Effects of perioperative ERAS pathway management VS traditional management on clinical outcomes in laparoscopic-assisted radical resection of distal gastric cancer The GISSG18-01 Randomized Clinical Trial

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Abstract
Background: As well known, the incidence of gastric cancer in East Asian countries is much higher than the international average. Therefore, improving the prognosis of patients and establishing effective clinical pathways are important topics for the prevention and treatment of gastric cancer. At present, the enhanced recovery after surgery (ERAS) pathway is widely used in the field of gastric surgery. Many RCT studies have proven that the ERAS regimen can not improve the short-term clinical outcomes of gastric cancer patients. However, a prospective study on the effect of the ERAS pathway on the prognosis of gastric cancer patients has not been reported. This trial aims to confirm whether ERAS pathway can improve disease-free survival (DFS) and overall survival (OS) in patients undergoing laparoscopic-assisted radical resection for distal gastric cancer.

Methods/design: This study is a prospective, multicenter, randomized controlled trial (RCT). This experiment will include randomly divided groups, the experimental group and the control group, according to a proportion of 1:1. The perioperative period of the experimental group will be managed according to the ERAS pathway, and the control group will be managed according to the traditional management mode. An estimated 400 patients will be enrolled. The main endpoint is to compare the 3-year OS and PFS between the two groups.

Discussion: This RCT should demonstrate whether ERAS pathway is superior to traditional treatment on inflammatory indexes, short-term clinical outcome and survival for laparoscopic assisted radical resection of distal gastric cancer. Our data can provide evidence that the ERAS pathway improves survival in patients with gastric cancer.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1900022438. Registered on 11 April 2019

Introduction

Background and rationale

Around the world, gastric cancer is a common malignant tumour and has the third highest mortality rate. In 2018, there were more than 1.3 million new cases of gastric cancer and more than 780 000 deaths [1]. In the past 30 years, the incidence of gastric cancer has decreased, but it is still very high in East Asian countries [2]. There are more than 400,000 new cases of gastric cancer in China each
year. The 5-year overall survival rate of patients with gastric cancer is approximately 30%, but this rate is significantly lower than that in South Korea and Japan [3]. How to improve the comprehensive treatment effect of gastric cancer, ensure the quality and safety of the perioperative period, improve the prognosis of patients, and establish an effective clinical pathway is an important subject for the prevention and treatment of gastric cancer in China. At present, there are many treatment methods for gastric cancer, such as surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, surgical resection is an effective way to improve the survival of patients.

Among the surgical options, D2 radical gastrectomy has become the standard surgical method for advanced gastric cancer. Since Kitano et al. first reported laparoscopic-assisted gastrectomy (LAG) for early gastric cancer in 1994, laparoscopic gastric cancer surgery has developed rapidly worldwide, especially in countries with a high incidence, such as Japan, South Korea and China [4]. Laparoscopic surgery has unique minimally invasive advantages, but in view of the need for D2 lymph node dissection for advanced gastric cancer, the operation is difficult and complex, and the initial laparoscopic surgery is only used for the treatment of early gastric cancer. After more than ten years of research, large samples of multicentre clinical data have confirmed the safety, feasibility and effectiveness of laparoscopic radical gastrectomy in the treatment of early gastric cancer [5]. The CLASS-01 latest findings: laparoscopic distal gastric cancer D2 radical resection performed by an experienced team is safe and feasible in the treatment of locally advanced gastric cancer [6].

Reviewing the development of gastric cancer surgery, we find that its main direction is gradually changing from "standard and open surgical resection" to "individualized and accurate minimally invasive surgery", which further improves the safety of the operation and the quality of life of the patients after the operation [7]. The new minimally invasive surgery guided by the concept of laparoscopic minimally invasive surgery not only reduces the surgical incision but also in minimizes the tissue trauma and maximizes functional preservation on the basis of radical oncology [8].

The concept of enhanced recovery after surgery (ERAS) was first proposed by Kehlet and was an important milestone in the development of surgery in recent years. Its core goal is to adopt a series of optimized measures with evidence-based medical evidence during the perioperative period to reduce
the physiological and psychological stress of patients to accelerate their recovery [9]. In contrast to traditional perioperative management, ERAS pathway combines new techniques in anaesthesiology, pain, nutrition, psychology and surgery with traditional perioperative management by integrating medical interventions to speed up the postoperative rehabilitation of surgical patients and ultimately improve the clinical outcome of patients [10]. Our centre published the first international randomized controlled trial (RCT) study on the effect of ERAS on the short-term outcomes of postoperative patients with gastric cancer, proving that the ERAS regimen is safe and feasible for perioperative gastric cancer patients compared with the traditional perioperative treatment regimen [11]. The ERAS pathway can reduce postoperative stress, shorten the hospital stay, and improve the quality of life of patients, and does not increase the incidence of postoperative complications. Recent studies have shown that surgical stress can also affect the long-term oncological results of digestive tract tumours [12]. The mechanism behind this effect may be immunosuppression, as well as changes in the immune response leading to a higher recurrence rate and more distant metastases. Surgical trauma can cause local and systemic inflammation, which can also lead to the rapid growth of residual and micrometastatic diseases [13-15]. The ERAS pathway can reduce the systemic inflammatory response, facilitate the early reversal of the human stress response and has been shown to significantly reduce the incidence of postoperative complications; thus, it has the potential to improve the long-term oncology results. These results suggest that the application of the ERAS management pathway may not only improve short-term outcomes such as hospitalization days, postoperative complications and mortality but also benefit tumour patients in terms of long-term survival. The Swedish scientist Olle Ljungqvist et al. showed that ERAS pathway management plays a positive role in the long-term survival of patients with colorectal cancer [16]. However, a prospective study on the effect of the ERAS pathway on the prognosis of gastric cancer has not been reported.

Objectives
The purpose of this study was to investigate the impact of perioperative ERAS pathway management on the clinical safety and prognosis of patients undergoing laparoscopic-assisted distal gastric cancer radical surgery.
Trial Design
This experiment will include randomly divided groups, the experimental group and the control group, according to a proportion of 1:1. The perioperative period of the experimental group will be managed according to the ERAS pathway, and the control group will be managed according to the traditional management mode. After admission, imaging and haematological examinations will be performed, the risk assessments of NRS2002, VTE, ASA and ACS will be administered, the contraindications will be excluded, and then laparoscopic radical resection of distal gastric cancer (D2, BI, BII, Roux-en-Y) will be performed under anaesthesia.

The trial will assess the clinical safety of ERAS pathway management and its impact on long-term survival. To explore the effect of the ERAS pathway on inflammatory indexes (leukocyte, neutrophil percentage, CPR, PCT, α-TNF, IL-6). Before starting the trial, the sample size was calculated according to survival rate, follow-up time, inferior value, grouping ratio, test efficiency, and loss of follow-up rate. A complete checklist of items according to Standardized Protocol Items: Recommendations for Intervention Trials (2013) is provided [17].

Methods: Participants, Interventions And Outcomes

Participant selection and Randomization

From the 14 hospitals listed in Table 1, patients diagnosed with middle and lower gastric adenocarcinoma who underwent laparoscopic-assisted radical resection of distal gastric cancer will be recruited. A total of 400 eligible patients will be identified and randomly (1:1) enrolled in the ERAS group and the traditional treatment group. Figure 1 shows the test group flow chart.

Table 1. Fourteen Experienced Surgical Centers
| Number | Center | Department or Participant |
|--------|--------|---------------------------|
| 01 | Section of Surgical Pathophysiology | Henrik Kehlet |
| 02 | Affiliated Hospital of Qingdao University | Gastrointestinal Surgery Yanbin |
| 03 | Shandong Provinical Hospital | Leping Li |
| 04 | Qilu Hospital of Shandong University | Qingsi He |
| 05 | Qianfoshan Hospital of Shandong Province | Lijian Xia |
| 06 | Second Hospital of Shandong University | Yinlu Ding |
| 07 | Yantai Yuhuangding Hospital | Lixin Jiang |
| 08 | Weihai Municipal Hospital | Huanhu Zhang |
| 09 | Weifang People's Hospital | Yinran Shi |
| 10 | Dongying People's Hospital | Hao Wang |
| 11 | Rizhao People's Hospital | Xizeng Hui |
| 12 | Qingdao Municipal Hospital | Weizheng Mao |
| 13 | Jining People's Hospital | Xianqun Chu |
| 14 | Weihai Central Hospital | Xinjian Wang |

For randomization, a central dynamic, stratified strategy was adopted. The randomization sequence was generated using the Pocock-Simon minimization method in SAS version 9.3 (SAS Institute Inc) and stratified by participating site (14 hospitals), and surgical procedure (laparoscopic or robotic). Participating centres submitted the above information to the data center at the Department of Gastrointestinal surgery, affiliated Hospital of Qingdao University, Qingdao, China, where central randomization was performed. Information on treatment allocation was subsequently sent to each participating centre.

The inclusion criteria are as follows: 1) newly treated patients with no chemotherapy, radiotherapy or other anti-tumour treatment was performed before the beginning of the clinical trial, 2) patients aged between 18 and 75 years old, 3) patients with disease with a clinical stage of advanced T (1-4a), N (0-3), and M0 scheduled to undergo radical resection of distal gastric cancer, 4) male or non-pregnant and lactating females, 5) patients pathologically diagnosed with gastric adenocarcinoma, 6) patients with T stage T4a or below disease and no distant metastasis who underwent feasible standard D2 radical operation (AJCC 2018 8th edition) were judged by naked eye during operation, 7) patients with ECOG score 0-1; and 8) patients who voluntarily signed the informed consent form.

The exclusion criteria were as follows: 1) other malignant tumours within 5 years; 2) any M1 disease was found during the operation; 3) severe or uncontrolled medical diseases and infections were found at the same time; 4) use of opioid analgesics or hormones within 7 days before the operation; 5)
severe or uncontrollable mental illness; 6) any unstable condition or condition that may endanger the safety and compliance of the patient; and 7) treatment with anticancer drugs in other clinical trials.

**Perioperative management**

Before surgery, chest Computed Tomography (CT), total abdominal CT, pelvic CT and upper abdominal enhanced CT will be performed to confirm the size and location of the tumour, and distant organ metastasis will be excluded according to the evaluation of two experienced radiologists. Upper abdominal artery angiography (CTA) will be used to evaluate the variation in the gastric supply arteries of patients, reduce the risk of intraoperative bleeding and guide lymph node dissection. Echocardiography and pulmonary function tests will be used to evaluate the tolerance of cardiopulmonary function to laparoscopic surgery.

Laparoscopic-assisted radical resection of distal gastric cancer (D2 B-I/B-II/Roux-en-Y) will be performed under general anaesthesia. During the operation, we will follow the basic principles of tumour treatment, master the appropriate scope of gastrectomy, perform fine lymph node dissection and gastrointestinal reconstruction, and record the amount of intraoperative infusion, blood loss, operation time, and use of opioids and muscle relaxants.

After the operation, if adverse reactions occur in the trial, they should be closely observed and actively treated. All drugs used should be recorded and described on the CRF. Laboratory examinations will be performed before the operation, 2, 4 and 7 day after the operation. The contents of the examination will include routine blood, liver and kidney function, electrolyte, procalcitonin, C-reactive protein and IL-6. For patients with pathological II stage or above, 6-8 cycles of SOX-based adjuvant chemotherapy will be required. Finally, according to the actual situation of the patients, the oncology experts will choose the scheme and the duration of treatment.

**Intervention protocols**

Laparoscopic-assisted radical resection of distal gastric cancer will be performed by an experienced surgical team from the 14 centres listed in Table 1. All of these centres perform at least 100 gastric cancer operations each year. Lymph node resection will be performed under laparoscopy, the main anastomosis will be performed with the assistance of a small midline incision (< 8 cm). According to
the research programme, the ERAS group will actively carry out pre-rehabilitation before the operation, including lifestyle intervention, exercise advice, diet guidance, and health education (outpatient and hospitalization individualized condition consultation and answer). The specific interventions are shown in Table 2, but target-oriented liquid management and early EN after operation require our special attention. The goals of goal-directed therapy (GDT) are to maintain central euvoelemia whilst avoiding salt and water excess and 24 h postoperative fluid balance on +1 to 1.5 l. Intraoperative detection indicators: blood pressure, cardiac output, estimated blood loss, end tidal carbon dioxide and heart rate. Maintenance fluid flow rate 1~4mlkg-1h-1 (predicted body weight), while avoiding large deviations from "zero balance" [18]. The well-defined principles for oral intake in the ERAS groups: drinking a small amount of water and chew xylitol on the day of operation; drinking 500~1000ml water and chewing Xylitol on postoperative day (POD) 1; oral enteral nutrition (EN) (mainly polypeptide) and chewing Xylitol on POD2; oral EN (mainly integrin type) and chewing Xylitol on POD3; oral EN, a small amount of semifluid and chewing Xylitol on POD4; oral EN, semifluid (mainly) and chewing Xylitol on POD5, but the patients in the traditional treatment group began sequential EN support treatment according to the diet pattern of the ERAS group after anal exhaust.

**Study endpoints**

The main endpoint is to compare the 3-year overall survival (OS) rate and progression-free survival (PFS) rate between the ERAS pathway management group and the traditional treatment group.

The secondary endpoints are the total incidence of postoperative complications, incidence of major complications, 30-day re-hospitalization rate, 30-day mortality rate, hospitalization days and hospitalization costs as well as other short-term clinical outcomes.

The exploratory results are the changes (preoperation and about day 2, 4 and 7 after surgery) in inflammatory indexes (leukocyte, neutrophil percentage, CPR, PCT, α-TNF, IL-6).

| Programme clauses                                      | ERAS group |
|--------------------------------------------------------|------------|
| **Preoperative**                                       | *Yes*      |
| *Health education, exercise advice, dietary guidance*  |            |
| Preoperative | 
| --- | 
| *Organ function evaluation | Yes |
| *pre-rehabilitation treatment | Yes |
| *MDT, Clinical Decision Making | Yes |
| *Preoperative nutritional assessment and intervention | Yes |
| Intestinal preparation | 
| Enteral nutrition | No mechanical bowel preparation |
| *Preoperative fasting and abstinence from drinking | 
| Fasting 6 hours before operation | 2-hour oral glucose infusion 200 ml |

**Intraoperative**

| Check | 
| --- | 
| *Intraoperative safety checklist | Yes |
| Local anesthesia in the deep layers of the incision at the end of surgery | Local anesthesia (30 ml 0.25% bupivacaine) |
| Prevention of antibiotic use | Yes |
| *Surgical incision | Small midline (8cm) incision of upper abdomen |
| *Precision Surgery | Laparoscopic or robotic surgery |
| *Anesthesia mode | General anesthesia combined with epidural injection |
| Intraoperative heat preservation | Yes |

**Postoperative**

| Urinary catheter | Remove within 24 hours |

| Gastric tube | 
| --- | 
| *Early bedside activity | Start soberly and plan your activities |
| *Postoperative analgesia | Multimodal analgesia |
| *Target-oriented liquid management | Yes |
| Prevention of deep venous thrombosis | 
| *Early EN after operation | Sequential EN treatment after awakening of anesthesia |

**Notes**

* Core provisions of perioperative ERAS pathway management. 
Abbreviations: NSAID, Non-steroidal anti-inflammatory drugs; EN, Enteral nutrition. 
* a dose/drug: ropivacaine 500mg + lidocaine 400mg and liquid velocity: 2ml/h 
* b Heat preservation measures: pre-heating fluid replenishment, thermal blanket, heater 
* c Extubation indication: The drainage fluid is light red or clear, 24 hours less than 20 ml and pancreatic amylase >500 U/L. 
* d The criteria of removal of nasogastric tube: Recovery of intestinal peristalsis, anal exhaust and oral clear fluid. 
* e Multimodal analgesia POD1~2 patient controlled epidural analgesia (Lidocaine + Ropivacaine), POD3~5 re-50mg is injected intravenously. 
* f Opioids: POD1~2 Tramadol 50mg q8h, when the VAS≥4 tramadol 50mg is injected intravenously (dose ≤ 4
**Data collection**

Once the informed consent form is signed, the clinical researchers will collect baseline data such as age, sex, body mass index and complications. The laboratory indexes (routine blood, liver and kidney function, electrolyte, CEA, CA199, CA724, CA242, AFP, hepatitis + HIV+ syphilis, blood coagulation routine, blood type) will also be tested and recorded before and during hospitalization. The designated surgeon recorded the details of the procedure, such as the surgical approach, the location of the tumour, lymph node metastasis, and pathological TNM staging.

Starting on day 1 after the operation, the clinical observation data (extubation time, food intake, activity, anastomotic leakage, first exhaust and defecation time, postoperative hospital stay, complications, etc.) will also be recorded by nurses every day to evaluate postoperative recovery. Clinicians will be responsible for patient management and will not be involved in data collection. The specific discharge criteria in the 2 groups: Oral analgesics can control pain well (VAS≤4); oral semi-fluid food without intravenous rehydration; voluntary out-of-bed exercise (6 hours a day or up to preoperative level); the family provides adequate out-of-hospital care; the patient was discharged voluntarily; no surgical complications such as fever, abdominal pain, infection and so on. In addition, the contact information and address of each patient will be confirmed before discharge. Follow-up will be conducted by telephone within 24 hours after discharge, focusing on dietary tolerance, pain, defecation and any discomfort symptoms.

**Follow-up**

After the operation, a special follow-up team will be responsible for the follow-up, and the first outpatient review will begin 30 days after the operation, particularly, this follow-up is very important. From 0-2 years after the operation: follow-up every 3 months, each will include routine blood, biochemical routine, digestive tract tumour indicators and imaging examinations, and endoscopic examinations will be performed once a year. Each follow-up will assess the adjuvant treatment, postoperative recovery and short-term and long-term side effects, and the schedule of visits and procedures conducted at each visit are summarised in Figure 2.

From 2-3 years after the operation: follow-up every 6 months, and the content will be the same as
above.

**Statistical analysis**

The classification variables will be tested by the chi-square test or Fisher’s exact test, and the continuous variables will be tested by the independent t-test. DFS will be defined as the time from surgery to death or recurrence of gastric cancer, whichever occurs first. The Kaplan-Meier method will be used to generate survival curves, and the log-rank will be used to compare the differences between survival curves. The HRs and 95% CIs will be calculated with the Cox proportional regression model. The variables will be selected into the final multivariable model by the step-by-step method, and significance levels of 0.25 and 0.15 will be used as the criteria for entry and stay. \( P < 0.05 \) will be considered statistically significant. Data analysis will be performed using SPSS® software package version 22.0 (SPSS Inc., Chicago, IL, USA).

**Sample size estimate**

This experiment adopts the design of a non-inferiority test, and the calculation of sample size is based on the following historical data and assumptions. Previous studies have shown that the overall 5-year survival rate for gastric cancer patients is approximately 50%. The centre followed up patients who underwent radical resection of gastric cancer under the management of ERAS from 2011 to 2014, and the 5-year survival rate was approximately 65%. Assuming that the selected patients needed 10 months, the median follow-up time is approximately 3 years, and the non-inferiority threshold is set at 1.33, according to a 1:1 random ratio. Assuming a significance level of \( \alpha = 0.05 \) (bilateral) and test efficiency \( 1-\beta = 80\% \), the withdrawal rate of either branch group should be 10%, and the total sample requires at least 400 patients (200 in the test group and 200 in the control group).

**Strengths and limitations of this study**

The feasibility of ERAS pathway management in improving long-term prognosis has not been determined in a prospective randomized study. This trial will be the first multicentre randomized controlled clinical trial to evaluate the impact of perioperative ERAS pathway management on clinical outcomes and long-term prognoses of laparoscopic-assisted radical resection for distal gastric cancer. The main outcome is to compare the 3-year overall survival rate and progression-free survival rate.
between the two groups.

In this study, the ERAS group will have some difficulties in completely implementing all interventions in the programme due to individual differences, compliance, medical factors and other reasons. We will integrate the factors involved in the clinical pathway. It is proposed that the core provisions of perioperative ERAS pathway management are preoperative education, preoperative organ function evaluation, preoperative pre-rehabilitation, multi-mode analgesia, accurate surgery, early activity, early oral feeding, and thrombus prevention; these core provisions will be easy to implement.

Discussion
The core of the ERAS concept is to use perioperative optimization measures based on evidence-based medicine to reduce surgical trauma, stress response, and promote postoperative recovery. This concept subverts the thinking and principle of perioperative management formed in the past hundred years, and creates a new concept of rehabilitation. The ERAS pathway can not only improve the early clinical outcomes of patients with gastric cancer, but also hopefully improve the survival rate of patients. This study is a prospective, multicenter, open, randomized controlled clinical trial, aiming to provide important evidence support to achieve this goal.

In recent years, many international large-scale gastric surgery centers have begun to explore the ERAS pathway for gastric cancer. The application of ERAS pathway in perioperative management of gastric surgery has been repeatedly proved to be able to reduce postoperative complications, shorten postoperative hospital stay, relieve postoperative pain and reduce total hospitalization costs [19–20]. Unfortunately, the ERAS pathway has limited research on improving the survival of patients with gastric cancer. Current observational studies have shown a significant association between ERAS compliance and colorectal cancer survival, In patients with ≥70% adherence to ERAS interventions, the risk of 5-year cancer-specific death was lowered by 42%, HR 0.58 (0.39–0.88, cox regression) compared to all other patients (≤ 70% adherence) [16]. At present, one mechanism of ERAS pathway to improve this result is to reduce surgical stress response [21]. Some studies have shown that perioperative stress can not only affect tumor recurrence [22–23], but also stimulate dormant micrometastasis and minimal residual cancer [24–26]. In addition, under the ERAS management
mode, the immune function after operation can be better preserved. Studies have shown that surgery is related to short-term immunosuppression after operation [26]. Pro-inflammatory cytokines released after surgery, such as TNF-α and TGF-β, have also been shown to stimulate tumor cell adhesion [27-28]. Patients managed by ERAS pathway have better preservation of cell-mediated immunity [29] and immune function [30], less stress response, thereby inhibiting tumor recurrence and metastasis, and improving patient survival time.

Overall, the ERAS pathway has been proven to be a safe and effective perioperative management model in the current literature. In particular, the ERAS pathway has also shown promising results in improving the survival rate of patients with gastric cancer. Confirmation of these results is essential by means of RCTs.

**Trial status**

The enrollment of this study is ongoing at the time of manuscript submission. The protocol version is 1.1, GISSG18-01, 10 March 2019. The trial will be ongoing from 10 April 2019 to 30 June 2020

**Abbreviations**

ERAS: enhanced recovery after surgery; DFS: disease-free survival; OS: overall survival LAG: laparoscopic-assisted gastrectomy; CT: computed tomography; CTA: abdominal artery angiography; GDT: goal-directed therapy; POD: postoperative day; EN: enteral nutrition

**Declarations**

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**Authors’ contributions**

Yanbing Zhou, Leping Li, Qingsi He, Lixin Jiang, Huanhu Zhang, Yiran Shi, Hao Wang, Xizeng Hui, Xianqun Chu, Weizheng Mao, and Xin Wang, as surgeons, operate at each center. Hongqing Zhuo, Xiaodong Liu, Ying Kong, Zengwu Yao, Liang Wang, Yang Yu, Xujie Wang and Yulong Tian were the
main coordination and data recorders; Yanbing Zhou and Henrik Kehlet tested the feasibility of the study. The research manuscript was written by Henrik Kehlet, Yanbing Zhou and Yulong Tian. All the authors approved the final version of the manuscript. All authors participated in the design, drafting and revision of the research programme, finally approved the version to be published and agreed to be responsible for all aspects of the work.

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**Availability of data and materials**

Data from this randomized controlled study are unavailable at the time of publication. Individual participant data are available upon request.

**Ethics approval and consent to participate**

The study will be conducted according to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. Written informed consent will be obtained from each participant. The study has been approved by the Ethics Committee of the affiliated Hospital of Qingdao University (QYFYKYLL 2018-34) and similar approvals have been obtained at other centres as needed. Prior to participating in a clinical study, the written informed consent of each participant and his guardian must be obtained. The results of the study will be presented at academic meetings and will be published in peer-reviewed journals. This trial has been registered with the China Clinical Trials Registry: CHiCTR1900022438 (date of registration: April 11, 2019).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Figures
Figure 1

Flow of Patient Enrollment and Randomization

**Abbreviations:** ERAS: enhanced recovery after surgery, POD: postoperative day
| TIMEPOINT | Screen | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|-----------|--------|----|---|---|---|---|---|---|---|---|---|---|----|----|
| ENROLMENT: |        |    |   |   |   |   |   |   |   |   |   |   |    |    |
| informed consent |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Audit and acceptance standards |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Demographics |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Medical history |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Inclusion/Exclusion |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| INTERVENTIONS: |        |    |   |   |   |   |   |   |   |   |   |   |    |    |
| Preoperative intervention |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Intraoperative intervention |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Postoperative intervention |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| ASSESSMENTS: |        |    |   |   |   |   |   |   |   |   |   |   |    |    |
| Laboratory examination |        | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  |
| Physical examination |        | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  |
| Imaging data |        | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  |
| Gastroscopy |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Adverse events |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Compliance |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Pathological report |        | x  | x  |    |   |   |   |   |   |   |   |   |    |    |
| Surgical record |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Chemotherapy information |        | x  |    |   |   |   |   |   |   |   |   |   |    |    |
| Tumor assessment |        | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  |
| Follow-up questionnaires |        | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  | x  |

Figure 2

Flow chart of Multi-center clinical trial for the schedule of enrollment, interventions, and assessments. Notes: The character "x" indicates the project that must be completed during the research phase; -1, 2 weeks before operation; 0, perioperation; 1, adjuvant chemotherapy time; follow-up 2–11 corresponding time points are: 2, 3 months after operation, 3, 6 months after operation, 4, 9 months after operation, 5, 12 months after operation, 6, 15 months after operation, 7, 18 months after operation, 8, 21 months after operation, 9, 24 months after operation, 10, 30 months after operation, 11, 36 months after operation.

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