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Laparoscopic or open distal gastrectomy after neoadjuvant chemotherapy for advanced gastric cancer: study protocol for a randomised phase II trial

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ABSTRACT

Introduction Current guidelines recommend open gastrectomy with D2 lymph node dissection and adjuvant chemotherapy as the standard treatment for advanced gastric cancer. However, the prognosis is not satisfactory. Perioperative chemotherapy has been proposed to improve survival. Although still in debate, the efficacy of laparoscopic distal gastrectomy (LDG) in patients with advanced gastric cancer has been demonstrated in a few trials. Therefore, LDG after neoadjuvant chemotherapy can be a candidate for future standard treatment on advanced distal gastric cancer. We propose a randomised phase II trial to compare LDG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for advanced gastric cancer.

Methods and analysis To test the efficacy and safety, a randomised, open-label, single-centre, phase II trial was designed to evaluate the non-inferiority of LDG compared with ODG after neoadjuvant chemotherapy, with 3-year recurrence-free survival as the primary endpoint. The chosen critical value of a non-inferiority margin was an increase of <8%. The study started in 2015 and enrolled 96 patients according to a prior sample size calculation. Intention-to-treat and per-protocol approach will be used for efficacy analysis, and as-treated analysis will be applied for safety analysis. The survival curves will be constructed as time-to-event plots using the Kaplan-Meier method and compared using log-rank tests and Cox proportional hazards model. All statistical analyses will be conducted in standard statistical software with a significance level of 0.05.

Ethics and dissemination This study was approved by the Peking University Cancer Hospital Ethics Committee. The results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT02404753; Pre-results.

Strengths and limitations of this study

- The proposed study is one of the few randomised trials to compare laparoscopic distal gastrectomy with open distal gastrectomy after neoadjuvant chemotherapy for distal advanced gastric cancer.
- This trial aims to evaluate the efficacy and safety using short-term and long-term endpoints.
- We designed this study to be sufficiently powered to identify non-inferiority in terms of 3-year recurrence-free survival, although it may be underpowered to detect non-difference on other outcomes.
- This is a phase II trial performed at a single medical centre; thus, if the non-inferiority of laparoscopic surgery is proven, a subsequent larger multicentre phase III verification clinical trial may be needed.

INTRODUCTION

Gastric cancer is one of the most common malignant tumours and the second leading cause of cancer death worldwide. Due to the difficulty of screening and early diagnosis, approximately 80% of patients with gastric cancer in China are already at advanced stage (ie, tumour, node, metastases (TNM) stages II and III) at first hospital visit. The established treatment for advanced gastric cancer is open gastrectomy with D2 lymph node dissection, and postoperative adjuvant chemotherapy of S-1 for 1 year or combination therapy with capecitabine and oxaliplatin for 6 months.[1] Although such a treatment regimen is effective, the prognosis of patients is not satisfactory, which calls for a more intensive chemotherapy. From theoretical perspectives, an intensified chemotherapy can be better tolerated and complied by patients if being administered before the surgery. By far, two large European phase III trials, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, and the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) and the Fédération Francophone de Cancérologie Digestive (FFCD) 9703 study, have provided supportive evidence that preoperative (neoadjuvant) chemotherapy results in high compliance, as

well as other favourable factors such as high rate of R0 resection and tumour regression, which lead to a better prognosis.[2 3]

Laparoscopic gastrectomy has been used as a superior alternative to open gastrectomy to treat early gastric cancer.[4] Although still in debate, the application of laparoscopic surgery in advanced gastric cancer has drawn increasing attention over the years. The most recent meta-analysis published in 2016 concluded that laparoscopic gastrectomy for advanced gastric cancer appeared to be comparable with open gastrectomy in the number of lymph nodes achieved, overall survival and disease-free survival, but had advantages over open gastrectomy in terms of faster postoperative recovery.[5] However, 25 out of the 26 studies included in this analysis are retrospective, and randomised trials on laparoscopic versus open gastrectomy for advanced gastric cancer are scarce.[6] Thus, more research providing higher level of evidence is needed.

It is therefore worthwhile to compare the safety and efficacy of laparoscopic and open gastrectomy when combining with neoadjuvant chemotherapy. There have been a few randomised trials comparing laparoscopic with open gastrectomy,[7–9] and multiple on comparing gastrectomy with gastrectomy+neoadjuvant chemotherapy for advanced gastric cancer,[10] but very few on the comparison between laparoscopic gastrectomy+neoadjuvant chemotherapy and open gastrectomy+neoadjuvant chemotherapy. To our best knowledge, only one similar trial was proposed to be carried out from 2011 to 2014 in Japan, but results have yet to be published.[11] A retrospective study recently conducted by our team suggested that laparoscopic gastrectomy after neoadjuvant chemotherapy had comparable safety and efficacy as open gastrectomy in perioperative period.[12] In particular, laparoscopic distal gastrectomy after neoadjuvant chemotherapy did not increase operation time, blood loss, postoperative complications and length of stay in the hospital compared with open gastrectomy. Additionally, patients in laparoscopy group can benefit from the shortened length of incision and faster recovery of gastrointestinal functioning. However, no significant difference was found between the two groups in proximal and distal margin, and the number of resected lymph nodes.

The present study therefore aims to evaluate the safety and efficacy of laparoscopic gastrectomy after neoadjuvant chemotherapy for distal advanced gastric cancer using a randomised phase II clinical trial design, and to provide theoretical basis for conducting a multicentre phase III verification clinical trial.

METHODS AND ANALYSIS

Trial design

The current study is a prospective, randomised, open-label, single-centre, non-inferiority phase II clinical trial using a parallel-arm design. The study is designed on the hypothesis of non-inferiority on the basis of prior study comparing laparoscopic and open gastrectomy for advanced gastric cancer.[7] The study takes place in the Gastrointestinal Cancer Center of Peking University Cancer Hospital and Institute. Patient enrolment started on 23 April 2015, and the trial is expected to end in 2020. Figure 1 summarises the design of the trial, and each of the trial's aspects is described in detail below.

Eligibility criteria

The inclusion criteria are ambulatory men or women aged 18–80; Karnofsky score ≥70%; histologically proven gastric adenocarcinoma on biopsy (including Lauren classification); proven clinical stage of cT2n+M0 or cT3-4a/n+M0 by baseline ultrasound endoscope, enhanced CT/MRI examination or diagnostic laparoscopy using Habermann standards; no past chemotherapy or radiotherapy before diagnosis; tumour located in the middle and lower third of the stomach; achievable naked-eye complete resection (R0/1) via distal subtotal gastrectomy plus D2 lymphadenectomy; haematology and biochemistry index meet the following: haemoglobin ≥80 g/L, absolute neutrophil count ≥1.5×10^9/L, platelet ≥100×10^9/L, Alanine transaminase (ALT) and Aspartate transaminase (AST) ≤2.5 times the upper limit of normal value, Alkaline phosphatase (ALP) ≤2.5 times the upper limit of normal value, serum total bilirubin <1.5 times the upper limit of normal value, serum creatinine <1 times the upper limit of normal value, and serum albumin ≥30 g/L; no severe concomitant disease that leads to survival <5 years; willing and able to comply with the study protocol; and written consent agreement before enrolment and fully aware of the right to quit the study at any time with no loss.

Patients are excluded from the study if they meet one of the following: pregnant or breastfeeding; uncontrolled seizure, central nervous system diseases or mental disorders; history of upper abdominal surgery (except for laparoscopic cholecystectomy); history of gastric surgery (including diagnosis procedure such as endoscopic submucosal dissection and endoscopic mucosal resection); other malignant diseases in 5 years (except for cured skin carcinoma and cervical carcinoma in situ); clinically severe or active heart diseases, such as symptomatic coronary heart disease, the New York Heart Association (NYHA) grade II or above congestive heart failure, severe arrhythmia, or myocardial infarction in 6 months; cerebral haemorrhage or infarction in 6 months; organ transplant recipient under immunosuppressive therapy; severe uncontrolled repeated infection or other severe uncontrolled concomitant diseases; medium or severe renal damage (creatinine clearance rate ≤50 mL/min or serum creatinine greater than the upper limit of normal value); other diseases requiring synchronous surgery; requiring emergent surgery due to oncological emergency (eg, bleeding, perforation, obstruction); forced expiratory volume in 1 s <50% of expected value; and participated in other studies 4 weeks before the randomisation.

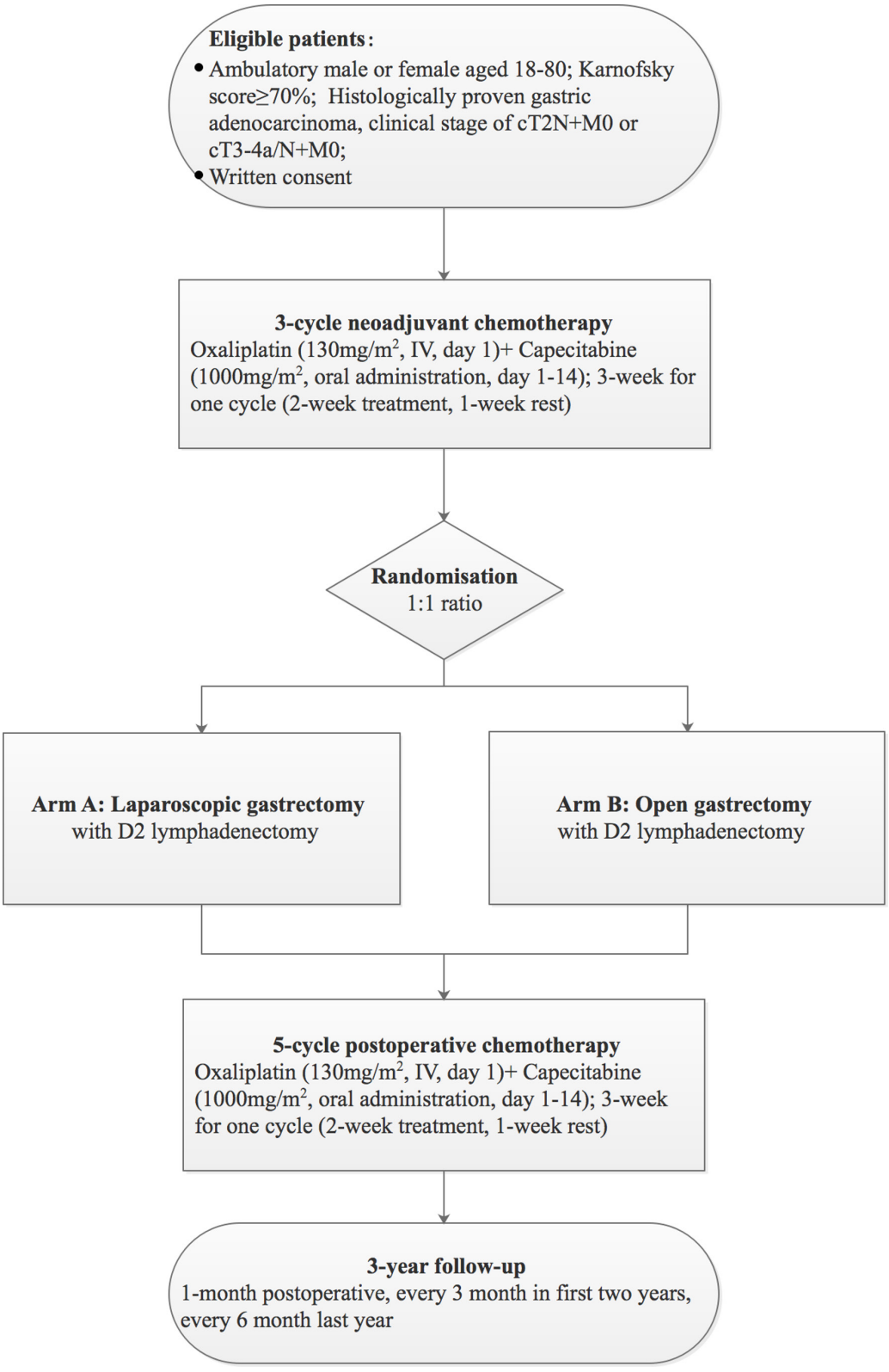

Figure 1 Flow chart.

Randomisation and blinding

Patients are enrolled by the oncologists on the team. Eligible patients treated with advanced gastric cancer at the Gastrointestinal Cancer Center of Peking University Cancer Hospital and Institute first receive neoadjuvant chemotherapy with three cycles (3 weeks for one cycle) of intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle) plus oral capecitabine (1000 mg/m^2 twice daily on days 1–14 of each cycle). Three weeks after the completion of neoadjuvant chemotherapy, assessment on the resectability of the tumour is conducted on the basis of vital sign examination, physical examination, laboratory

tests, electrocardiograph, lung function examination and tumour evaluation. Patients who passed the resectability confirmation are then randomised to receive either laparoscopic distal gastrectomy with D2 lymph node dissection (group A) or open distal gastrectomy with D2 lymph node dissection (group B) on a 1:1 ratio. Randomisation is achieved using random number table by the data manager and allocation is not concealed. While blinding surgeons or participants is not feasible, pathologists are blinded on the types of surgical approach.

Treatments

A standard laparoscopic or open distal gastrectomy with D2 lymphadenectomy (including lymph nodes of numbers 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p and 12a) is performed by two experienced surgeons, according to the Japanese Gastric Cancer Treatment Guidelines 2014 (V.4)[1] and the Japanese Classification of Gastric Carcinoma (3rd English edition).[13]

In the open group, an approximately 20–25 cm incision is made from the falciform process to the periumbilical area. In the laparoscopic group, one 10 mm trocar for the camera is inserted below the umbilicus. Another three 10 mm ports are inserted in the left upper quadrants 2 cm below the left lower rib margins, the right and left flank areas, respectively. One 5 mm trocar is lastly placed on the right upper quadrants 2 cm below the right lower rib margins. Anastomosis is performed using the instrumental method. The specimen was pulled out through a small median incision under the xiphoid (about 6–8 cm).[12]

For those who underwent laparoscopic gastrectomy, the case is required to be converted to open surgery if one of the following happens: confluent lymph nodes with long axis >3 cm, severe or life-threatening intraoperative complications such as intra-abdominal massive haemorrhage, severe organ damage, or other technical or instrumental factors that require conversion to open surgery.

All patients are managed by a standardised clinical pathway after the surgery. Discharge is recommended when the patients have tolerated more than 2 days of soft diet without abdominal pain or fever. All patients start to accept five cycles of oxaliplatin and capecitabine regimens for postoperative adjuvant chemotherapy within 6 weeks postsurgery. Dose reductions or interruptions are allowed to manage potentially serious or life-threatening adverse events (AEs). In cases of oxaliplatin-related neurological AEs, capecitabine can be continued as monotherapy. Oxaliplatin monotherapy is not allowed. Palliative and supportive care are offered as needed for disease-related symptoms.

Outcomes

The primary endpoint is 3-year recurrence-free survival (RFS) rate. Recurrence includes any recurrence (local or regional, or distant) and death due to any cause (both gastric cancer and non-gastric cancer causes of death).[14] The secondary endpoints are overall survival, radicalness of surgery, 30-day postoperative surgical morbidity and mortality, 2-week postoperative recovery index, cycles of postoperative chemotherapy, and up to 1-year postoperative quality of life. The radicalness of surgery includes assessments on the number of lymph nodes retrieved and the length of resection margin. Postoperative complications are defined as complications occurring within 30 days after surgery, and will be classified according to the Clavien-Dindo classification system.[15 16] Hospital mortality is defined as death occurring within 30 days after initial surgery, regardless of the cause. Postoperative recovery index considers blood loss, first aerofluxus time, first defaecating time, first time on a liquid diet, time of pulling gastric tube and drainage, and length of hospital stay. Postoperative pain intensity is measured by using a Visual Analogue Scale up to 72 hours after surgery.[17 18] The time of applying intravenous patient-controlled analgesia and rescue morphine consumption is recorded. One-year postoperative quality of life is assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires (QLQ-C30 and EORTC-QLQ-STO22).[19 20]

Adverse events

AEs are any unfavourable or unintended events that affect the patients of the study, regardless of the relevance to the treatment. Any AEs are recorded in detail on the case report form (CRF) and include time of occurrence, duration, relevance to the treatment, stopping or continuing of the treatment, and others. Events are defined as serious adverse events (SAEs) if they lead to death, prolongation of hospitalisation, permanent or severe disability, teratogenesis or carcinogenesis, and significant clinical sequela. The occurrence of SAEs will be reported to Peking University Cancer Hospital EthicsCommittee within 24 hours of the initial discovery.

Sample size

Due to the lack of results from previous similar research, a double-criteria approach described in the paper of Neuenschwander *et al*[21] was used to calculate the required sample size in order to identify non-inferiority of laparoscopic versus open gastrectomy in terms of RFS. The first criterion was that the HR estimate was smaller than a critical threshold of 1.12, which corresponded to a difference of 8% in the 3-year RFS between two arms. As suggested by the paper, this number was chosen on the basis of clinical considerations. The second criterion required that the upper estimated one-sided 95% confidence bound of the non-inferiority margin was smaller than 1.59, which was calculated based on prior clinical research on laparoscopic gastrectomy after neoadjuvant chemotherapy, as well as on open gastrectomy after neoadjuvant chemotherapy.[22 23]

On the basis of this approach, a sample size of 80 (40 per arm) is planned, with a type I error of 0.05 (two-sided) and a statistical power of 80%. The total sample size is 96 (48 per am) after taking account of a 20% dropout rate in each group. The planned recruitment period is 2 years and the follow-up duration is 3 years.

Data collection and analysis

Trained oncologists collect data via datasheets on paper daily until the patient's discharge. Initial staging and therapeutic efficiency assessment include endoscopy, endoscopic ultrasound, non-contrast-enhanced CT scan of the thorax, and contrast-enhanced CT scan of the abdomen and pelvis. MRI examination will be used as an alternative to CT scan if the patient is allergic to radiocontrast agent or has other contraindications on CT examination. Laparoscopy and peritoneal washings for malignant cells are conducted before and after neoadjuvant chemotherapy. Tumour response evaluation after neoadjuvant chemotherapy includes both imageological and pathological examinations. The former is conducted according to the Response Evaluation Criteria in Solid Tumours (V.1.1).[24] The latter is performed in accordance with the Tumour Regression Grade Standards of the National Comprehensive Cancer Network clinical practice guidelines in oncology for gastric cancer (V.3.2015).[25] Gastrectomy specimens are open along the greater curvature, and macroscopic examination is conducted before representative blocks are taken from the tumour and its surrounding areas, and paraffin-embedded. All removed lymph nodes are embedded separately. Microscopic features are reported according to the seventh edition of the International Union Against Cancer TNM classification.[26]

Information on prognostic status is collected via follow-up up to 3 years after the last treatment. Follow-up is conducted on a 3-month basis in the first 2 years and every half year in the third year. To promote participant retention and complete follow-up, three attempts are made to contact and remind the participants to come to the hospital for follow-up, and their transportation fees are covered by the research project. Every follow-up, participants receive physical examinations (ie, height, weight, Karnofsky score and others), laboratory tests (including blood cell test, blood biochemical test and serum tumour marker test) and imageological examinations (including ultrasonography, enhanced CT/MRI, endoscopy and chest radiograph). Tumour assessment will be conducted if recurrence is suspected, and further treatments such as surgery or chemotherapy will be performed when needed and will be recorded on the CRF. Data entry in EpiData is completed by two independent staff, with a third staff monitoring the quality.

Intention-to-treat and per-protocol approach will be used for efficacy analysis. As-treated analysis will be applied for safety analysis. For variables with a significant amount of missingness, multiple imputations will be conducted for the purpose of sensitivity analysis. In terms of descriptive analysis, categorical data will be presented as number and percentage. Continuous variable will be presented as mean and SD if normally distributed, or as median and range otherwise. The primary analysis in this study aims to compare the 3-year RFS rate between laparoscopic and open gastrectomy after neoadjuvant chemotherapy. The date of recurrence is defined as the date of all-cause death or when a clinician judges recurrence considering all information including serum tumour and the results of imageological examination. The RFS curves will be constructed as time-to-event plots using the Kaplan-Meier method. Log-rank tests will be used to make a simple comparison of the survival curves. Cox proportional hazards model will be performed to compare RFS after taking into account potential confounders. The overall survival will also be analysed in the same manner. Subgroup analyses will be conducted by age group, tumour location, body mass index category and TNM stage. All statistical analyses will be conducted in standard statistical software with a significance level of 0.05.

Data monitoring, auditing and interim analysis

Data monitoring and auditing are conducted by the funding agency annually. An interim analysis will be performed by an independent statistician when half of the patients have been randomised. The trial will be stopped if one treatment is found to be statistically more beneficial or harmful than the other.

Patient and public involvement

The development of current research question and outcome measures was informed by patients' priorities, experience and preferences in a way that minimally invasive surgery may be a safe and effective option for patients with advanced gastric cancer. Patients were not involved during the phase of study design; however, patients' concerns and questions were addressed during patient recruitment and study implementation. The summarised results of the current study will be published in peer-reviewed journals, but participating patients will not be particularly notified with these results. Indicators of intervention burden will be partially patient self-reported, such as first aerofluxus time, first defaecating time and first time on a liquid diet, while the other endpoints will be assessed by the research investigators.

ETHICS AND DISSEMINATION

On the completion of the study, at least two manuscripts with the results of the primary study will be published in a peer-reviewed journal. The deidentified data sets generated from the current study will be publicly available via an appropriate data archive 6 months after the completion of the trial.

Contributors JJ was the principal investigator of the study. JJ and ZiL developed the research idea and directed the study. FS designed the study in detail, wrote the grant except for the statistical analyses part, and monitored the implementation of the study. XY was responsible for the statistical analyses part of the protocol and preparing this manuscript. LZ, HR, SL, YJ, RM, KX, ZhL, YW, CY, YZ and FP participated in participant enrollment and data collection as this randomised trial is ongoing. All authors edited and approved the final version of this manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was approved by Peking University Cancer Hospital Ethics Committee in accordance with the Chinese legislation and the Declaration of Helsinki. The committee judged the study design, ethics, feasibility, level of non-inferiority and safety rules.

Provenance and peer review Not commissioned; externally peer reviewed.

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