Gastroenterology Report, 6(4), 2018, 317–319

doi: 10.1093/gastro/goy013
Advance Access Publication Date: 17 May 2018
Study protocol

STUDY PROTOCOL

Morbidity and mortality of elderly patients with advanced gastric cancer after laparoscopy-assisted or open distal gastrectomy: a randomized–controlled trial

Jun Luo†, Yu Zhu†, Hao Liu, Yan-Feng Hu, Tuan-Jie Li, Tian Lin, Tao Chen, Hao Chen, Xin-Hua Chen, Jiang Yu and Guo-Xin Li*

Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, P. R. China

*Corresponding author. Department of General Surgery, Nanfang Hospital, Southern Medical University, North Guangzhou Road 1838, 510-515 Guangzhou, China. Tel: +86-20-61641681; Fax: +86-20-61641683; Email: gzliguoxin@163.com

†Jun Luo and Yu Zhu contributed equally to this work in the design of the study and preparation of the manuscript and should be both considered as co-first authors.

Abstract

Laparoscopy-assisted distal gastrectomy (LDG) combined with D2 lymphadenectomy may be safely performed in patients with advanced gastric cancer (AGC) by experienced surgeons at specialized high-volume institutions as shown in the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS)-01. However, studies focusing on the use of LDG in patients with gastric cancer older than 65 years are rare. This study was designed to investigate the morbidity and mortality of elderly patients with gastric cancer who underwent laparoscopic-assisted or open distal gastrectomy (ODG). In this prospective, randomized, open, parallel controlled trial, patients older than 65 years with tumor located at the middle or lower part of the stomach will be enrolled in this study. Patients will be randomly divided into a laparoscopic group and an open surgery group. The early post-operative complications, intra-operative complications and post-operative recovery will be compared between the two groups. This trial will provide valuable clinical evidence for the objective assessment of the feasibility, short-term safety, and potential benefits of LDG compared with ODG for gastric cancer in the elderly patients. This trial has been registered on ClinicalTrials.gov. (Identifier: NCT02246153.) in September 22, 2014.

Key words: Laparoscopic gastrectomy; advanced gastric cancer; elderly patients; morbidity; mortality

Background

China has gradually entered an aging society. In China, the average age of gastric cancer patients was 65 years and patients aged 75 years or over accounted for approximately 29% [1]. Radical gastrectomy is the commonly used surgery treatment for gastric cancer. However, old age is regarded as a high-risk factor in many aspects of medicine and major surgery, since many elderly patients had multiple comorbidities, such as hypertension, diabetes and coronary heart disease. Thus, some clinicians suggested that surgeons must be willing to perform limited surgery in elderly patients [2].

Laparoscopy-assisted distal gastrectomy (LDG) for the treatment of early gastric cancer has been supported by high-quality

Submitted: 16 January 2018; **Accepted:** 22 January 2018

evidence; however, high-quality evidence for advanced gastric cancer based on large prospective randomized–controlled trials (RCTs), such as the Japan Clinical Oncology Group (JCOG) 0901 and Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-02, is still awaited. In recent years, with improvements in laparoscopic surgical techniques, laparoscopic surgery for gastric cancer has been adopted widely around the world. Chinese scholars reported that experienced surgeons can safely perform laparoscopy-assisted gastrectomy with D2 lymphadenectomy for gastric cancer in (CLASS)-01 [3]. However, with the rapid growth of the aging population throughout the world, more elderly patients undergo gastrectomy for gastric cancer. Although there are several completed RCTs of laparoscopic treatment of early gastric cancer and ongoing RCTs of laparoscopic treatment of locally advanced gastric cancer, there are rare studies specializing in gastric cancer patients older than 65 years [4].

Yu *et al.* [5] demonstrated pulmonary problems as early post-operative complications in patients with gastric cancer after LDG, and thought that the potential benefits of laparoscopy-assisted gastrectomy should not be denied in elderly patients with resectable gastric cancer because age >65 years seems not to be associated with an increased risk of post-operative complications after the patients have conditioned the pre-operative comorbidities. The above data suggest that laparoscopy-assisted gastrectomy for gastric cancer in elderly patients may be safe and effective on the basis of adequate assessment and effective treatment for pre-operative complications.

Based on existing scientific problems in elderly patients with gastric cancer, the comparison of intra-operative and post-operative complications between LDG and ODG for patients older than 65 years with gastric cancer based on an RCT is warranted. Here, we introduce the protocol of an RCT comparing LDG and ODG with D2 lymph adenectomy for elderly patients with gastric cancer.

Methods

Objectives

The purpose of the RCT is (i) to demonstrate the efficacy of LDG compared with ODG with D2 lymphadenectomy for elderly patients who are clinically diagnosed with gastric cancer and (ii) to provide a theoretical basis for the application of laparoscopic surgery in elderly patients.

Study design

This RCT is an investigator-initiated, randomized–controlled, parallel-group study, comparing LDG and ODG for elderly patients with gastric cancer. The performance of this RCT, on 202 OGC patients older than 65 years, will be monitored and organized by the Nanfang Hospital of Southern Medical University, Guangzhou, Guangdong, China.

This is a non-inferiority study, with the incidence of post-operative complications (including death) as the main index for evaluating effectiveness. Based on the results of previous research and this one, with two groups, the post-operative complication occurrence rate is 24%, δ (non-inferiority margin)-=15%, $\alpha=0.05$ and the power is 80%, calculated by NCSS PASS (NCSS LLC, Kaysville, Utah).

Study population

Inclusion criteria

1. age over 65 years;
2. primary gastric adenocarcinoma (papillary, tubular, mucinous, signet ring cell or poorly differentiated) confirmed pathologically by endoscopic biopsy;
3. cT1-4aN0-3M0 tumors at pre-operative evaluation according to the *Seventh Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual* (TNM AJCC-7th tumor staging);
4. expected curative resection through distal subtotal gastrectomy with D2 lymphadenectomy;
5. performance status of 0 or 1 on ECOG (the Eastern Cooperative Oncology Group) scale;
6. ASA (American Society of Anaesthesiologists) score class I, II or III; and
7. written informed consent.

Exclusion criteria

1. severe mental disorder;
2. history of previous upper abdominal surgery (except laparoscopic cholecystectomy);
3. history of previous gastrectomy, endoscopic mucosal resection or endoscopic submucosal dissection;
4. early gastric cancer feasible for endoscopic sub-mucosal dissection;
5. enlarged or bulky regional lymph node with a diameter over 3 cm by pre-operative imaging;
6. history of other malignant diseases within the past 5 years;
7. history of previous neoadjuvant chemotherapy or radiotherapy;
8. history of unstable angina or myocardial infarction within the past 6 months;
9. history of cerebrovascular accident within the past 6 months;
10. history of continuous systematic administration of corticosteroids within 1 month;
11. requirement of simultaneous surgery for other diseases;
12. emergency surgery due to complication (bleeding, obstruction or perforation) caused by gastric cancer; and
13. forced expiratory volume per second less than 50% of predicted values.

Study protocol

Nanfang Hospital will manage this clinical trial and provide an allocation number with a pre-generated randomized code for the patients who meet the inclusion and exclusion criteria. As soon as the participating surgeons obtain informed consent from the patients, we will fill in baseline data of patients' pre-operative evaluation and clinical examination, which are collected 1 week before operation.

Study treatment

OGD and LDG will be performed using the same principles. First, through intra-operative exploration, the procedure will be directly performed if ascites is present in the abdominal cavity, or it will be performed by administering 100 mL of saline solution into the abdominal cavity, which will then be collected and sampled in the Douglas fossa. Second, D2 lymphadenopathy will be performed; lymph nodes that will be resected include Nos 1, 3, 4 sb, 4d, 5, 6, 7, 8a, 9, 11p and 12a.

Post-operative care

The ward staff will evaluate the patients every morning and afternoon for the presence of any issues affecting recovery. The intensity of pain, time to ambulation, diet schedule and time to first flatus will be recorded daily until discharged; laboratory

findings will be recorded on the first and fifth days after operation [6]. Participants will be discharged once they are able to tolerate a soft diet and ambulate independently (defined as being able to walk a predefined distance or go to the bathroom independently).

Outcome measurements

Primary endpoints

The primary outcomes will be early post-operative complication, which will be assessed 30 days after operation and classified according to the Clavien-Dindo Classification and Accordion Classification, including incision-related complications (such as infection, effusion, crack and healing), peritoneal effusion or abscess, abdominal bleeding, gastrointestinal bleeding, intestinal obstruction, intestinal paralysis, anastomotic stenosis, anastomotic fistula, intestinal fistula, lymphatic leakage, pancreatic fistula, gastroparesis, pancreatitis, pneumonia, urinary system infection, renal failure, liver failure, cardio cerebrovascular events (including thrombosis and embolism), prolonged hospitalization days and secondary inpatient visits.

Secondary endpoints

The secondary outcomes will include not only pulmonary complications after operation within 30 days of operation, but also intra-operative complications and post-operative recovery, which will be divided into morbidity observed during operation and morbidity observed within 30 days after surgery. Post-operative recovery (time to first ambulation, flatus, liquid diet, soft diet and duration of hospital stay) will be measured daily in the hospital and from participant self-reports. Intensity of pain will be measured using a horizontal visual analogue scale (VAS; a 0- to 10-cm scale with 0 on the left edge representing no wound pain and 10 on the right edge representing as the worst possible wound pain) [7]. Operative outcomes will include operation time, estimated blood loss during operation, incision length, pneumoperitoneum-related complications, anesthesia-related complications and death.

Discussion

This study is an RCT recruiting a large number of patients to compare LDG and ODG with D2 lymphadenectomy in elderly patients with gastric cancer (GC). The number of patients with advanced gastric cancer will be up to 202, which is far greater than the number of patients with early gastric cancer, with China's actual condition taken into consideration.

The most concerning issue in laparoscopy-assisted gastrectomy for elderly people with gastric cancer is the pneumoperitoneum; however, the slight and transient impairment of cardiopulmonary functions due to carbon dioxide pneumoperitoneum does not lead to severe morbidities in elderly patients [8]. Among all types of early morbidities, intra-abdominal morbidity and trocar-related morbidity must be particularly considered, as these have also been used to evaluate the safety and efficacy of surgery by patients.

Despite its increasing clinical application, the risks and benefits of laparoscopy-assisted gastrectomy for gastric cancer in elderly patients remain unclear. This trial aims to compare LDG with ODG for gastric cancer in elderly patients using a large-scale RCT. The results of this trial will provide valuable clinical evidence for the objective assessment of the feasibility, short-term safety and potential benefits of LDG compared with ODG for GC in elderly patients.

Trial Status

Recruitment began at the first site in September 2014. The recruitment status of the present trial is ongoing and a mid-term analysis will be performed when half the total number of subjects is recruited. We will have recruited 100 patients by the time of submitting this paper.

Ethical Approval and Consent to Participate

The trial received ethical approval from the Medical Ethics Committee of Nanfang Hospital on 15 September 2014 (reference number: NFEC-2014–067). The study will be performed according to the Declaration of Helsinki and the ICH GCP E6 guidelines. Participants must provide signed and dated written informed consent prior to undergoing the procedures. The participants will be informed that participation in the trial is voluntary and that they can withdraw consent at any time without giving reasons. According to the ethics committee, this clinical trial is effective as long as the first case of the patient's time is within the expiry date (20 August 2015) of the ethical approval and the first patient in this trial was enrolled on 16 December 2014.

Funding

This trial is supported by the Research Fund of Public Welfare in Health Industry, National Health and Family Planning Commission of China (No. 201402015).

Conflict of interest statement: none declared.

References

1. Siegel R, Ma J, Zou Z *et al*. Cancer statistics, 2014. *CA Cancer J Clin* 2014;**64**:9–29.
2. Kim MG, Kim HS, Kim BS *et al*. The impact of old age on surgical outcomes of totally laparoscopic gastrectomy for gastric cancer. *Surg Endosc* 2013;**27**:3990–97.
3. Hu Y, Huang C, Sun Y *et al*. Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial. *J Clin Oncol* 2016;**34**:1350–57.
4. Zeng YK, Yang ZL, Peng JS *et al*. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: evidence from randomized and nonrandomized clinical trials. *Ann Surg* 2012;**256**:39–52.
5. Yu J, Hu J, Huang C *et al*. The impact of age and comorbidity on postoperative complications in patients with advanced gastric cancer after laparoscopic D2 gastrectomy: results from the Chinese laparoscropic gastrointestinal surgery study (CLASS) group. *Eur J Surg Oncol* 2013;**39**:1144–49.
6. Hur H, Lee HY, Lee HJ *et al*. Efficacy of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer: the protocol of the KLASS-02 multicenter randomized controlled clinical trial. *BMC Cancer* 2015;**15**:355.
7. Bond MR, Pilowsky I. Subjective assessment of pain and its relationship to the administration of analgesics in patients with advanced cancer. *J Psychosom Res* 1966;**10**:203–08.
8. Suzuki S, Nakamura T, Imanishi T *et al*. Carbon dioxide pneumoperitoneum led to no severe morbidities for the elderly during laparoscopic-assisted distal gastrectomy. *Ann Surg Oncol* 2015;**22**:1548–54.