study.
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9 **Treatment**

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11 **Lymphadenectomy:** A D2 lymph nodes (LNs) dissection will be regularly conducted
12 according to the Japanese gastric cancer treatment guidelines 2014 (ver. 4)^[17].
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15 **Reconstruction of anastomosis:** After undergoing lymphadenectomy, the abdominal
16 oesophagus will be routinely mobilized. The subsequent conventional transection will be
17 substituted by ligation of the cardia (or oesophagus above the upper margin of the tumour)
18 using a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm
19 endoscopic linear stapler per usual.
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25 **FETE group (Figure 2):** Throughout the course of reconstruction, the ligature rope will be
26 held to lower the oesophagus to allow easier detachment from the posterior mediastinum.
27 Next, a hole will be made on the posterior wall of the oesophagus, 2 to 3 cm above the
28 ligature rope. Then, another hole will be made at the anti-mesenteric border of the jejunum,
29 25 cm distal to the ligament of Treitz, serving as an entrance for the second stapler. Then, a
30 side-to-side OJ will be performed through two holes, creating an entry hole. The following
31 FETE will be modified in a “latter transected” fashion.
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39 **Overlap group (Figure 3):** The jejunum will be intracorporeally transected 20 cm distal to the
40 ligament of Treitz using a linear stapler. The distal side of the jejunum will be additionally
41 removed to avoid excessive tension on the anastomosis of the OJ. A small enterotomy will be
42 created at 7cm distal to the stapler line on the antimesenteric side of the jejunal limb. Another
43 small hole will be made on the left wall of the oesophagus, 2 to 3 cm above the ligature rope.
44 After one fork of the stapler is inserted into the opening to form a jejunal limb towards the oral
45 side of the lumen, the jejunal limb will be dragged up and positioned at the left side of the
46 abdominal oesophagus. Another fork of the linear stapler will be inserted carefully into the hole
47 of the oesophagus. After each fork has been completely inserted into each lumen, the firing of
48 the stapler will convert the two openings into a single-entry hole to create an end-to-side OJ.
49 The entry hole will be simultaneously closed together as the oesophagus is being transected
50 with the stapler.
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Outcomes

The primary purpose of the present study is to compare the QoL outcomes between the FETE and Overlap groups (1, 3, 6, 9, and 12 months after surgery)^[18] using the EORTC QLQ-C30 and QLQ-STO22 questionnaires^[19, 20]. The EORTC QLQ-C30 was designed as a multidimensional assessment of QoL, including 5 scales of functional assessment, 3 symptom scales, a global health status, and 6 single items. A higher score indicates a better status in functioning domains, but a worse status in symptom domains. The EORTC STO22 was designed specifically for examining QoL in gastric cancer patients. It contains 22 questions including 5 symptom scales and 4 single items. Higher scores indicate a worse status. Early postoperative complications (anastomotic leakage, pulmonary complication, bleeding, pancreatic fistula) between FETE and Overlap groups will also be compared. Early postoperative complication is defined as an event observed within 30 days after surgery.

Adverse events

Adverse events (AEs) are any disadvantageous or uncertain events that affect the subject, regardless of its association to the treatment procedure. All AEs are recorded on the case report form (CRF) in detail, including occurrence, duration, prognosis, severity, and relevance to the treatment. If such events result in death, disability, dysfunction, teratogenesis, or prolonged hospitalization, it is defined as serious adverse events (SAEs). The occurrence of SAEs will be reported to the Huashan Hospital Committee within 24 hours.

Sample size

In the present study, the postoperative quality of life of patients is the main evaluation index, which is set as a non-inferiority study. According to the data of the retrospective study in China, the QoL scores of the OJ Overlap group and FETE group are increased by 17 points relative to the preoperative baseline^[19], with a standard deviation of D-value of 6.5 points and a non-inferiority margin of 4 points. According to $\alpha = 0.025$, $\beta = 0.20$, the sample size of 86 (43 per group) was calculated by the PASS 2020 software. The final sample size is 96 (48 per group) after considering a 10% dropout rate in each group. Our team is capable of performing 150 TLTG procedures annually, therefore the planned recruitment period is 2 years, with a 1-year follow-up period.

Data collection

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4 Data collection will be performed by trained professionals via paper-form datasheets from
5 inpatient and outpatient records until 1 year after the surgery. All relevant data will remain
6 anonymous and will only be accessible to relevant researchers and statisticians.
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9 **Preoperative records**

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11 Initial staging and diagnosis include endoscopy, endoscopic pathology, endoscopic
12 ultrasound, non-contrast enhanced CT scan of the chest, and contrast-enhanced CT scan of
13 the abdomen. The patient's age, sex, weight, ASA classification, Eastern Cooperative
14 Oncology Group (ECOG) score, haemoglobin, C-reactive protein (CRP), comorbidities, history
15 of abdominal surgery, QoL, and tumour markers were recorded.
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20 **Intraoperative records**

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22 The type of OJ, operation time, blood loss (and blood transfusion), anastomosis time, intra-
23 abdominal adhesion, specimen measurement (margin), and relevant complications were
24 recorded.
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29 **Postoperative records**

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31 Pathological diagnosis, postoperative complications (anastomotic leakage, anastomotic
32 bleeding, abdominal bleeding, abdominal infection, and intestinal obstruction), postoperative
33 mortality, postoperative hospital stay, postoperative time to first aerofluxus, postoperative time
34 to liquid diet, postoperative time to soft food diet, postoperative C-reactive protein, and
35 evaluation of postoperative biological markers were recorded.
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40 **Follow-up records**

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42 The follow-up medical history and physical examination, adjuvant therapy and completion,
43 questionnaire results, laboratory results, imaging and endoscopic examination results were
44 recorded.
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48 Patient follow-up in the outpatient clinic abided by postoperative standards. The follow-up
49 period and parameters were summarized in Table 1.
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51 **Data analysis**

52 Data processing of QoL scale

- 53 1. Raw Score (RS)=(Q1+Q2+Q?)/n, (Q: score of each item; n: number of all items)
- 54 2. Functional field: standard score (SS)=[1-(RS-1)/R(Range)] ×100
- 55 3. Symptom field and general health field: SS=[(RS-1)/R(Range)] ×100

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4 Continuous data are expressed as mean \pm standard deviation ($\bar{x}\pm S$), while categorical data
5 are shown as percentage (%). The D-value between the standard score of postoperative and
6 preoperative QoL is the comparative indicator. Student's t-tests will be used to compare
7 continuous variables, while Chi-square tests or Fisher's tests will be used to compare
8 categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software.
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10 A *p*-value of less than 0.05 will be considered statistically significant.
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15 **Patient informed consent**

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17 All participants should sufficiently understand the instructions detailed in the written
18 informed consent form (Appendix 1). All patients will be given the opportunity to ask questions
19 and be provided with a comprehensive response. Patients may choose not to participate in the
20 study or withdraw at any time after notifying the researchers to ensure that patient rights to
21 treatment will not be affected. All participants are required to provide written informed consent
22 before participating in the trial.
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29 **Data monitoring and interim analysis**

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31 Data monitoring and interim analysis will be conducted annually by a specialist committee
32 organised by the funding organization (Shanghai ShenKang Hospital Development Center). An
33 independent statistician will be invited to evaluate study outcomes after enrolment of over 60%
34 participants. If a significant difference is noticed between the two intervention methods, the
35 institution HIRB will be notified to determine whether early termination is necessary.
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40 **Ethics and dissemination**

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42 This study has been approved by the Hospital Institutional Review Board (HIRB) of
43 Huashan Hospital, Fudan University (2020-1055). Upon completion of the study, the results of
44 the primary study will be published in a peer-reviewed journal.
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FIGURE LEGENDS**Figure 1. Study Flowchart****Figure 2. TLTG FETE SPLT**

A. The oesophagus is pulled to the right and a hole is made on the posterior wall of the oesophagus, 2 to 3 cm above the ligature rope. B. The mesentery of the jejunum 25 cm distal to the ligament of Treitz is mobilized to ensure blood supply. C. Another hole is made at the anti-mesenteric border of the jejunum. D. The lateral posterior wall of the oesophagus is anastomosed with the jejunum. E. The jejunum is checked for injury. F. The entry hole is closed. G. The jejunojejunostomy is performed at the jejunum, 40 to 45 cm distal to OJ. H. The entry hole is closed. I. A drainage tube is placed posteriorly to OJ.

Figure 3. TLTG Overlap SPLT

Step 1 and step 2 of the Overlap method are consistent with the FETE method, followed by: A. The jejunum 20 cm distal to the ligament of Treitz is transected using a linear stapler. B. A small enterotomy will be made 6 cm distal to the stapler line on the anti-mesenteric side of the jejunal limb. C. The lateral posterior wall of the oesophagus is anastomosed with the distal jejunum. D. The entry hole is closed. E. A small hole is made in the proximal jejunum. F. The jejunojejunostomy is performed at the jejunum 40 to 45 cm distal to OJ. G. The entry hole is closed. H. A drainage tube is placed posteriorly to OJ.

Table 1. Follow-up arrangements

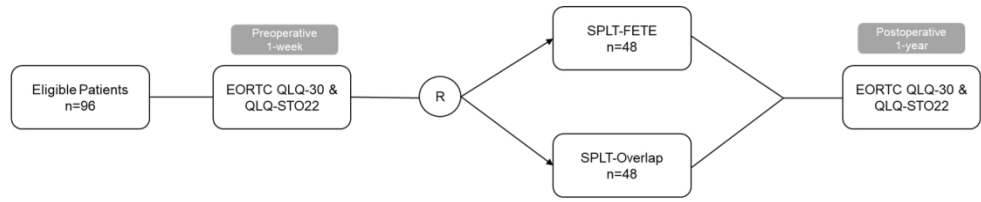
	Observation Period					
	Preoperative	Postoperative	Postoperative	Postoperative	Postoperative	Postoperative
	1 week	1 month	3 months	6 months	9 months	12 months
Patient Informed Consent	✓	✓	X	X	X	X
Previous Surgery	✓	✓	X	X	X	X
ASA Class	✓	✓	X	X	X	X
ECOG Scale	✓	✓	X	X	X	X
Weight	✓	✓	✓	✓	✓	✓
Blood routine test	✓	✓	✓	✓	✓	✓
CRP	✓	✓	X	X	X	X
Tumour markers	✓	X	✓	✓	✓	✓
CT Scan	✓	X	X	✓	X	✓
Endoscopy	✓	X	✓	X	X	✓
EORTC QLQ-C30	✓	✓	✓	✓	✓	✓
QLQ-STO22	✓	✓	✓	✓	✓	✓

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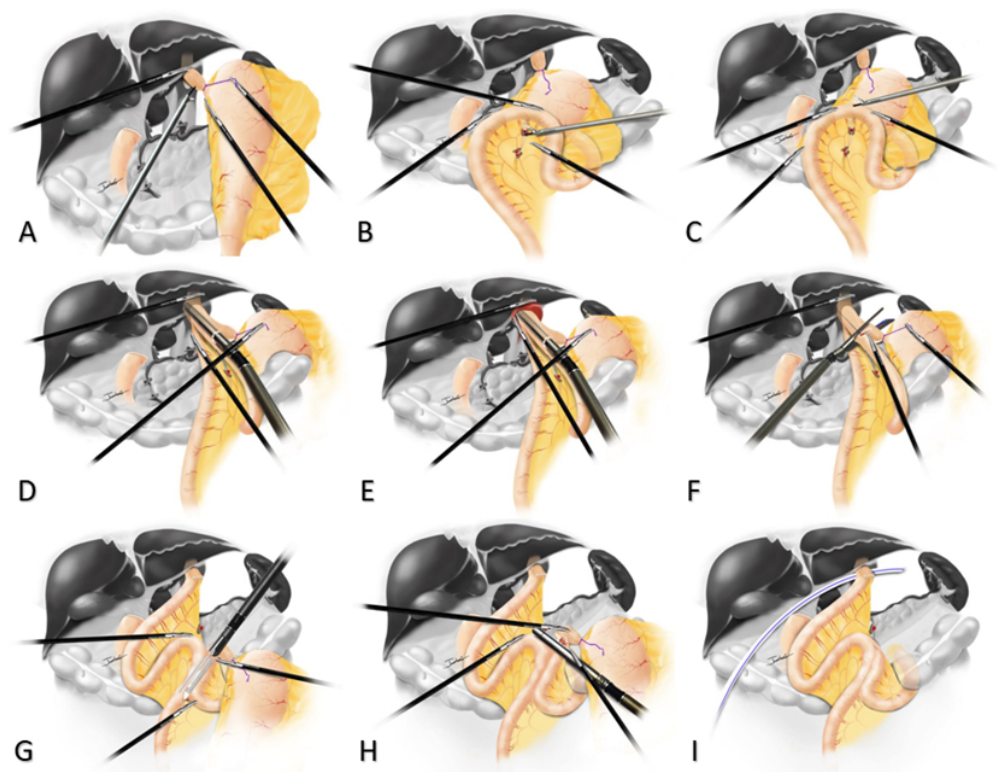


Study Flowchart

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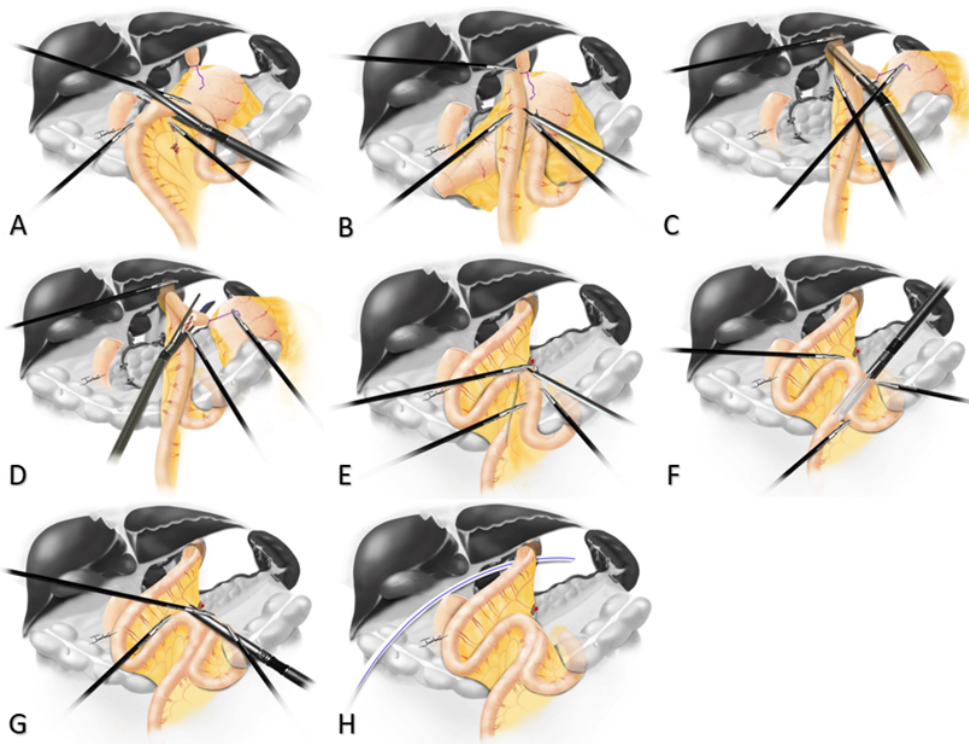
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TLTG FETE SPLT

146x113mm (144 x 144 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-058844 on 15 April 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



TLTG Overlap SPLT

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3, 7)
	2b	All items from the World Health Organization Trial Registration Data Set (n/a)
Protocol version	3	Date and version identifier (Appendix 1)
Funding	4	Sources and types of financial, material, and other support (Page 2)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Page 1)
	5b	Name and contact information for the trial sponsor (Page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 11)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 11)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Page 5-6)
	6b	Explanation for choice of comparators (Page 5-6)
Objectives	7	Specific objectives or hypotheses (Page 9)

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Page 7-9)**

Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 6)**

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(Page 7)**

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 8-9)**

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(Page 6, 9)**

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Page 9-10)**

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Page 10)**

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Page 9-10)**

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended **(Page 7, Figure 1)**

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 7-8)**

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size **(Page 9-10)**

Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Page 9-10)
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9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Page 9-10)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (Page 7-10)
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (n/a)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (n/a)
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page 9-10)
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 9-10)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page 9-
46			10)
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48			
49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 10-11)
52			
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54		20b	Methods for any additional analyses (eg, subgroup and adjusted
55			analyses) (n/a)
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (n/a)
60			

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Page 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (Page 11)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Page 9)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Page 11)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 3 and 11)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Page 11)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Page 11)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Page 10)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 1)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Page 10)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (n/a)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 11-12) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (n/a) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (n/a) |

16 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Page 11, Appendix 1) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (n/a) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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BMJ Open

The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058844.R3
Article Type:	Protocol
Date Submitted by the Author:	08-Mar-2022
Complete List of Authors:	Wang, Jian; Fudan University, Department of General Surgery Tseng, Yujen; Fudan University, Department of Digestive Diseases Hong, Jun; Fudan University, Department of General Surgery Hua, Lu-chun; Fudan University, Department of General Surgery Wang, Ya-ping; Fudan University, Department of General Surgery Hao, Han-kun; Fudan University, Department of General Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Research methods
Keywords:	SURGERY, Gastrointestinal tumours < GASTROENTEROLOGY, Clinical trials < THERAPEUTICS

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Manuscripts

Title Page

Title: The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

Running Title: study protocol for comparing different esophagojejunostomy methods

Type of Manuscript: Protocol

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Word Count: 2324

Contributions: Jian Wang and Yu-jen Tseng performed acquisition, analysis and interpretation of data; Jian Wang, Yu-jen Tseng and Jun Hong drafted the manuscript; Lu-Chun Hua, Han-Kun Hao, Ya-Ping Wang provided critical revision of the manuscript; All authors have reviewed and approved of the final version manuscript for submission.

Conflicts of Interest: All authors declare no conflict of interest.

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5 Center (No. SHDC2020CR3038B), the Huashan Hospital Fudan University Research Starting
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8 (No.IDF151039/006).
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ABSTRACT

Introduction: Gastric cancer is the fifth most common cancer worldwide and the detection rate of proximal gastric cancer has been increasing. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) is increasingly performed for adenocarcinoma of the esophagogastric junction. However, totally laparoscopic total gastrectomy (TLTG) is only performed by a few surgeons due to difficulty associated with oesophagojejunostomy (OJ), in which there is no consensus on a standardised anastomosis technique. We propose a randomized trial to compare functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) for oesophagojejunostomy.

Methods and analysis: A prospective, randomized, open-label, single-centre, interventional trial has been designed to evaluate the quality of life (QoL) outcomes and safety of FETE and Overlap, with a 1-year follow-up as the primary endpoint. The trial began in 2020 and is scheduled to enrol 96 patients according to a previous sample size calculation. Patients were randomly allocated to the FETE or Overlap groups with a follow-up of one year to assess QoL after the procedure. All relevant clinical data including biological markers were collected. The primary indicator is the D-value between the postoperative and preoperative QoL. Student's t-tests will be used to compare continuous variables, while Chi-square tests or Fisher's tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software. A *p*-value of less than 0.05 will be considered statistically significant.

Ethics and dissemination: This study has been approved by the Hospital Institutional Review Board (HIRB) of Huashan Hospital, Fudan University (2020-1055). The results will be submitted for publication in peer-reviewed journals.

Trial registration number: ChiCTR2000035583.

Strengths and limitations of this study

- The current study is one of few randomised clinical trials aimed at comparing functional end-to-end anastomosis with side-to-side anastomosis for oesophagojejunostomy in totally laparoscopic total gastrectomy.
- The quality of life of patients and procedural safety of two different oesophagojejunostomy techniques will be compared, with a one-year follow-up period.

- The study results are limited to a single centre.

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INTRODUCTION

Gastric cancer is the fifth most common cancer, following breast cancer (11.7%), lung cancer (11.4%), colorectal cancer (10%), and prostate cancer (7.3%)^[1]. In 2020, the estimated number of new cases of gastric cancer is 1,089,103 worldwide (5.6% of all incident cancer cases), with new deaths of 768,793 (7.7% of all sites). The highest incidence rates are in Japan (male population) and Mongolia (female population). Gastric cancer is the fourth leading cause of cancer death in both sexes worldwide, with an estimated gastric cancer death of 769,000 in 2020 (equivalent to one in every 13 deaths globally). In recent years, the detection rate of proximal gastric cancer has been increasing ^[2]. Currently, surgical resection using gastrectomy and proper perigastric lymphadenectomy is the only treatment option to enhance the survival rate of patients with gastric cancer. Laparoscopic total gastrectomy (LTG) has been performed since 1999^[3]. Evidence from several studies have demonstrated that totally laparoscopic total gastrectomy (TLTG) has the benefits of minimal blood loss, less postoperative pain, faster bowel function recovery, shorter duration of hospitalisation, and lower postoperative morbidity, at the cost of longer operative time compared with open total gastrectomy (OTG) ^[4-6]. TLTG has not been widely adapted due to difficulties associated with oesophagojejunostomy (OJ). When performing OTG, OJ with a circular stapling device is generally accepted as a substitute for hand-sutured anastomosis. However, there are two disadvantages to this technique: first, purse-string suturing is a mandatory step; second, it can be difficult to introduce the anvil of the circular stapler into the oesophagus. These disadvantages become more complicated in laparoscopic surgery than in open surgery. However, purse-string suturing and anvil introduction are not necessary when performing OJ with linear staplers. Two types of OJ have been reported using linear staplers, including the functional end-to-end anastomosis ^[7] and the side-to-side anastomosis (or the overlap method) ^[8]. The functional end-to-end procedure is performed by inserting the linear stapler into the oesophagus through a small hole on the left side of the oesophageal stump, while simultaneously lifting the jejunum to insert the stapler through a small hole on the opposite side of the jejunal mesentery. The entry holes are closed using the linear stapler, usually one at a time. In contrast, the overlap method is performed by creating holes on the left side of the oesophageal stump and 6 to 7 cm from the jejunal stump. After stapling, the entry hole is closed using hand-sewn sutures. Based on our retrospective

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4 study, the FETE group had poorer QoL outcomes compared with the Overlap group shortly
5 after surgery, while the rates of postoperative complications were similar between the two
6 groups. However, there is no agreement on the standard anastomosis technique for OJ [6, 9-11].
7
8 A retrospective study in South Korea showed that laparoscopic OJ with the Overlap method is
9 associated with less postoperative pain and anastomotic complications compared to FETE [12].
10
11 To date, there is no prospective study to compare which method is more reasonable based on
12 QoL outcomes and procedural safety of patients undergoing TLTG. We hypothesise that gastric
13 cancer patients undergoing TLTG with either FETE or Overlap intracorporeal OJ experience
14 different QoL and surgical sequelae after the procedure.
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20 21 **Institutional data**

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23 Our institution is one of the leading institutions in Shanghai, China affiliated to Fudan
24 University. Our surgeons perform over 500 gastrectomies annually, with over 200 cases
25 performed via laparoscopy. We have previously reported several novel reconstruction methods
26 in performing totally laparoscopic proximal gastrectomy, distal gastrectomy, and total
27 gastrectomy [13-15]. Self-pulling and latter transected (SPLT) reconstruction is one of our novel
28 and routine method in performing laparoscopic total gastrectomy. The operational procedure
29 and difficulty of anastomosis have been simplified, which effectively resolved problems
30 associated with traditional OJ, such as oesophageal retraction after transection, difficulty in
31 opening the oesophagus, difficulty in closing entry holes, complex technical requirements,
32 higher cost (cheaper than traditional linear anastomosis), and difficulty in promotion. The results
33 of a retrospective study of 100 TLTG+SPLT cases suggest that SPLT is a safe and feasible
34 procedure [16]. Our surgeons have surpassed the learning curve for this procedure and have
35 successfully performed over 150 SPLT surgeries.
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48 **METHODS AND ANALYSIS**

49 **Patient and Public Involvement**

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51 Patients and the public were not involved in the design and conduct of the trial. The results
52 of the study will be disseminated through a peer-reviewed journal. Study participants will not
53 be individually informed of study results.
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58 **Trial design**

59 The current study is a prospective, randomized, open-label, single-centre, interventional
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4 trial using a parallel-arm design which would commence from October 1, 2020 through
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6 September 30, 2022. Subjects will be randomised to receive one of two interventions: FETE or
7
8 Overlap. Figure 1 shows an overview of the trial design and each aspect of the trial is introduced
9
10 in detail below. Clinical trial registration is completed in the Chinese Clinical Trial Registry,
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12 ChiCTR2000035583.

13
14 **Inclusion criteria:** 1. Patients between 18 to 75 years old; 2. Primary gastric adenocarcinoma
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16 confirmed pathologically by endoscopic biopsy; 3. Locally advanced tumour in the upper or
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18 middle-third of the stomach, or locally advanced adenocarcinoma of the oesophagogastric
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20 junction (AEG) with Siewert type II or III (cT1-4a, N-/+, M0); 4. No distant metastasis, no direct
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22 invasion of the pancreas, spleen, or other neighbouring organs found on preoperative
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24 examinations; 5. Performance status of 0 or 1 on the ECOG (Eastern Cooperative Oncology
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26 Group) scale; 6. ASA (American Society of Anesthesiology) class I to III; 7. Written informed
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28 consent.

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30 **Exclusion Criteria:** 1. Pregnant or breastfeeding women; 2. Suffering from severe mental
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32 disorders; 3. History of previous upper abdominal surgery (except for laparoscopic
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34 cholecystectomy); 4. Enlarged or bulky regional lymph node (diameter over 3 cm) found on
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36 preoperative imaging including enlarged or bulky No.10 lymph node; 5. History of other
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38 malignant diseases within the past 5 years; 6. History of unstable angina or myocardial
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40 infarction within the past 6 months. 7. History of cerebrovascular accident within the past 6
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42 months; 8. Emergency surgery (bleeding, obstruction, perforation) caused by gastric cancer.

43 **Contrast and grouping**

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45 Patients are enrolled by the clinical research coordinator (CRC) on the team.

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47 Patients who meet the eligibility criteria are randomized to receive either laparoscopic OJ
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49 with FETE-SPLT or Overlap-SPLT on a 1:1 ratio. SPSS software is used to generate the
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51 random sequence, and the subjects are coded according to the order of entering the group.
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53 The random sequence number corresponding to the coding sequence of patients will be
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55 randomly divided into two groups (odd numbers into the SPLT-FETE group and even numbers
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57 into the SPLT Overlap Group). Blinding surgeons or participants is not feasible in this study.

58 **Treatment**

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4 **Lymphadenectomy:** A D2 lymph nodes (LNs) dissection will be regularly conducted
5 according to the Japanese gastric cancer treatment guidelines 2014 (ver. 4)^[17].
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7 **Reconstruction of anastomosis:** After undergoing lymphadenectomy, the abdominal
8 oesophagus will be routinely mobilized. The subsequent conventional transection will be
9 substituted by ligation of the cardia (or oesophagus above the upper margin of the tumour)
10 using a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm
11 endoscopic linear stapler per usual.
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16 **FETE group (Figure 2):** Throughout the course of reconstruction, the ligature rope will be
17 held to lower the oesophagus to allow easier detachment from the posterior mediastinum.
18 Next, a hole will be made on the posterior wall of the oesophagus, 2 to 3 cm above the
19 ligature rope. Then, another hole will be made at the anti-mesenteric border of the jejunum,
20 25 cm distal to the ligament of Treitz, serving as an entrance for the second stapler. Then, a
21 side-to-side OJ will be performed through two holes, creating an entry hole. The following
22 FETE will be modified in a “latter transected” fashion.
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30 **Overlap group (Figure 3):** The jejunum will be intracorporeally transected 20 cm distal to the
31 ligament of Treitz using a linear stapler. The distal side of the jejunum will be additionally
32 removed to avoid excessive tension on the anastomosis of the OJ. A small enterotomy will be
33 created at 7cm distal to the stapler line on the antimesenteric side of the jejunal limb. Another
34 small hole will be made on the left wall of the oesophagus, 2 to 3 cm above the ligature rope.
35 After one fork of the stapler is inserted into the opening to form a jejunal limb towards the oral
36 side of the lumen, the jejunal limb will be dragged up and positioned at the left side of the
37 abdominal oesophagus. Another fork of the linear stapler will be inserted carefully into the hole
38 of the oesophagus. After each fork has been completely inserted into each lumen, the firing of
39 the stapler will convert the two openings into a single-entry hole to create an end-to-side OJ.
40 The entry hole will be simultaneously closed together as the oesophagus is being transected
41 with the stapler.
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54 **Outcomes**

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56 The primary purpose of the present study is to compare the QoL outcomes between the
57 FETE and Overlap groups (1, 3, 6, 9, and 12 months after surgery)^[18] using the EORTC QLQ-
58 C30 and QLQ-STO22 questionnaires^[19, 20]. The EORTC QLQ-C30 was designed as a
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3 multidimensional assessment of QoL, including 5 scales of functional assessment, 3 symptom
4 scales, a global health status, and 6 single items. A higher score indicates a better status in
5 functioning domains, but a worse status in symptom domains. The EORTC STO22 was
6 designed specifically for examining QoL in gastric cancer patients. It contains 22 questions
7 including 5 symptom scales and 4 single items. Higher scores indicate a worse status. Early
8 postoperative complications (anastomotic leakage, pulmonary complication, bleeding,
9 pancreatic fistula) between FETE and Overlap groups will also be compared. Early
10 postoperative complication is defined as an event observed within 30 days after surgery.

11 12 13 14 15 16 17 18 19 **Adverse events**

20
21 Adverse events (AEs) are any disadvantageous or uncertain events that affect the subject,
22 regardless of its association to the treatment procedure. All AEs are recorded on the case report
23 form (CRF) in detail, including occurrence, duration, prognosis, severity, and relevance to the
24 treatment. If such events result in death, disability, dysfunction, teratogenesis, or prolonged
25 hospitalization, it is defined as serious adverse events (SAEs). The occurrence of SAEs will be
26 reported to the Huashan Hospital Committee within 24 hours.

27 28 29 30 31 32 33 **Sample size**

34
35 In the present study, the postoperative quality of life of patients is the main evaluation index,
36 which is set as a non-inferiority study. According to the data of the retrospective study in China,
37 the QoL scores of the OJ Overlap group and FETE group are increased by 17 points relative
38 to the preoperative baseline^[19], with a standard deviation of D-value of 6.5 points and a non-
39 inferiority margin of 4 points. According to $\alpha = 0.025$, $\beta = 0.20$, the sample size of 86 (43 per
40 group) was calculated by the PASS 2020 software. The final sample size is 96 (48 per group)
41 after considering a 10% dropout rate in each group. Our team is capable of performing 150
42 TLTG procedures annually, therefore the planned recruitment period is 2 years, with a 1-year
43 follow-up period.

44 45 46 47 48 49 50 51 52 **Data collection**

53
54 Data collection will be performed by trained professionals via paper-form datasheets from
55 inpatient and outpatient records until 1 year after the surgery. All relevant data will remain
56 anonymous and will only be accessible to relevant researchers and statisticians.

57 58 59 60 **Preoperative records**

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4 Initial staging and diagnosis include endoscopy, endoscopic pathology, endoscopic
5 ultrasound, non-contrast enhanced CT scan of the chest, and contrast-enhanced CT scan of
6 the abdomen. The patient's age, sex, weight, ASA classification, Eastern Cooperative
7 Oncology Group (ECOG) score, haemoglobin, C-reactive protein (CRP), comorbidities, history
8 of abdominal surgery, QoL, and tumour markers were recorded.
9
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13 **Intraoperative records**

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15 The type of OJ, operation time, blood loss (and blood transfusion), anastomosis time, intra-
16 abdominal adhesion, specimen measurement (margin), and relevant complications were
17 recorded.
18
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20

21 **Postoperative records**

22
23 Pathological diagnosis, postoperative complications (anastomotic leakage, anastomotic
24 bleeding, abdominal bleeding, abdominal infection, and intestinal obstruction), postoperative
25 mortality, postoperative hospital stay, postoperative time to first aerofluxus, postoperative time
26 to liquid diet, postoperative time to soft food diet, postoperative C-reactive protein, and
27 evaluation of postoperative biological markers were recorded.
28
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33 **Follow-up records**

34
35 The follow-up medical history and physical examination, adjuvant therapy and completion,
36 questionnaire results, laboratory results, imaging and endoscopic examination results were
37 recorded.
38
39

40
41 Patient follow-up in the outpatient clinic abided by postoperative standards. The follow-up
42 period and parameters were summarized in Table 1.
43

44 **Data analysis**

45
46 Data processing of QoL scale

- 47
48 1. Raw Score (RS)=(Q1+Q2+Q?)/n, (Q: score of each item; n: number of all items)
- 49
50 2. Functional field: standard score (SS)=[1-(RS-1)/R(Range)] ×100
- 51
52 3. Symptom field and general health field: SS=[(RS-1)/R(Range)] ×100

53
54 Continuous data are expressed as mean ± standard deviation ($\bar{x}\pm S$), while categorical data
55 are shown as percentage (%). The D-value between the standard score of postoperative and
56 preoperative QoL is the comparative indicator. Student's t-tests will be used to compare
57 continuous variables, while Chi-square tests or Fisher's tests will be used to compare
58
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4 categorical variables. Statistical analysis will be performed with SPSS 23.0 statistical software.

5 A *p*-value of less than 0.05 will be considered statistically significant.

6 7 **Patient informed consent**

8
9 All participants should sufficiently understand the instructions detailed in the written
10 informed consent form (Appendix 1). All patients will be given the opportunity to ask questions
11 and be provided with a comprehensive response. Patients may choose not to participate in the
12 study or withdraw at any time after notifying the researchers to ensure that patient rights to
13 treatment will not be affected. All participants are required to provide written informed consent
14 before participating in the trial.

15 16 17 **Data monitoring and interim analysis**

18
19 Data monitoring and interim analysis will be conducted annually by a specialist committee
20 organised by the funding organization (Shanghai ShenKang Hospital Development Center). An
21 independent statistician will be invited to evaluate study outcomes after enrolment of over 60%
22 participants. If a significant difference is noticed between the two intervention methods, the
23 institution HIRB will be notified to determine whether early termination is necessary.

24 25 26 **Ethics and dissemination**

27
28 This study has been approved by the Hospital Institutional Review Board (HIRB) of
29 Huashan Hospital, Fudan University (2020-1055). Upon completion of the study, the results of
30 the primary study will be published in a peer-reviewed journal.
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FIGURE LEGENDS**Figure 1. Study Flowchart****Figure 2. TLTG FETE SPLT**

A. The oesophagus is pulled to the right and a hole is made on the posterior wall of the oesophagus, 2 to 3 cm above the ligature rope. B. The mesentery of the jejunum 25 cm distal to the ligament of Treitz is mobilized to ensure blood supply. C. Another hole is made at the anti-mesenteric border of the jejunum. D. The lateral posterior wall of the oesophagus is anastomosed with the jejunum. E. The jejunum is checked for injury. F. The entry hole is closed. G. The jejunojejunostomy is performed at the jejunum, 40 to 45 cm distal to OJ. H. The entry hole is closed. I. A drainage tube is placed posteriorly to OJ.

Figure 3. TLTG Overlap SPLT

Step 1 and step 2 of the Overlap method are consistent with the FETE method, followed by: A. The jejunum 20 cm distal to the ligament of Treitz is transected using a linear stapler. B. A small enterotomy will be made 6 cm distal to the stapler line on the anti-mesenteric side of the jejunal limb. C. The lateral posterior wall of the oesophagus is anastomosed with the distal jejunum. D. The entry hole is closed. E. A small hole is made in the proximal jejunum. F. The jejunojejunostomy is performed at the jejunum 40 to 45 cm distal to OJ. G. The entry hole is closed. H. A drainage tube is placed posteriorly to OJ.

Table 1. Follow-up arrangements

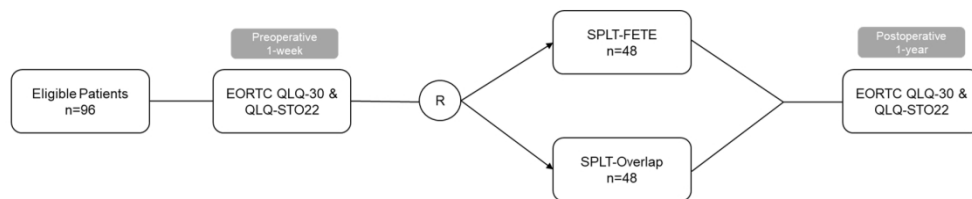
	Observation Period					
	Preoperative	Postoperative	Postoperative	Postoperative	Postoperative	Postoperative
	1 week	1 month	3 months	6 months	9 months	12 months
Patient Informed Consent	✓	✓	X	X	X	X
Previous Surgery	✓	✓	X	X	X	X
ASA Class	✓	✓	X	X	X	X
ECOG Scale	✓	✓	X	X	X	X
Weight	✓	✓	✓	✓	✓	✓
Blood routine test	✓	✓	✓	✓	✓	✓
CRP	✓	✓	X	X	X	X
Tumour markers	✓	X	✓	✓	✓	✓
CT Scan	✓	X	X	✓	X	✓
Endoscopy	✓	X	✓	X	X	✓
EORTC QLQ-C30	✓	✓	✓	✓	✓	✓
QLQ-STO22	✓	✓	✓	✓	✓	✓

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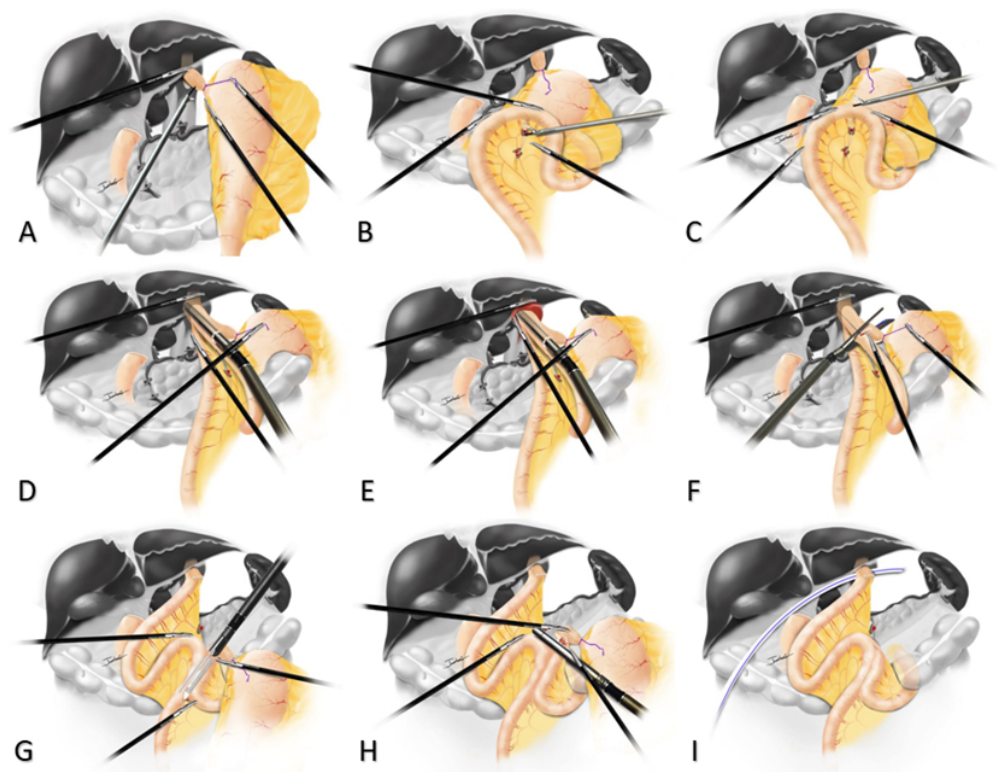


Study Flowchart

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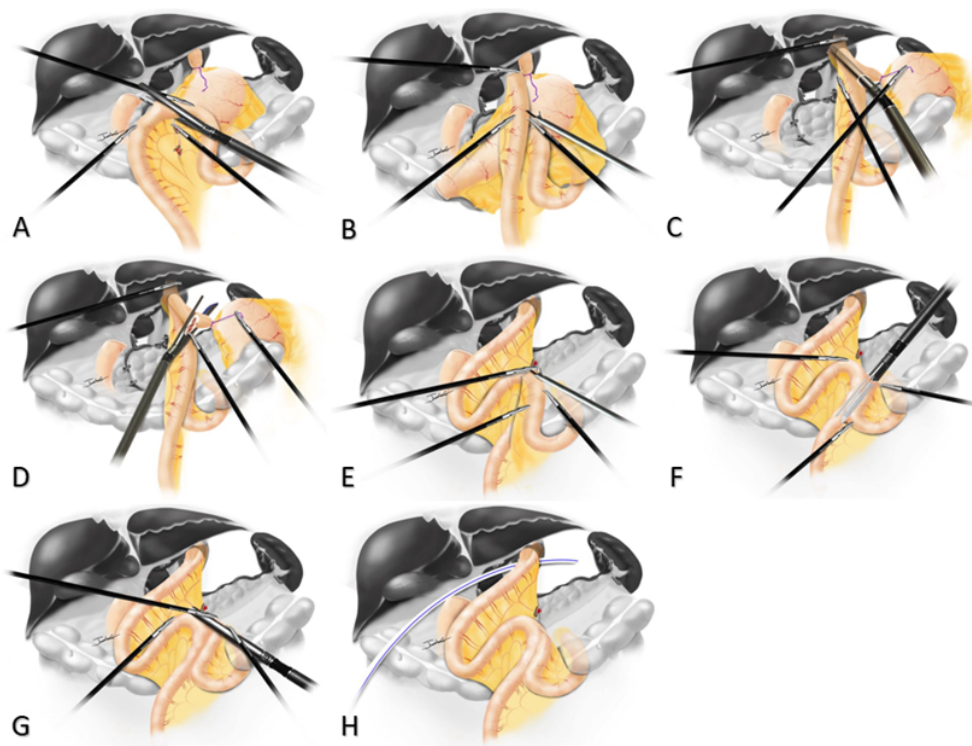
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TLTG FETE SPLT

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TLTG Overlap SPLT

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Informed consent

(Translated version for reference)

Project Title: The effect of different esophagojejunostomy methods on the quality of life of gastric cancer patients after totally laparoscopic total gastrectomy with self-pulling and latter transected technique: study protocol for a randomized trial

Project Number: KY2021-496

Version: 01, March 30, 2021

Version of Informed consent: 02, May 15, 2021

Research Institution: Department of General Surgery, Huashan Hospital, Fudan University

Principal Investigator: Hankun Hao, Yaping Wang

You will be invited to participate in a clinical trial. You can decide whether to participate in this trial with the information provided. If you have any question about the trial, please contact the researcher.

You volunteer to participate in this study. This study has been reviewed by the ethics committee of this research institution.

Background and Objective

Gastric cancer is one of the most common cancers in China, while surgery is the most effective treatment for locally advanced gastric cancer. Prof. Kitano first reported laparoscopic assisted radical gastrectomy for distal gastric cancer in 1994. Laparoscopic surgery has since been recognized and widely promoted in the surgical treatment of gastric cancer. Compared with open surgery, laparoscopic surgery is less invasive with faster recovery. Laparoscopic gastrectomy can be divided into laparoscopic-assisted gastrectomy (extracorporeal anastomosis) and totally laparoscopic total gastrectomy (intracorporeal anastomosis) according to different anastomosis techniques. Laparoscopic total gastrectomy has been performed since 1999 by Prof. Uyama. Compared with open total gastrectomy, totally laparoscopic total gastrectomy developed more slowly due to difficulty associated with esophagojejunostomy. However, totally laparoscopic total gastrectomy can avoid disadvantages of laparoscopic assisted total gastrectomy, such as open incision and difficulty in exposure of the surgical field. Therefore, totally laparoscopic total gastrectomy is more commonly used in clinical practice. Roux-en-Y is the most common esophagojejunostomy

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4 method in total gastrectomy. Totally laparoscopic total gastrectomy can be divided into circular
5
6 stapler anastomosis and linear stapler anastomosis according to the type of stapler used.
7
8 Compared with circular stapler anastomosis, linear stapler anastomosis has the advantages of
9
10 no purse-string suturing, no anvil placement, and better vision. There are two methods in linear
11
12 esophagojejunostomy for totally laparoscopic total gastrectomy: the functional end-to-end
13
14 (FETE) method and the Overlap method. The advantage of FETE esophagojejunostomy is that
15
16 closing entry hole does not result in stenosis of the lumen. The disadvantage is that retrograde
17
18 anastomosis requires a larger esophageal hiatal space, which in theory may cause evacuation
19
20 obstruction. Overlap has the advantages of a smaller space requirement, lower mesenteric
21
22 tension, and unobstructed jejunal evacuation. The disadvantage of this method is that the
23
24 closing of entry holes may cause jejunum stenosis, and hand-sewn anastomosis is often
25
26 required. The procedure is difficult and requires a longer operation time, which makes it difficult
27
28 to promote in clinical practice.

29
30 The Self-pulling and latter transected (SPLT) technique was first created by Prof. Hankun
31
32 Hao and has effectively resolved the shortcomings of traditional esophagojejunostomy, such as
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34 esophageal retraction after transection, difficulty in opening the esophagus, difficulty in closing
35
36 entry holes, complex technical requirements, higher cost (cheaper than traditional linear
37
38 anastomosis), and difficulty in promotion. Our surgeons have surpassed the learning curve for
39
40 this procedure and have successfully performed over 150 SPLT surgeries, which confirmed that
41
42 SPLT is a simple, safe, feasible and economical procedure. The results of research have been
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44 published in Surg Endoscopy and Chinese Journal of Gastrointestinal Surgery. The evaluation
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46 of postoperative quality of life is an important standard of surgical quality in addition to the
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48 postoperative survival of patients with gastric cancer. High quality of life should be preferred in
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50 the case of similar postoperative survival. The difference in alimentary canal reconstruction is
51
52 the main factor affecting the postoperative quality of life, especially the diet of patients with
53
54 gastric cancer. There is no prospective research on the quality of life comparing different
55
56 laparoscopic esophagojejunostomy methods (Overlap and FETE). EORTC QLQ-C30 and
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58 QLQ-STO22 scales are the most common questionnaires used to evaluate the quality of life
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60 after radical gastrectomy. The current study is a prospective, randomized, open-label, single-
center, interventional trial. We hypothesize that gastric cancer patients undergoing TLTG with

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4 either FETE or Overlap intracorporeal esophagojejunostomy experience different quality of life
5
6 and surgical safety after the procedure.

7 Methods

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9 According to the data of a retrospective study conducted in China, the final sample size is
10
11 96 (48 Overlap group and 48 FETE group).

12
13 Randomization principle: If you agree to participate in this study, a designated medical
14
15 profile will be established at the time you enter this study. The SPSS software will be used to
16
17 generate random sequences, which will correspond to your coding sequence, which will
18
19 randomly allocate you into the Overlap or FETE group.

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21 Your basic information will be collected and recorded by a dedicated physician. Records
22
23 include your name, age, sex, weight, ASA classification, Eastern Cooperative Oncology Group
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25 (ECOG) score, hemoglobin, C-reactive protein (CRP), comorbidities, history of abdominal
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27 surgery, tumor markers, intraoperative conditions, TNM staging, postoperative conditions,
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29 regular questionnaire survey, and follow-up.

30
31 After entering the study, you will receive liquid diet for preoperative bowel preparation on
32
33 one day before the procedure and prophylactic antibiotics (a single dose of second-generation
34
35 cephalosporin) will be given half an hour before the procedure. We will perform D2 / D2 + lymph
36
37 node dissection according to the location of the tumor, and complete esophagojejunostomy with
38
39 SPLT-Overlap or SPLT-FETE. The procedure requires a linear cutting stapler, several reloads,
40
41 and a negative pressure drainage. During the course of the treatment, it is necessary to record
42
43 your relevant data (anastomosis method, operation duration, time of reconstruction, blood loss),
44
45 postoperative complications (anastomotic leakage, anastomotic bleeding, infection, etc.),
46
47 postoperative hospital stay, postoperative quality of life, and postoperative follow-up (medical
48
49 history, physical examination, tumor markers, chest and abdominal CT). We hope that you will
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51 follow-up at the designated outpatient clinic according to follow-up instructions of postoperative
52
53 gastric cancer, which includes one visit every 3 months within 2 years after the procedure, one
54
55 visit every 6 months starting from the 3rd year after the procedures. Gastroscopy should be
56
57 repeated annually for a consecutive 3 years after the procedure.

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59 Risk: All your personal information will remain confidential. Your treatment procedure will
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be in strict accordance with current clinical guidelines. The relatively new anastomosis methods

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4 may increase the incidence of postoperative complications, such as anastomotic leakage,
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6 anastomotic bleeding, intestinal obstruction, and infection. Very few patients require a second
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8 surgical procedure.

9
10 Benefit: You will receive advanced laparoscopic gastrectomy techniques for the treatment
11
12 of your condition, with relevant perioperative management, records, and evaluation. We will
13
14 provide necessary suggestions for your treatment and recommendations to improve your
15
16 postoperative quality of life.

17
18 Expense: No additional expenditure is required for participating in this study. You will not
19
20 receive additional compensation.

21
22 Compensation: Two anastomosis methods in this study are proven effective techniques. If
23
24 harm (except surgical complications and adverse drug reactions) occurs, the medical team will
25
26 try their best to reverse any damage. There is no additional compensation for participating in
27
28 this study.

29
30 Your responsibilities: Provide authentic information about your medical history and current
31
32 physical condition. Inform the researchers about any discomfort during the study. Inform
33
34 researchers whether you have participated in other studies or are participating in other studies.

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36 Privacy issues: If you decide to participate in the study, your personal data will remain
37
38 confidential. Your medical information will be identified with the coding number rather than your
39
40 name. Information that can identify you will not be disclosed, other than to members of the
41
42 research team, unless permission is granted. All researchers are required to keep your identity
43
44 confidential. Your files will be stored in a locked filing cabinet for research purposes only. To
45
46 ensure that the research is carried out in accordance with these provisions, if necessary, the
47
48 members of government authorities or the ethics review committee can consult your personal
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50 data within the research institute. When the results of this study are published, no personal
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52 information will be disclosed.

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54 You can decide not to participate in the study or notify the researchers at any time to
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56 withdraw from the study. Your data will not be included in the research results, and your medical
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58 treatment and rights will not be affected. You can also discuss your treatment plan with your
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60 attending physician.

If you require other treatments or do not comply with the research plan or suffer from

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4 research-related harm, the researcher can terminate your participation in this study.

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6 You can always request information about the research progress. If new security
7 information related to this study occurs, you will be notified. If you have any questions or
8 concerns related to this study or experience any discomfort during the course of the study,
9 please contact Dr. Yaping Wang, Tel: 86-18917760598.
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14 If you have any questions or concerns about your rights and health, please contact Cuiyun
15 Wu, member of Ethics Committee, Tel: 021-52888045.
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For peer review only

Signature Page

I have read this informed consent.

I have had the opportunity to ask questions and received adequate response.

I understand that participating in this study is voluntary.

I can choose not to participate in this study or decide to withdraw from the study at any time, without discrimination and my medical treatment and rights will not be affected.

If I require other treatments or do not comply with the research plan or suffer from research-related harm, the researcher can terminate my participation in this study.

I will receive a copy of the informed consent.

Name of Participant:

Signature of Participant:

Date:

I have accurately informed the participant. He/she has read and understood the informed consent and was given the opportunity to ask questions.

Name of researcher:

Researchers' signature:

Date:

(Ps: Witness signature is required if the participant is not literate and proxy signature is required if the participant is incapacitated.)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3, 7)
	2b	All items from the World Health Organization Trial Registration Data Set (n/a)
Protocol version	3	Date and version identifier (Appendix 1)
Funding	4	Sources and types of financial, material, and other support (Page 2)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Page 1)
	5b	Name and contact information for the trial sponsor (Page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 11)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 11)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Page 5-6)
	6b	Explanation for choice of comparators (Page 5-6)
Objectives	7	Specific objectives or hypotheses (Page 9)

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Page 7-9)**

Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 6)**

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(Page 7)**

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 8-9)**

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(Page 6, 9)**

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(Page 9-10)**

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Page 10)**

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Page 9-10)**

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended **(Page 7, Figure 1)**

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 7-8)**

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size **(Page 9-10)**

Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Page 9-10)
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Page 9-10)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (Page 7-10)
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (n/a)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (n/a)
26			
27			

Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page 9-10)
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 9-10)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page 9-
46			10)
47			
48			
49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 10-11)
52			
53			
54		20b	Methods for any additional analyses (eg, subgroup and adjusted
55			analyses) (n/a)
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (n/a)
60			

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Page 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (Page 11)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Page 9)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Page 11)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 3 and 11)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Page 11)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Page 11)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Page 10)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 1)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Page 10)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (n/a)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 11-12) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (n/a) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (n/a) |

16 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Page 11, Appendix 1) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (n/a) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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