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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 trail

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Title Page

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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 trail aims to evaluate procedural safety and quality of life during a one-year

postoperative follow-up.

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

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

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

Institutional data

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

METHODS AND ANALYSIS

Patient and Public Involvement

Laparoscopic surgery has become a leading trend for the treatment of various malignant diseases, including gastric cancer. Different methods of total laparoscopic total gastrectomy, including functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) for esophagojejunostomy (EJ) are both accepted methods in clinical practice. However, there is currently no consensus comparing the two techniques in terms of procedural safety and long-term quality of life. Based on our retrospective study, the SPLT technique is easier, cheaper

and a more feasible method compared to traditional EJ. Patients did not participate in the design of the study. However, prior to enrollment, each patient will be thoroughly informed on the purpose of the study and the different interventional methods. Should the patient prefer one method over another, he or she will no longer participate in the present trial. We predict that the study results will help distinguish the different impacts on quality of life between the two anastomosis techniques, which will provide scientific evidence for future decision making.

Trial design

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

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

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

Contrast and grouping

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

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

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

Treatment

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

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

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

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

a stapler.

Outcomes

The primary purpose of the present study is to compare the QoL between FETE and Overlap groups (1, 3, 6, 9,12 months after surgery)[18] with EORTC QLQ-C30 and QLQ-STO22[19, 20]. The EORTC QLQ-C30 is designed as a multidimensional assessment of QoL including 5 scales on functional assessment, 3 symptom scales, a global health status, and 6 single items. Higher score indicates a better status in functioning domains, but a worse status in symptom domains. The EORTC STO22 is designed specifically for examining QoL of 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 event that affect the subject, regardless of its association to the treatment procedure. All AEs are recorded on the case report form (CRF) in detail, such as occurrence, duration, prognosis, severity, relevance to the treatment, and such. If events are defined as serious adverse events (SAEs), which results in death, disability, dysfunction, teratogenesis, or prolonged hospitalization. The occurrence of SAEs will be reported to the Huashan Hospital Committee within 24 hours.

Sample size

In the present study, 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 EJ Overlap group and FETE group are increased by 17 points relative to the preoperative baseline, 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) is 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 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(Range)] ×100
3. Symptom field and general health field: SS=[(RS-1)/R(Range)] ×100

Continuous data are expressed as mean ± standard deviation ($\bar{x}$±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. All patients will be given the opportunity to ask questions and 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 patient rights to treatment will not be affected. All participants are required to provide a written informed consent before participating in the trail.

Expectation

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 esophagojejunostomy with TLTG-SPLT in the near future to further validate the advances of the procedure. Study results will allow more AEG patients to benefit from the TLTG-SPLT technique.

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 1 week	Postoperative 1 month	Postoperative 3 months	Postoperative 6 months	Postoperative 9 months	Postoperative 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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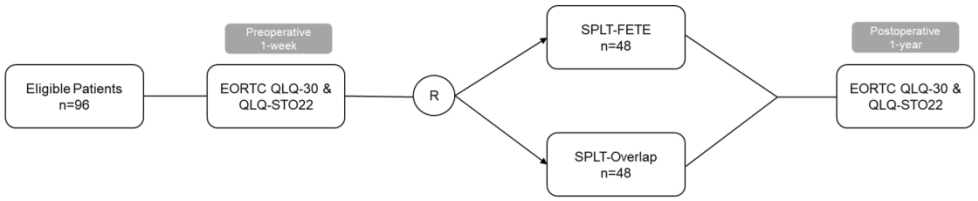

Study Flowchart

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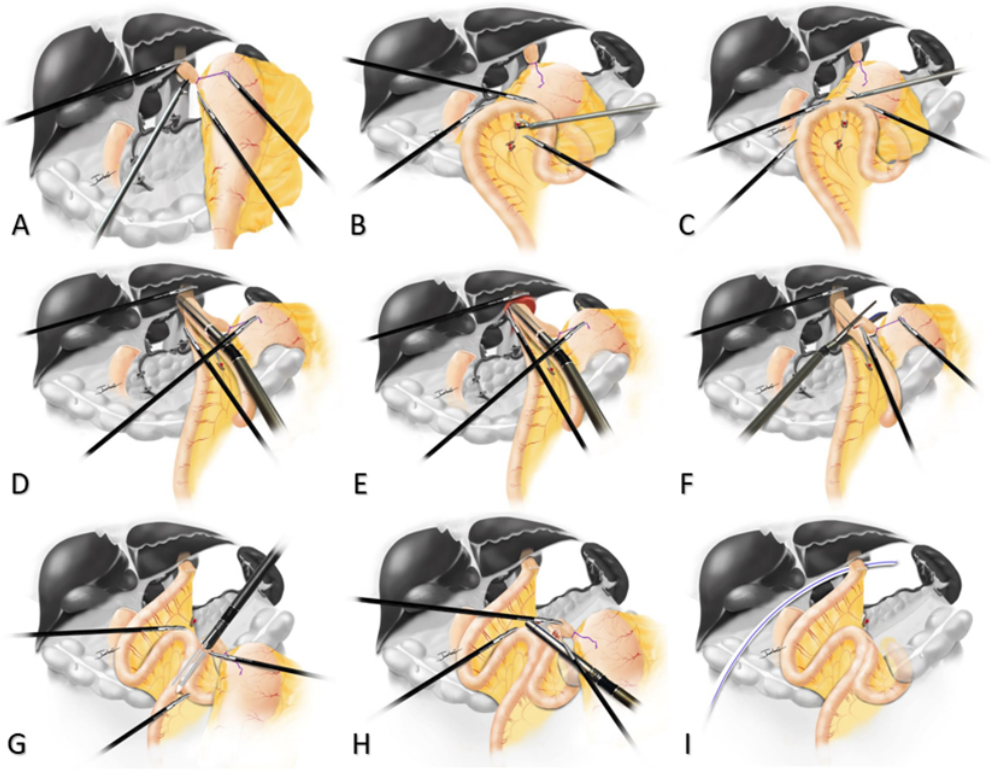

TLTG FETE SPLT

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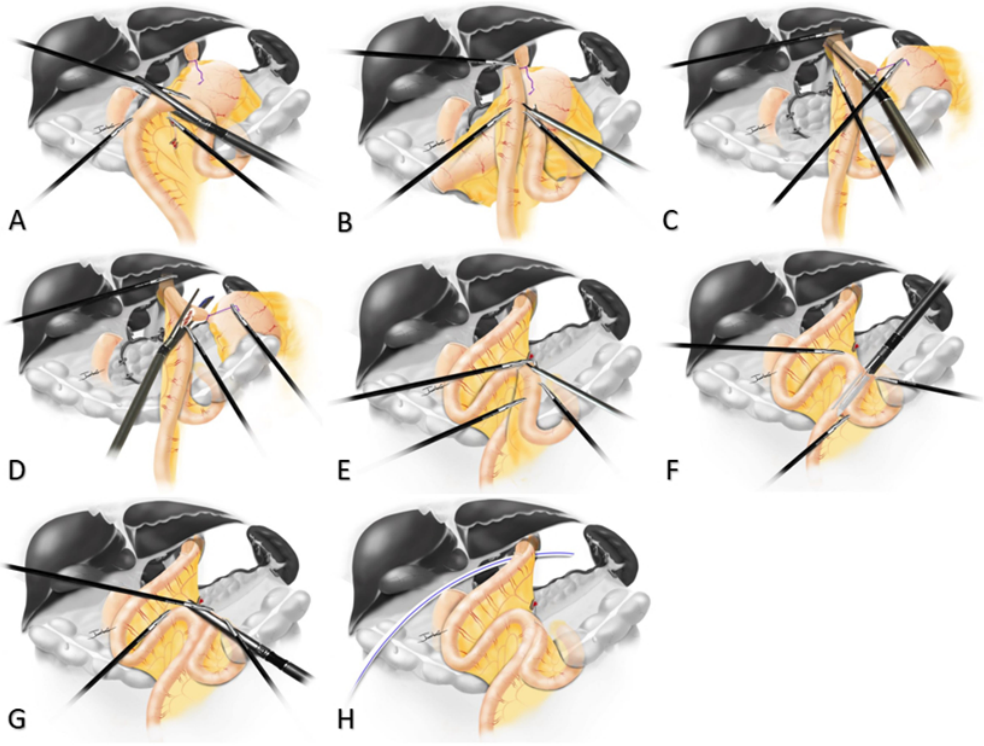

TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

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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

one-year follow-up period.

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

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

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

Institutional data

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

METHODS AND ANALYSIS

Patient and Public Involvement

Laparoscopic surgery has become a leading trend for the treatment of various malignant diseases, including gastric cancer. Different methods of total laparoscopic total gastrectomy, including functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) 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

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

Trial design

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

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

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

Contrast and grouping

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

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

Treatment

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

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

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

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

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

Outcomes

The primary purpose of the present study is to compare the QoL between FETE and Overlap groups (1, 3, 6, 9,12 months after surgery)[18] using the EORTC QLQ-C30 and QLQ-STO22 questionnaires[19, 20]. The EORTC QLQ-C30 is designed as a multidimensional assessment of QoL, including 5 scales on 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 is designed specifically for examining QoL of 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 EJ 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) is 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

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

Preoperative records

Initial staging and diagnosis include endoscopy, endoscopic pathology, endoscopic ultrasound, non-contrast enhanced CT scan of the chest, and contrast-enhanced CT scan of the abdomen. 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 hospital stay, postoperative time to first aerofluxus, 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, adjuvant therapy and completion, questionnaire results, laboratory results, imaging and endoscopic examination results were recorded.

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

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 ($\bar{x}$±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

esophagojejunostomy with TLTG-SPLT in the near future to further validate the advantages of the procedure. Study results will allow more AEG patients to benefit from the TLTG-SPLT technique.

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	✓	✓	✗	✗	✗	✗
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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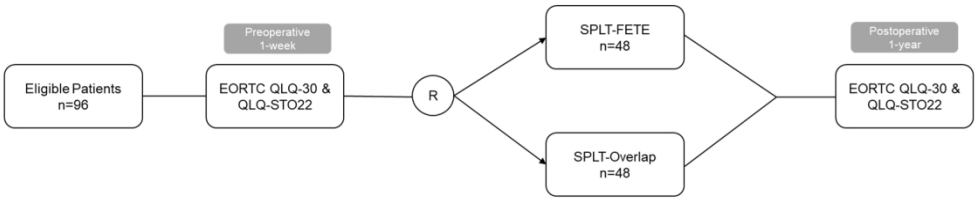

Study Flowchart

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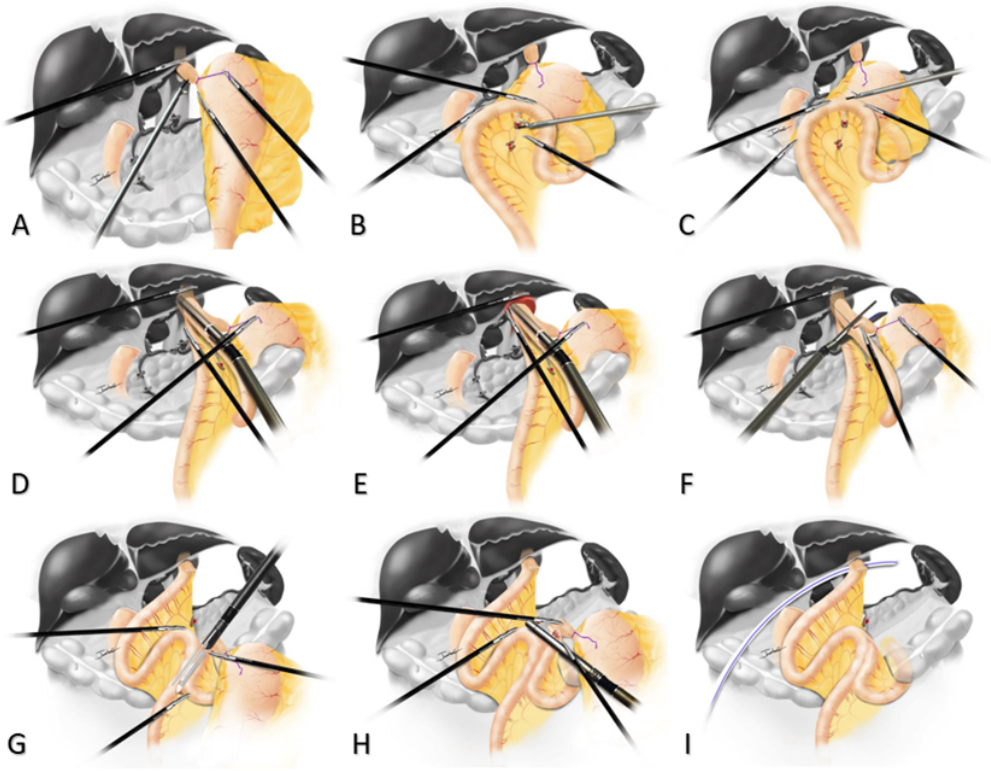

TLTG FETE SPLT

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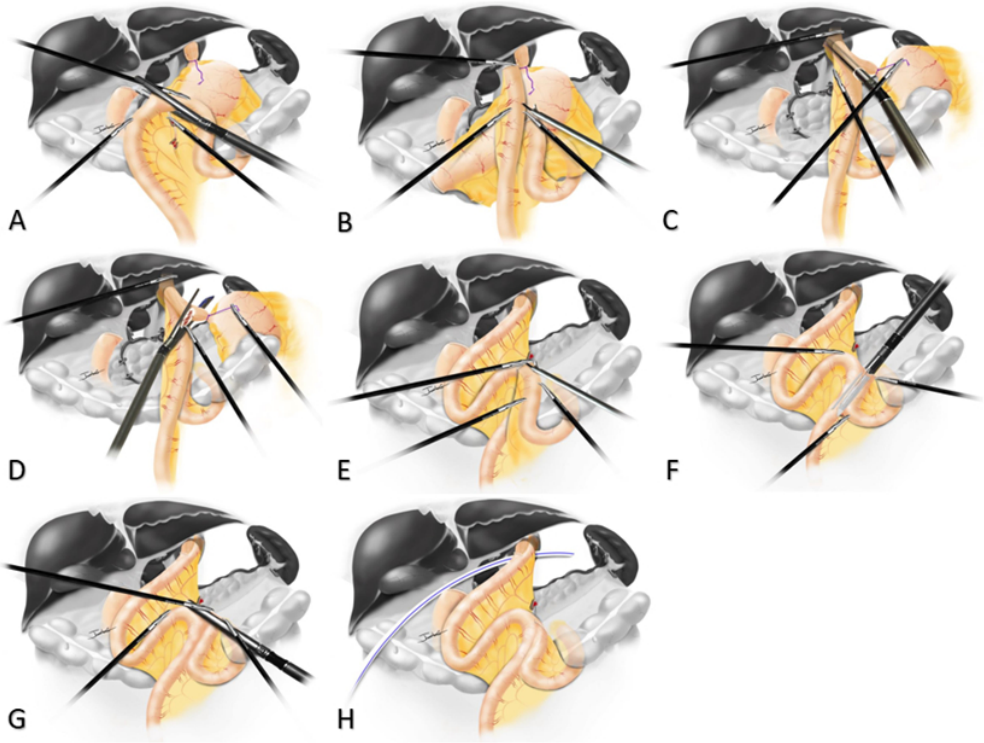

TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

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 difficultly 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

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

The Self-pulling and latter transected (SPLT) technique was first created by Prof. Hankun Hao and has effectively resolved the shortcomings of traditional esophagojejunostomy, such as esophageal retraction after transection, difficulty in opening the esophagus, difficulty in closing entry holes, complex technical requirements, higher cost (cheaper than traditional linear anastomosis), and difficulty in promotion. Our surgeons have surpassed the learning curve for this procedure and have successfully performed over 150 SPLT surgeries, which confirmed that SPLT is a simple, safe, feasible and economical procedure. The results of research have been published in Surg Endoscopy and Chinese Journal of Gastrointestinal Surgery. The evaluation of postoperative quality of life is an important standard of surgical quality in addition to the postoperative survival of patients with gastric cancer. High quality of life should be preferred in the case of similar postoperative survival. The difference in alimentary canal reconstruction is the main factor affecting the postoperative quality of life, especially the diet of patients with gastric cancer. There is no prospective research on the quality of life comparing different laparoscopic esophagojejunostomy methods (Overlap and FETE). EORTC QLQ-C30 and QLQ-STO22 scales are the most common questionnaires used to evaluate the quality of life 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 either FETE or Overlap intracorporeal esophagojejunostomy experience different quality of life and surgical safety after the procedure.

Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.)

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)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 9-10)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 9-10)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 7-10)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(n/a)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(n/a)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 9-10)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 9-10)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 9-10)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 10-11)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(n/a)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(n/a)**

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)**

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)**
Appendices		
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)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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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Title Page

Title: The effect of different oesophagojejunostomy 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 randomised trial

Running Title: study protocol for comparing different oesophagojejunostomy 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 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 result is limited to a single-centre study.
- Future multicentre studies may be warranted to further validate study results.

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

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

Institutional data

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

METHODS AND ANALYSIS

Patient and Public Involvement

The present study design was concocted based on previous clinical experience and patient feedback. Prior to enrolment, each patient will be thoroughly informed on the purpose of the study and the different interventional methods. Should the patient prefer one method over another, he or she will no longer participate in the present trial. Quality of life (QoL), will be assessed by the EORTC QLQ-C30 and QLQ-STO22 questionaries, which primarily include

patient self-reported symptoms and functional assessment. The results of the study will be disseminated through a peer-reviewed journal. Study participants will not be individually informed of study results.

Trial design

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

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

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

Contrast and grouping

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

Patients who meet the eligibility criteria are randomized to receive either laparoscopic OJ with FETE-SPLT or Overlap-SPLT on a 1:1 ratio. SPSS software is used to generate the random sequence, and the subjects are coded according to the order of entering the group.

The random sequence number corresponding to the coding sequence of patients will be randomly divided into two groups (odd numbers into the SPLT-FETE group and even numbers into the SPLT Overlap Group). Blinding surgeons or participants is not feasible in this study.

Treatment

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

Reconstruction of anastomosis: After undergoing lymphadenectomy, the abdominal oesophagus will be routinely mobilized. The subsequent conventional transection will be substituted by ligation of the cardia (or oesophagus above the upper margin of the tumour) using a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm endoscopic linear stapler per usual.

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

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

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

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

Preoperative records

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

Intraoperative records

The type of OJ, 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 hospital stay, postoperative time to first aerofluxus, 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, adjuvant therapy and completion, questionnaire results, laboratory results, imaging and endoscopic examination results were recorded.

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

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 ($\bar{x}$±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 form (Appendix 1). All patients will be given the opportunity to ask questions and be provided with a comprehensive response. Patients may choose not to participate in the study 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 organised by the funding organization (Shanghai ShenKang Hospital Development Center). An independent statistician will be invited to evaluate study outcomes after enrolment 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.

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

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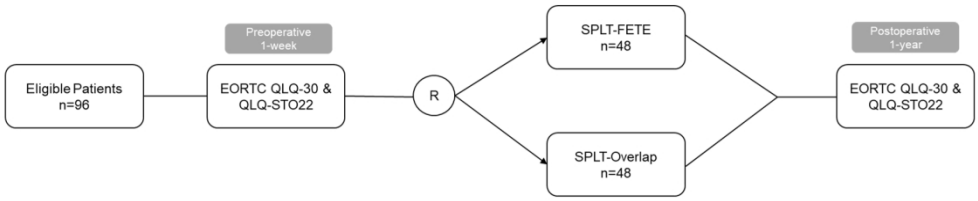

Study Flowchart

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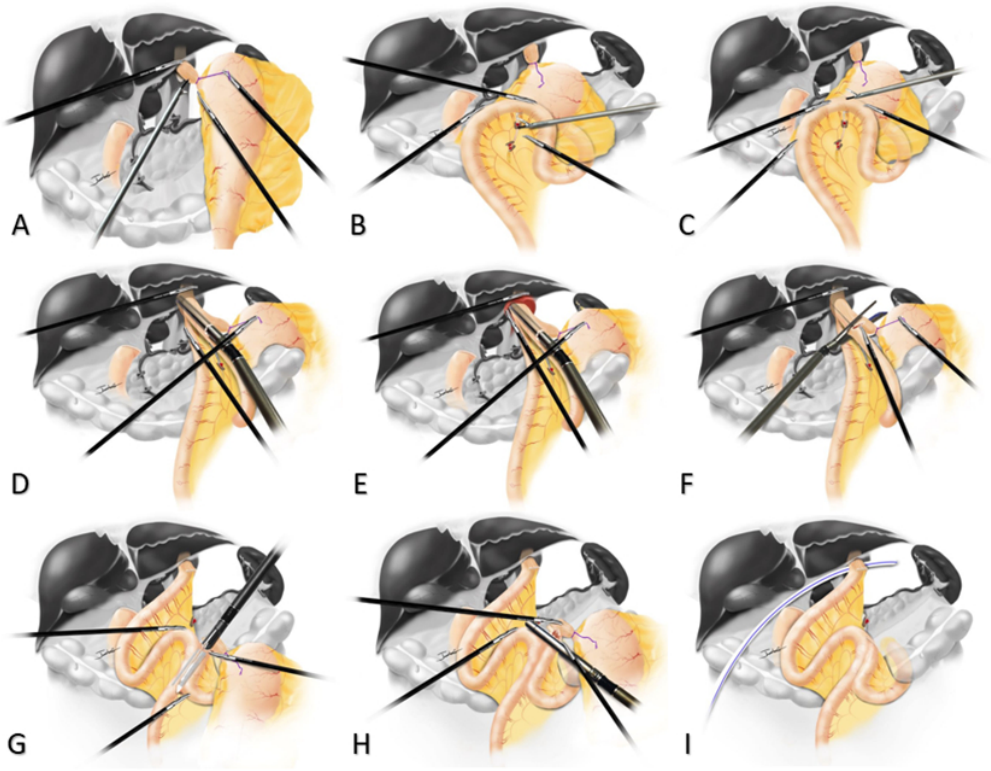

TLTG FETE SPLT

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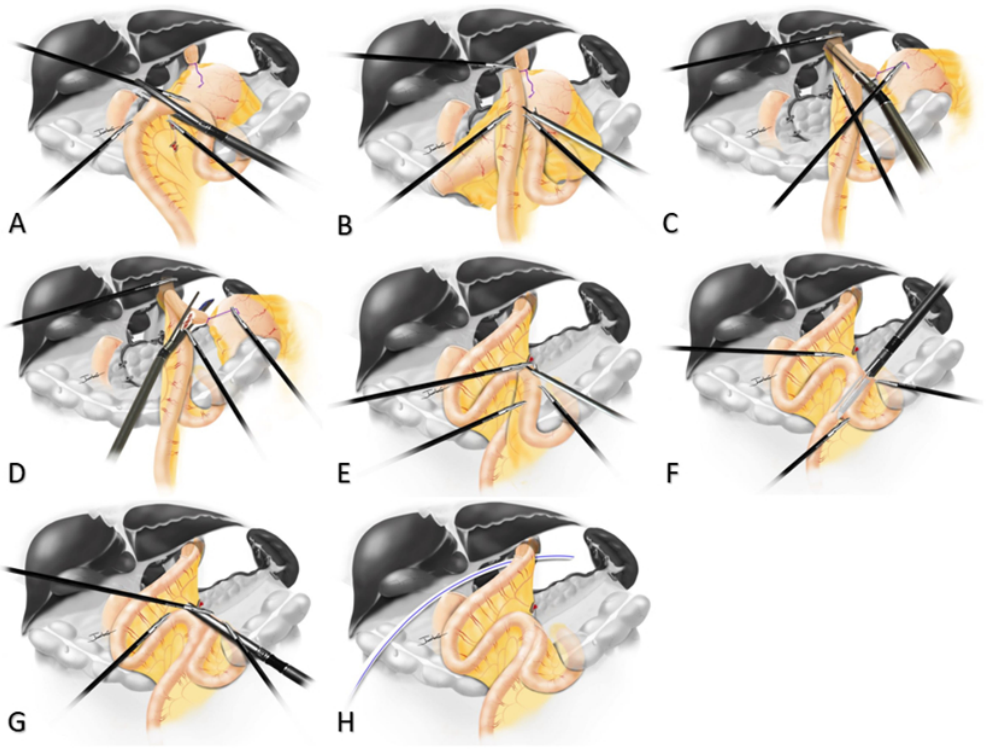

TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

SPIRIT
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)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 9-10)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 9-10)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 7-10)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(n/a)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(n/a)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 9-10)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 9-10)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 9-10)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 10-11)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(n/a)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(n/a)**

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)**

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)**
Appendices		
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)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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

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

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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.

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

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

Institutional data

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

METHODS AND ANALYSIS

Patient and Public Involvement

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

Trial design

The current study is a prospective, randomized, open-label, single-centre, interventional

trial using a parallel-arm design which would commence from October 1, 2020 through September 30, 2022. Subjects will be randomised to receive one of two interventions: FETE or Overlap. Figure 1 shows an overview of the trial design and each aspect of the trial is introduced in detail below. Clinical trial registration is completed in the Chinese Clinical Trial Registry, ChiCTR2000035583.

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

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

Contrast and grouping

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

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

Treatment

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

Reconstruction of anastomosis: After undergoing lymphadenectomy, the abdominal oesophagus will be routinely mobilized. The subsequent conventional transection will be substituted by ligation of the cardia (or oesophagus above the upper margin of the tumour) using a sterilized hemp rope. Transection of the duodenum will be performed with a 60-mm endoscopic linear stapler per usual.

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

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

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

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

Preoperative records

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

Intraoperative records

The type of OJ, 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 hospital stay, postoperative time to first aerofluxus, 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, adjuvant therapy and completion, questionnaire results, laboratory results, imaging and endoscopic examination results were recorded.

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

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 form (Appendix 1). All patients will be given the opportunity to ask questions and be provided with a comprehensive response. Patients may choose not to participate in the study 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 organised by the funding organization (Shanghai ShenKang Hospital Development Center). An independent statistician will be invited to evaluate study outcomes after enrolment 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.

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

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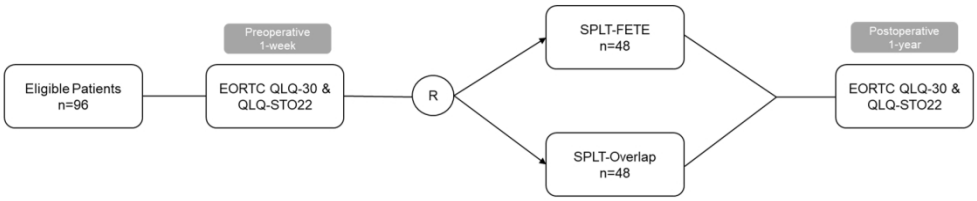

Study Flowchart

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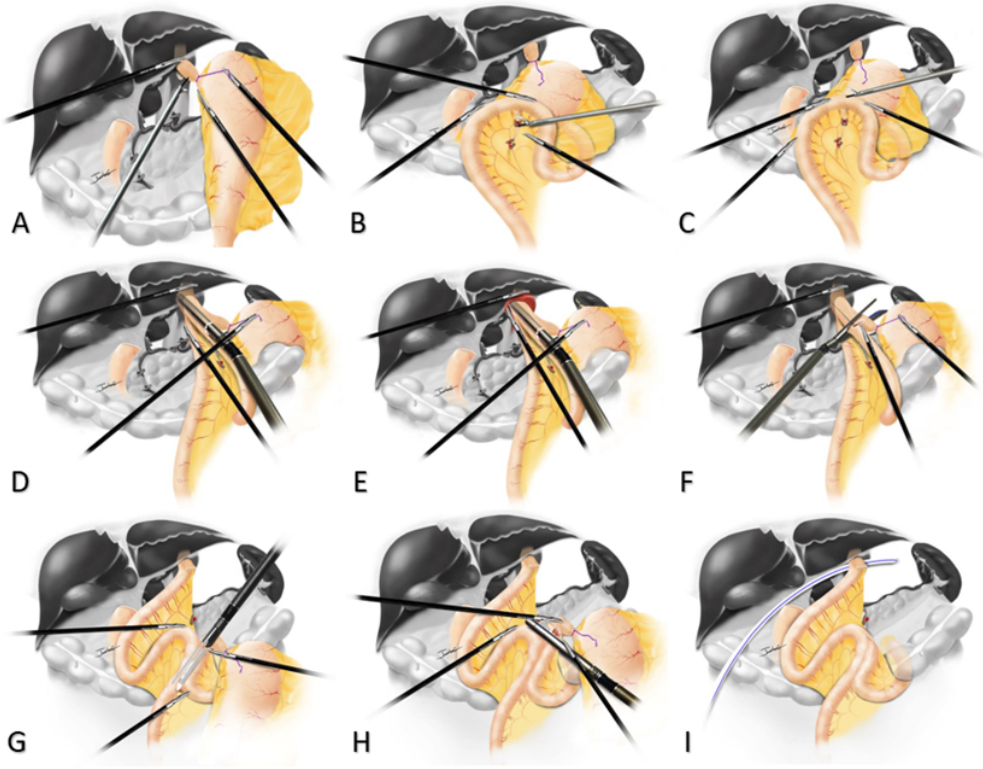
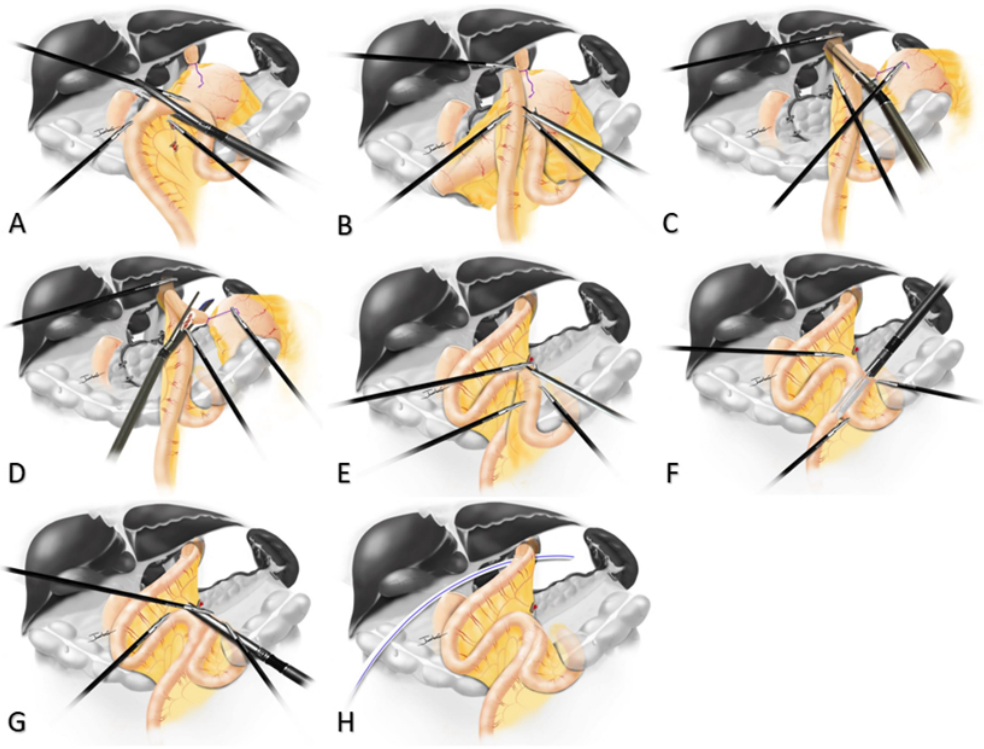


TLTG FETE SPLT

146x113mm (144 x 144 DPI)



TLTG Overlap SPLT

146x109mm (144 x 144 DPI)

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 difficultly 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

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

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

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

Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.)

SPIRIT
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)**

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:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(Page 9-10)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(Page 9-10)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(Page 7-10)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(n/a)**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(n/a)**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 9-10)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Page 9-10)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 9-10)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 10-11)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(n/a)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(n/a)**

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)**

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)**
Appendices		
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)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.