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

Jian Wang, Yujen Tseng, Jun Hong, Lu-Chun Hua, Ya-Ping Wang, Han-Kun Hao

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 oesophagogastric junction. However, totally LTG (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 randomised trial to compare functional end-to-end anastomosis (FETE) and side-to-side anastomosis (Overlap) for OJ.

Methods and analysis A prospective, randomised, 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 1 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 $\chi^2$ tests or Fisher’s exact tests will be used to compare categorical variables. Statistical analysis will be performed with SPSS V.23.0 statistical software. A $p<0.05$ will be considered statistically significant.

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

Trial registration number ChiCTR2000035583.

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%). 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. 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. Evidence from several studies have demonstrated that totally LTG (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).\textsuperscript{4–6} TLTG has not been widely adapted due to difficulties associated with oesophagojejunoanastomosis (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 (FETE) anastomosis\textsuperscript{7} and the side-to-side anastomosis (or the overlap method).\textsuperscript{8} The FETE 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 6–7 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 quality of life (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.\textsuperscript{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 with FETE.\textsuperscript{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 patients with gastric cancer 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.\textsuperscript{13–15} Self-pulling and latter transected (SPLT) reconstruction is one of our novel and routine method in performing LTG. 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.\textsuperscript{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, randomised, open-label, single-centre, interventional trial using a parallel-arm design which would commence from 1 October 2020 to 30 September 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.

Inclusion criteria
(1) Patients between 18 and 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 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 one on the ECOG (Eastern Cooperative Oncology Group) scale; (6) ASA

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**Figure 1** Study flow chart. EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FETE, functional end-to-end; QLQ-ST022, Quality of Life Questionnaire of Stomach; SPLT, self-pulling and latter transected.
(American Society of Anesthesiology) class I–III and (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 (LN) (diameter over 3 cm) found on preoperative imaging including enlarged or bulky No.10 LN; 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 on the team.

Patients who meet the eligibility criteria are randomised 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-Overlap Group). Blinding surgeons or participants is not feasible in this study.

Treatment
Lymphadenectomy
A D2 LNs dissection will be regularly conducted according to the Japanese gastric cancer treatment guidelines 2014 (V.4).17

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

FETE group
Throughout the course of reconstruction, the ligature rope will be held to lower the oesophagus to allow easier detachment from the posterior mediastinum (figure 2). Next, a hole will be made on the posterior wall of the oesophagus, 2–3 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
The jejunum will be intracorporeally transected 20 cm distal to the ligament of Treitz using a linear stapler (figure 3). 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 7 cm 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, 2–3 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 this study is to compare the QoL outcomes between the FETE and Overlap groups (1, 3, 6, 9 and 12 months after surgery) using the EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) and QLQ-STO22 (Quality of Life Questionnaire of Stomach)
Sample size

In this study, the postoperative QoL 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, with an SD 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, 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 (anastomatic leakage, anastomatic 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 CRP 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 summarised in table 1.

Data analysis

Data processing of QoL scale

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 in detail, including occurrence, duration, prognosis, severity and relevance to the treatment. If such events result in death, disability, dysfunction, teratogenesis, or prolonged hospitalisation, it is defined as serious AEs (SAEs). The occurrence of SAEs will be reported to the Huashan Hospital Committee within 24 hours.

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be affected. All participants are required to provide written
researchers to ensure that patient rights to treatment will not
opportunity to ask questions and be provided with a compre-
supplemental appendix 1). All patients will be given the
All participants should sufficiently understand the instruc-
tions detailed in the written informed consent form (online
1. Raw Score (RS)=(Q1 +Q2+Q3)/n, (Q: score of each
2. Functional field: standard score (SS)=[(RS-1)/
R(Range)]×100.
3. Symptom field and general health field: SS=[(RS-1)/R(Range)]×100.
Continuous data are expressed as mean±SD (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
χ² tests or Fisher’s exact tests will be used to compare
categorical variables. Statistical analysis will be performed
with SPSS V.23.0 statistical software. A p<0.05 will be
considered statistically significant.

Patient informed consent
All participants should sufficiently understand the instruc-
tions detailed in the written informed consent form (online
supplemental appendix 1). All participants will be given the
opportunity to ask questions and be provided with a compre-
hensive 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 organisation (Shanghai ShenKang Hospital
Development Centre). 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 institu-
tion Hospital Institutional Review Board 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 Univer-
sity (2020-1055). On completion of the study, the results
of the primary study will be published in a peer-reviewed
journal.

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