Prehabilitation for Gastric Cancer Patients Receiving Neoadjuvant Chemotherapy: A Randomized Trial

Study Protocol

Research Sponsor: The Affiliated Hospital of Qingdao University

Date: 2024.7.27

QYFYEC2025-08

Table of Contents

Study Protocol Abstract:

Protocol Number	1.0
Protocol Title	Effect of Prehabilitation Combined with ERAS versus ERAS Perioperative Management on Clinical Outcomes of Laparoscopic (Robotic) Gastrectomy in Patients with Gastric Cancer Receiving Neoadjuvant Chemotherapy: A Single-Center Randomized Controlled Trial
Study Population	Patients aged 18-75 years receiving neoadjuvant therapy scheduled for laparoscopic (robotic) radical gastrectomy for gastric cancer.
Study Objective	To investigate the impact of prehabilitation combined with perioperative ERAS pathway management versus perioperative ERAS pathway management alone on short-term and long-term clinical outcomes in gastric cancer patients receiving neoadjuvant therapy undergoing laparoscopic (robotic) radical gastrectomy.
Study Design	This is a prospective, single-center, randomized, open-label, controlled clinical trial. It compares the effects of a 4-week tri-modal prehabilitation (exercise, nutrition, psychological intervention) combined with perioperative ERAS pathway management versus perioperative ERAS management alone on short-term and long-term clinical outcomes in gastric cancer patients receiving neoadjuvant chemotherapy undergoing laparoscopic (robotic) surgery. It also observes the safety, feasibility, and efficacy of the combined prehabilitation and ERAS pathway management in patients receiving neoadjuvant chemotherapy. The trial is designed with a 1:1 allocation ratio for the target number of effective cases between the experimental and control groups. The experimental group receives 4 weeks of tri-modal prehabilitation combined with perioperative ERAS pathway management, while the control group receives perioperative ERAS management alone until discharge. Relevant indicators and adverse events are recorded. Patients are followed up in the outpatient clinic until 3 years postoperatively or death.
Sample Size	Total sample size is 136 cases, 68 in each group. The sample size calculation is based on the following assumptions. According to our center's data and previous study results [2-4], the 30-day postoperative complication rate in neoadjuvant patients is approximately 25%. It is expected to decrease to 15% after combined multimodal prehabilitation and ERAS intervention. Assuming a 9-month recruitment period, a superiority margin of 0.3, a 1:1 randomization ratio, a significance level $\alpha=0.05$ (one-sided), a test power ($1-\beta=80\%$), and a dropout rate=10% in either group, a total sample size of at least 136 patients (68 in the experimental group, 68 in the control group) is required.
Randomization	All participants will be randomized to the experimental or control

Method	group using a random number table method, with a 1:1 allocation ratio.
Planned Study Period	Recruitment Start Date: December 2024
Planned Study Period	Recruitment End Date: November 2025
	Follow-up End Date: December 2025
	Preliminary Analysis Date: February 2026
Inclusion Criteria	1. 18 years ≤ Age ≤ 75 years.
Inclusion Criteria	2. ECOG score 0-2.
	3. ASA classification I-III.
Exclusion Criteria	4. Pathologically confirmed gastric adenocarcinoma (cT3-4N-M0) by endoscopy before neoadjuvant therapy, deemed suitable for radical resection by MDT discussion.
	5. Negative pregnancy test within one month, not pregnant or breastfeeding.
	6. Informed consent and ability to comply with the study protocol.
	1. Severe cardiac insufficiency (preoperative LVEF <30% or NYHA class IV).
Exclusion Criteria	2. Severe hepatic or renal insufficiency (Child-Pugh ≥10; creatinine clearance <25 ml/min).
Withdrawal Criteria	3. History of cerebral hemorrhage, cerebral infarction, TIA within six months, or presence of central nervous system diseases/psychiatric illnesses preventing completion of neoadjuvant therapy.
	4. Synchronous tumors or other diseases requiring simultaneous surgery (except laparoscopic cholecystectomy).
	5. Tumor complications (e.g., bleeding, perforation, obstruction) requiring emergency surgery.
	6. Severe infection or other severe comorbidities.
	7. Participation in other clinical trials.
	1. Participant requests to withdraw or discontinue the trial.
Withdrawal Criteria	2. After enrollment, the patient's condition changes, and the attending physician confirms the need for emergency surgery.
Outcome Measures	3. Violation of the trial protocol.
	Primary Endpoint:
Outcome Measures Safety Indicators	1.Incidence of 30-day postoperative complications. Non-surgical complications: Respiratory complications, urinary tract infection, pulmonary embolism, cerebrovascular accident, impaired liver/kidney function, etc. Surgical complications: Bleeding, anastomotic leak, anastomotic stenosis, intestinal obstruction, delayed gastric emptying, abdominal infection, surgical site infection, pancreatic leak, etc. Complication severity assessed using Clavien-Dindo classification (I-V).

	Secondary Endpoints:
	1. Pathological data: Type, size, location, stage, etc. 2. Surgical operation and short-term clinical outcomes. 3. Patient-Reported Outcomes (PRO). 4. 6-Minute Walk Test (6MWT).
	Adverse Events/Adverse Reactions/Serious Adverse Events/Serious Adverse Reactions: All adverse events during the trial intervention phase will be recorded. The investigator is responsible for ensuring all adverse events are accurately documented in the participant's medical records.
Statistical Analysis	All statistical analyses will be performed using SPSS version 26.0 or later. Unless otherwise specified, all statistical tests will use a two-sided test with $\alpha=0.05$, and confidence intervals will be two-sided 95%. Descriptive statistics (mean, median, standard deviation, min, max) will summarize continuous variables; counts and percentages for categorical variables. Enrollment/Withdrawal Analysis: Counts/percentages enrolled, completed, withdrawn. Demographics/Baseline Analysis: Descriptive statistics per group; t-test, χ^2 test, or rank-sum test for group comparability. Primary Outcome Analysis: χ^2 test for complication rates, etc. Secondary Outcomes Analysis: t-test, χ^2 test, rank-sum test; log-rank test for survival curves.
Follow-up	Prehabilitation patients will be followed during the prehabilitation period. All participants will be followed up at 30 days postoperatively. Outpatient follow-up every 2-3 months until 1 year postoperatively, recording disease information.

Study Protocol:

Title: Prehabilitation for Gastric Cancer Patients Receiving Neoadjuvant Chemotherapy: A Randomized Trial

1. Research Background

1.1 Epidemiology of Gastric Cancer

Gastric cancer is one of the most common malignancies worldwide. WHO and GLOBOCAN statistics show it ranks 5th in incidence and 4th in mortality [5]. China has about 400,000 new cases and 290,000 deaths annually [6], posing a significant disease burden. Data from the Chinese Gastrointestinal Cancer Surgery Alliance indicates that early gastric cancer accounts for only 20%, while locally advanced and advanced stages account for 70% and 10%, respectively [7]. Unlike Japan and Korea, where early detection and treatment are common, diagnosis in China often occurs at advanced stages, causing significant distress. The efficacy of treatment for advanced gastric cancer is inferior to early stages, with less than 50% achieving R0 resection, and over 50% of those having poor prognosis post-resection [8]. Neoadjuvant therapy offers hope, playing a vital role in treating advanced gastric cancer.

1.2 Application of Neoadjuvant Therapy

Neoadjuvant chemotherapy (NACT) for gastric cancer aims to reduce tumor stage and eliminate occult micrometastases, thereby increasing the rate of radical resection and the chance of cure. First proposed by Frei et al. [9] in 1982, it was first applied to gastric cancer by Wilke et al. [10] in 1989. NACT can reduce tumor size and stage, improving overall survival (OS) and progression-free survival (PFS). Japanese studies JCOG001 [11], JCOG0405 [12], JCOG1002 [13] showed promising results. JCOG0405 using cisplatin+S-1 reported 3-year and 5-year OS of 59% and 53%, superior to JCOG0001. JCOG1002 adding docetaxel showed no additional benefit. In Europe and the US, neoadjuvant therapy is standard for locally advanced gastric cancer. The European MAGIC trial [14] (ECF regimen) and the French FNCLCC/FFCD9703 trial [15] (PF regimen) showed similar benefits (tumor downstaging, increased R0 resection, prolonged OS). Our center participated in the RESOLVE study [16], confirming the non-inferiority of the SOX regimen to Capox, providing good RFS and increased R0 resection rates.

Although guidelines vary slightly, the combined modality of surgery plus NACT is firmly established as first-line treatment for advanced gastric cancer. However, while improving clinical outcomes, NACT also induces physiological and pathological changes. The tumor itself reduces tolerance to treatment, and chemotherapy decreases functional capacity and worsens malnutrition. This impaired state reduces the ability to cope with surgical stress, potentially increasing complications, worsening outcomes, and impairing prognosis. Jack et al. [17] first used CPET to show NACT is associated with reduced physical fitness and shortened 1-year OS. Sinclair et al. [18] and West et al. [19] found decreased cardiopulmonary function in gastroesophageal adenocarcinoma and rectal cancer patients, respectively, linked to perioperative complications. Cognitive impairment and neurotoxicity from chemotherapy also reduce quality of life [20]. This poorer health status is linked to reduced NACT tolerance, increased drug toxicity, nutritional risk, and clinical prognosis.

Therefore, robust perioperative management is needed to improve physical state or reduce functional decline. Preoperative prehabilitation is a crucial component.

1.3 Overview of Enhanced Recovery After Surgery (ERAS)

The ERAS concept, first proposed by Danish surgeon Kehlet [21], is a major milestone in surgery. Its core is the use of optimized, evidence-based perioperative measures to reduce physiological and psychological surgical stress, accelerating recovery. Unlike traditional care, ERAS integrates anesthesiology, pain control, nutrition, psychological adjustment, and surgery, combining interventions to enhance postoperative recovery and improve clinical endpoints. In China, Professor Jieshou Li first applied ERAS to gastrointestinal surgery in 2007 [22]. Our center published the first RCT on ERAS in gastric cancer surgery, showing its safety and feasibility, with advantages over traditional care: reduced stress, shorter hospital stay, improved quality of life, without increased complications [23]. Compared to conventional care, the ERAS group had significantly shorter postoperative stay (7.09d vs 8.67d, $P<0.001$), earlier first flatus, oral intake, and ambulation (2.50d vs 3.40d, $P<0.001$; 1.02d vs 3.64d, $P<0.001$; 1.47d vs 2.99d, $P<0.001$), and lower costs ($7621.75 vs $7814.16, $P=0.009$). Complication rates were higher in the conventional group (18.1% vs 12.3%, $P=0.030$). Inflammatory markers (CRP, PCT) differed significantly on POD 3/4 ($P<0.001$, $P=0.025$). ERAS also significantly improved 5-year OS and cancer-specific survival ($P=0.013$ and $P=0.032$), particularly in stage III patients ($P=0.044$). Adherence to ERAS improves short-term outcomes, 5-year OS, and cancer-specific survival after laparoscopic gastrectomy.

However, many ERAS studies exclude neoadjuvant therapy patients. We aim to evaluate whether these patients benefit from prehabilitation combined with ERAS.

1.4 Prehabilitation

Facing the challenges of NACT, prehabilitation has been integrated into clinical practice. Prehabilitation involves preoperative interventions to improve physiological and psychological state, enhancing the response to surgical stress. Introduced in the early 21st century, Carli [24] proposed a multimodal intervention centered on exercise (aerobic, resistance, breathing). Topp [25] introduced prehabilitation in ICU. Given the impact of cancer on quality of life, prehabilitation is needed in oncology. Since Kehlet's Fast-Track surgery [26] was introduced to surgical oncology, evolving into ERAS, it has become essential for improving outcomes in cancer patients [27].

However, ERAS primarily focuses on intra- and post-operative periods, lacking effective preoperative intervention. Prehabilitation, as a key preoperative component of ERAS, includes nutrition, exercise, and psychological interventions. Key elements include: ① Correcting preoperative anemia. ② Preventive analgesia (e.g., NSAIDs, COX-2 inhibitors) [28]. ③ Preoperative frailty assessment (e.g., Clinical Frailty Scale, CFS) and intervention [29]. ④ Preoperative exercise: Assess tolerance and create a plan to improve functional capacity [30]. ⑤ Preoperative cognitive assessment (e.g., MMSE, MoCA) and intervention if needed [31]. ⑥ Preoperative inflammation control: Consider steroids to reduce pain, inflammation, fatigue [32]. ⑦ Preoperative psychological intervention: Assess with HADS, provide support [33]. ⑧ Preoperative nutritional support: Screen with NRS2002. Provide support if: >10% weight loss in 6 months, NRS2002≥5, BMI<18.5 with poor condition, albumin<30g/L. Prefer oral/enteral route. Duration typically 7-10 days [34].

Francesco Carli et al. found prehabilitation increased 6-minute walk distance (6MWD) preoperatively (+36.9m vs -22.8m in controls) and postoperatively (+15.4m vs -81.8m in controls, P<.001), indicating improved cardiopulmonary function [35]. Prehabilitation improves preoperative and postoperative functional capacity, prevents decline in physical/nutritional status, and impacts cancer care continuity.

Current evidence lacks high-quality multicenter studies supporting prehabilitation. There's no standardized intervention duration. There's a need for patient-centered, multidisciplinary, individualized prehabilitation programs and determining the optimal duration to provide theoretical guidance and evidence for perioperative management.

2. Study Objectives

This study aims to compare the effects of prehabilitation combined with perioperative ERAS pathway management versus perioperative ERAS pathway management alone on short-term outcomes and long-term prognosis in gastric cancer patients receiving neoadjuvant chemotherapy undergoing laparoscopic (robotic) radical gastrectomy, and to explore its feasibility, safety, and clinical application prospects.

3. Study Design

3.1 Study Population

Eligible patients providing informed consent will be randomized using a SAS 9.4 generated random list by a staff member. The trial uses a 1:1 allocation ratio. The experimental group receives prehabilitation combined with ERAS management; the control group receives ERAS management alone. Both groups receive standard management from admission until discharge, with relevant indicators and adverse events recorded. Outpatient follow-up continues until 1 year postoperatively or death/recurrence.

3.2 Neoadjuvant Treatment Regimen and Efficacy Evaluation

All patients undergo Multidisciplinary Team (MDT) discussion (including rehabilitation, clinical nutrition, psychiatry, oncology, gastrointestinal surgery, radiology, pathology) to decide on NACT and determine the regimen. Regimens are primarily fluorouracil-based combined with other drugs (targeted therapy, immunotherapy, etc.), given for 2-4 cycles preoperatively. Options include: (1) SOX [36]: Oxaliplatin 130mg/m² iv d1 + S-1 40-60mg/m² po d1-14. (2) DOS [37]: Docetaxel 40mg/m² iv d1, Oxaliplatin 85mg/m² iv d1 + S-1 40-60mg/m² po bid d1-14. (3) FLOT [38]: Docetaxel 50 mg/m², Oxaliplatin 80 mg/m², Leucovorin 200 mg/m², Fluorouracil 2600 mg/m² 24h infusion, d1. (4) XELOX [39]: Oxaliplatin 130mg/m² iv d1 + Capecitabine 850-1000mg/m² po bid d1-14. HER-2, MMR, MSI, EBV testing determines use of trastuzumab, immunotherapy, etc.

Patients undergo regular imaging, endoscopy, pathology, tumor markers post-NACT to evaluate response. MDT reassesses after 2-4 cycles using imaging (RECIST 1.1: CR, PR, PD, SD) and postoperative pathology (CAP-TRG: 0-3). If CR/PR, radical surgery within 1 month (at least 1 week post-NACT). If SD, MDT decides surgery, continue 1-2 cycles, or switch regimen. If PD, MDT assesses resectability.

3.3 Intervention

Intervention Plan:

The study flowchart is shown in Figure 1. Enrollment occurs at the gastrointestinal

surgery outpatient clinic. The intervention period is from the end of NACT until surgery (4 weeks total). This is a prospective RCT with two groups: Multimodal Prehabilitation + Standard ERAS Management (Prehabilitation Group) and Standard ERAS Management alone (Control Group). At baseline (decision for NACT), comprehensive assessment is performed (cardiopulmonary function, 6MWD, nutrition, labs, CT, etc.). The Prehabilitation Group receives individualized prehabilitation guidance (exercise, breathing, nutrition, psychology) plus standard preoperative ERAS guidance. The Control Group receives standard preoperative ERAS guidance. Involvement includes hospital team and family/patient, monitored via wearable devices, WeChat, phone. NACT is 2-4 cycles, decided by MDT based on condition, fitness, response.

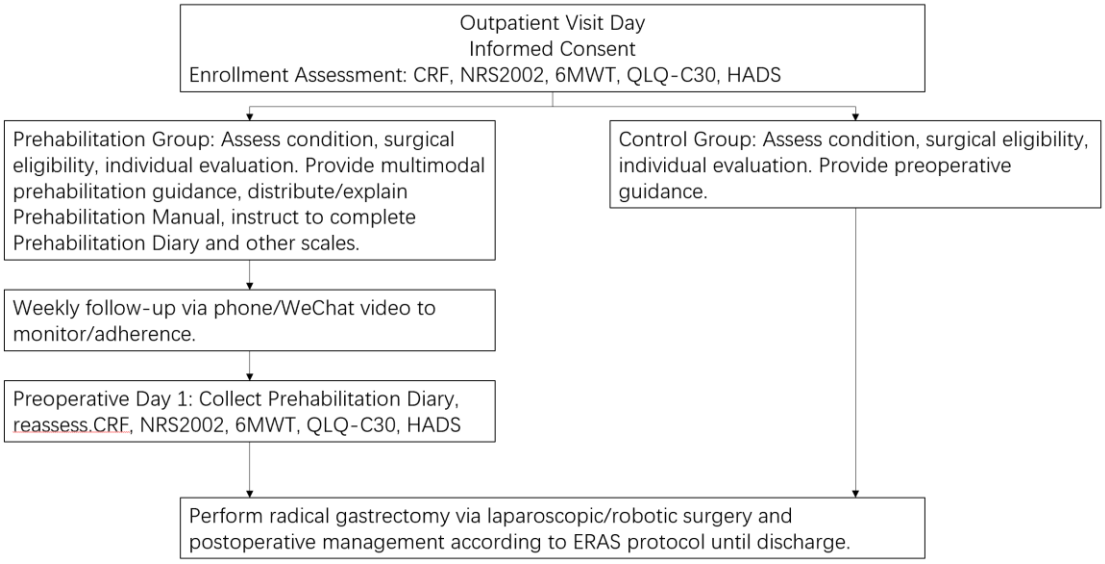

Figure 1. Flowchart for Multimodal Prehabilitation in Neoadjuvant Gastric Cancer Patients

The prehabilitation content, based on previous studies and local practice, is developed by GI surgery, rehabilitation, nutrition, and psychology. It includes exercise, nutrition, and psychology. After individual assessment, patients receive one-on-one counseling and education, the Prehabilitation Manual, and Prehabilitation Diary. Weekly follow-up assesses adherence. At admission, the diary is collected, and a questionnaire on prehabilitation strategies is completed. The manual and guidance include:

Group	Intervention Modality		Specific Measures
Prehabilitation Group	Exercise	Physical fitness training	Resistance & Endurance: At least 3 days/week, 2 sessions/day (aerobic & resistance alternating), 30min/session. Includes: 5min warm-up, 25min aerobic (stairs, jogging, brisk walking) OR 25min resistance (seated leg raises, wall push-ups, standing lateral

			raises, half-squats, sit-ups; 3-4 exercises/session, 3-4 sets/exercise, 12-15 reps/set optimal), 5min cool-down/stretching.
		Breathing	Breathing Training: Must quit smoking. Includes: • Balloon blowing: Start small, slow exhalation until breathless, hold 3-5s. • Back patting/coughing: Sit leaning forward, deep breath, immediately perform forceful cough. • Chest breathing: Hands on ribs, inspire against resistance, expand chest, hold 2-3s, I:E=1:3, 15 reps/set, 3 sets/time, 3 times/day. • Incentive spirometer: Use correctly, slow exhalation, hold 2-3s at target. 3 sets/time, 3 times/day.
	Nutrition Intervention		Advise healthy diet: avoid high-energy/fat; increase vegetables, fruit, fiber, micronutrients, high-quality protein. Aim for 1.5g protein/kg/day. If nutritional risk/malnutrition, provide ONS/EN (≥400kcal/day). If ONS/EN inadequate <3 days or <50% needs >1 week, use PN. Combine PN+EN for gastric outlet obstruction. Refer to nutrition clinic. Supplement iron, Vitamin D, multivitamins as needed.
	Psychological Intervention		Assess anxiety with HADS. Mild/moderate: Guided imagery, meditation, pleasant music with family help. Severe: Refer to psychology clinic.

Control Group	Traditional ERAS Preop Management	Preop Exercise	Quit smoking/limit alcohol; deep breathing exercises; appropriate activity.
		Preop Nutrition	Screen/assess nutritional status; dietary guidance, small frequent meals; supplemental PN/EN if needed for ≥1 week.
		Preop Psychological Care	Assess psychological state, family support, finances; communicate concerns, increase communication.

Assessment:

(1) Exercise Intensity: The intensity of exercise is evaluated through two aspects: the subjective fatigue rating (rating of perceived exertion, RPE), also known as the Borg scale, and the target heart rate.

The intensity of endurance training should be set within the modified Borg scale range of 13-16 points, that is, the subjective fatigue sensation is slightly strenuous or strenuous. If the patient feels that the exercise can be completed easily, the intensity can be appropriately increased. When the patient feels severe fatigue or slight shortness of breath, the intensity can be reduced. It is not recommended to exercise too intensely [40]. The target heart rate is calculated based on the patient's age, that is, target heart rate = (220 - age) * (70% - 80%). For example: for a 60-year-old patient, their target heart rate = (220 - 60) * (70% - 80%) = 112 - 128 beats.

During resistance training and endurance training, it is important to take breaks between groups to prevent muscle soreness and affect compliance.

(2) Pulmonary Function: Prehabilitation group assessed pre- and post-training; control group preoperatively. Best of 3 attempts recorded (FEV1, FVC, FEV1/FVC, MVV, PEF).

(3) 6-Minute Walk Test (6MWT) [41]: Prehabilitation group pre- and post-training; control group preoperatively. Conducted in a 15m corridor. Instructions given. Distance in 6 minutes recorded. Monitor for symptoms. BP, HR, SpO_2 pre/post. Interpretation: <150m severe cardiac impairment; 150-425m moderate; 426-550m mild.

Control Group Intervention:

Patients managed per center's gastric cancer ERAS pathway. Preop: smoking/alcohol cessation, coughing exercises, DVT prophylaxis, nutrition screening/support, communication. Surgery: laparoscopic/robotic. Anesthesia: epidural + general. Goal-directed fluid therapy. Postop: early ambulation, early tube removal, multimodal analgesia. See Table 1 for ERAS pathway details.

(Table 1) Gastric Cancer Perioperative ERAS Pathway Management Plan

Intervention Measure	**Whether to execute**
PRE-ADMISSION	
Preoperative organ function/risk assessment & clinical decision	Yes
Instruct patient to quit smoking/alcohol	Yes
Encourage patient/family participation	Ye
PREOPERATIVE MANAGEMENT	
MDT-led consultation, explain ERAS	Yes
Preoperative education, expectation management, discharge planning	Yes
Mental state assessment & intervention	No
Bowel preparation	Not routine, case-by-case
Fasting (solids 6h, clear liquids until 2h pre-op)	Yes
INTRAOPERATIVE MANAGEMENT	
Nasogastric tube	Not routine, case-by-case
Surgical incision	Minimize size for exposure
Anesthesia method	Epidural (Th7-11) + General Anesthesia
Intraoperative warming	Warming blanket, fluid warmer
Antibiotic prophylaxis	30min pre-incision, re-dose if >3h
Abdominal drain	Remove 24h postop
Wound closure	Absorbable suture
Pain management	
Urinary catheter	Remove 24h postop

IV fluids	Goal-directed therapy
Patient mobilization	Encourage; bedside day of surgery, ambulate POD1
Thromboprophylaxis plan	MDT assess/screen/intervene; risk assessment, TED stockings, IPC, mobilize (>6h), massage, prophylactic heparin
Nasogastric tube	Not routine, case-by-case
Surgical incision	Minimize size for exposure
POSTOPERATIVE MANAGEMENT	
Planned discharge, MD/nutritionist discharge instructions, 24h post-discharge call	Yes
Treatment review & summary	Yes
30-day post-discharge follow-up & management	Yes

ERAS: ENHANCED RECOVERY OF SURGERY; NSAIDS: NON-STEROIDAL ANTIINFLAMMATORY DRUGS; DVT: DEEP VENOUS THROMBOSIS

3.4 Surgical Procedure

Surgeons: Must have performed ≥50 laparoscopic-assisted gastrectomies with D2 lymphadenectomy.

Requirements: Minimally invasive approach. Laparoscopic access follows Chinese expert consensus. D2 radical lymphadenectomy per Japanese Gastric Cancer Association guidelines. Lymph node processing per Chinese expert consensus. Surgery type: Da Vinci robotic / Laparoscopic. Procedure: Total / Proximal / Distal Gastrectomy. Reconstruction: Billroth I / Billroth II / Roux-en-Y / Billroth II+Braun / Esophagojejunostomy Roux-en-Y. Postop complications graded by Clavien-Dindo.

3.5 Postoperative Adjuvant Chemotherapy

Both groups are reviewed ~1 month post-discharge. Decision for adjuvant chemotherapy based on pathology. If indicated, use SOX, XELOX, DOS, etc., based on tolerance/assessment.

4. Study Endpoints and Endpoint Measurements

Primary Endpoint: Incidence of 30-day postoperative complications (recorded during 1-month follow-up). Includes non-surgical (respiratory, UTI, PE, CVA, hepatic/renal

impairment) and surgical (bleeding, leak, stenosis, obstruction, delayed emptying, infection, pancreatic leak) complications. Severity by Clavien-Dindo.
Secondary Endpoints:
1.Pathological data.
2.Surgical operation & short-term outcomes.
3.Patient-Reported Outcomes (PRO).
4.6MWT.

5. Sample Size Estimation
Total sample size 136 (68/group). Based on assumed complication rate of 25% (control) vs 15% (intervention), 1:1 ratio, α=0.05 (one-sided), power=80%, dropout=10%, superiority margin=0.3.

6. Permissible Treatments and Medications During the Study
Treatments/medications for adverse events should be recorded in CRF. Includes: antipyretics/NSAIDs for fever; antibiotics for infection; PPIs; antidiarrheals; antiemetics (ondansetron); sedatives for insomnia; antihistamines for allergy; somatostatin for bloating; hemostatics/transfusions for bleeding; G-CSF for leukopenia; TPO for thrombocytopenia.

7. Measurements and Recorded Indicators
Data recorded in CRF for outpatient, preop, intraop, postop phases. Data entry into EpiData by two independent staff, quality monitored by a third.

7.1 Outpatient Enrollment Assessment: Demographics, medical history, personal history, labs, imaging (CT, CTA), echo, PFTs, tumor markers, NRS2002, HADS, 6MWD, QLQ-C30.

7.2 Preoperative Assessment: BMI, smoking status, ASA, NYHA, labs, echo, PFTs, NRS2002, HADS, 6MWD, VTE risk, ACS risk, education, consent.

7.3 Intraoperative Details: Surgery info, events (hypotension, hypertension, hypoxia), inputs/outputs, anesthesia/surgery times.

7.4 Postoperative Status & Short-term Outcomes: ICU admission, pain, drain removal time, flatus/defecation, first liquid intake, 30-day complications/mortality/reoperation/readmission, LOS, cost, pathology, PROs (nutrition, inflammation, fitness, psychology), HADS, 6MWD, QLQ-C30 at 30 days.

7.5 Adverse Events & Evaluation: Nausea, vomiting, bloating, postop complications are main AEs. Record all changes/reactions. Severity per NCI CTCAE v5.0.

7.6 Postoperative Follow-up Plan: For life guidance, complication treatment, detecting recurrence/second cancer. Follow-up at our center preferred. Schedule: In-hospital daily; weekly phone/WeChat first 30 days; outpatient at 30 days. Phone follow-up to reduce loss.

8. Statistical Analysis

8.1 Data Collection, Monitoring, Review, Interim Analysis: Hospital ethics committee reviews data semi-annually. Interim analysis by independent statistician when 50% randomized. Trial stops if intervention shows significant harm.

8.2 Statistical Analysis Plan: Use SPSS 26.0+. Two-sided α=0.05, 95% CIs unless specified. Descriptive stats for continuous (n, mean, median, SD, min, max) and

categorical (n, %) variables.

8.2.1 Enrollment/Withdrawal Analysis: Counts/percentages.

8.2.2 Demographics/Baseline Analysis: Descriptive stats per group; t-test, χ^2, rank-sum for comparability.

8.2.3 Primary Outcome Analysis: χ^2 test for complication rates.

8.2.4 Secondary Outcome Analysis: t-test, χ^2, rank-sum test; log-rank test for survival analysis.

8.3 Data Storage Plan: Electronic data backed up multiple times. Original records kept by investigator; uploaded to clinical trial registry.

9. Informed Consent

The investigator must fully explain the study purpose, potential side effects, and risks, ensuring patients understand their rights, risks, and benefits before participation. Participants must sign the informed consent form.

Reference:

1. Zhang Shuze, Li Fan, Yang Hanteng, et al. Selection of neoadjuvant chemotherapy cycles and surgical timing for advanced gastric cancer [J]. Cancer Prevention and Treatment,2021,34(06):581-586.
2. Liu, G., Cao, S., Liu, X., Tian, Y., Li, Z., Sun, Y., Zhong, H., Wang, K., & Zhou, Y. (2024). Short- and long-term outcomes following perioperative ERAS management in patients undergoing minimally invasive radical gastrectomy after neoadjuvant chemotherapy: A single-center retrospective propensity score matching study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 51(1), 109459. Advance online publication. .
3. Zhong, H., Liu, X., Tian, Y., Cao, S., Li, Z., Liu, G., Sun, Y., Zhang, X., Han, Z., Meng, C., Jia, Z., Wang, Q., & Zhou, Y. (2023). Comparison of short- and long-term outcomes between laparoscopic and open gastrectomy for locally advanced gastric cancer following neoadjuvant chemotherapy: a propensity score matching analysis.
4. Xing, J., Wang, Y., Shan, F., Li, S., Jia, Y., Ying, X., Zhang, Y., Li, Z., & Ji, J. (2021). Comparison of totally laparoscopic and laparoscopic assisted gastrectomy after neoadjuvant chemotherapy in locally advanced gastric cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 47(8), 2023–2030.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
7. Miao Rulin, Li Ziyu, Wu Aiwen. Data Report of the Chinese Gastrointestinal Tumor Surgery Alliance (2014-2016). Chinese Journal of Practical Surgery, 2018(1):90-93
8. Ajani JA, Bentrem DJ, Besh S, D'Amico TA, Das P, Denlinger C, Fakih MG, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hofstetter WL, Ilson DH, Keswani RN, Kleinberg LR, Korn WM, Lockhart AC, Meredith K, Mulcahy MF, Orringer MB, Posey JA, Sasson AR, Scott WJ, Strong VE, Varghese TK Jr, Warren G, Washington MK, Willett C, Wright CD, McMillian NR, Sundar H; National Comprehensive Cancer Network. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2013 May 1;11(5):531-46.
9. Frei E 3rd. Clinical cancer research: an embattled species. Cancer. 1982 Nov 15;50(10):1979-92.
10. Wilke H, Preusser P, Fink U, Gunzer U, Meyer HJ, Meyer J, Siewert JR, Achterrath W, Lenaz L, Knipp H, et al. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. J Clin Oncol. 1989 Sep;7(9):1318-26.
11. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito

S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg. 2009 Sep;96(9):1015-22.
12. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M; Stomach Cancer Study Group of the Japan Clinical Oncology Group. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. Br J Surg. 2014 May;101(6):653-60.
13. Ito S, Sano T, Mizusawa J, Takahari D, Katayama H, Katai H, Kawashima Y, Kinoshita T, Terashima M, Nashimoto A, Nakamori M, Onaya H, Sasako M. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. Gastric Cancer. 2017 Mar;20(2):322-331.
14. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11-20.
15. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011 May 1;29(13):1715-21.
16. Zhang X, Liang H, Li Z, Xue Y, Wang Y, Zhou Z, Yu J, Bu Z, Chen L, Du Y, Wang X, Wu A, Li G, Su X, Xiao G, Cui M, Wu D, Chen L, Wu X, Zhou Y, Zhang L, Dang C, He Y, Zhang Z, Sun Y, Li Y, Chen H, Bai Y, Qi C, Yu P, Zhu G, Suo J, Jia B, Li L, Huang C, Li F, Ye Y, Xu H, Wang X, Yuan Y, E JY, Ying X, Yao C, Shen L, Ji J; RESOLVE study group. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. Lancet Oncol. 2021 Aug;22(8):1081-1092. doi: 10.1016/S1470-2045(21)00297-7. Epub 2021 Jul 9. Erratum in: Lancet Oncol. 2021 Aug;22(8):e347.
17. Jack, S et al. “The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery.” European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology vol. 40,10 (2014): 1313-20.
18. Sinclair R, Navidi M, Griffin SM, Sumpter K. The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma. Ann R Coll Surg Engl. 2016 Jul;98(6):396-400.
19. West MA, Loughney L, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients. Eur J Surg Oncol. 2014 Nov;40(11):1421-8.

20. Nurgali K, Jagoe RT, Abalo R. Editorial: Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae? Front Pharmacol. 2018 Mar 22;9:245.
21. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997 May;78(5):606-17.
22. Jiang Zhiwei, Li Jieshou, Wang Zhiming, et al. Study on the Safety and efficacy of Enhanced recovery after Surgery in Gastric cancer patients [J]. Chinese Journal of Surgery,2007,45(19): 1314-1317.Tian YL, Cao SG, Liu XD, Li ZQ, Liu G, Zhang XQ, Sun YQ, Zhou X, Wang DS, Zhou YB. Short- and long-term outcomes associated with enhanced recovery after surgery protocol vs conventional management in patients undergoing laparoscopic gastrectomy. World J Gastroenterol. 2020 Oct 7;26(37):5646-5660.
23. Carli, Francesco, and Celena Scheede-Bergdahl. “Prehabilitation to enhance perioperative care.” Anesthesiology clinics vol. 33,1 (2015): 17-33.
24. Topp, Robert et al. “The effect of bed rest and potential of prehabilitation on patients in the intensive care unit.” AACN clinical issues vol. 13,2 (2002): 263-76.
25. Kehlet, Henrik, and Douglas W Wilmore. “Multimodal strategies to improve surgical outcome.” American journal of surgery vol. 183,6 (2002): 630-41.
26. Cappellini, M D et al. “Iron deficiency anaemia revisited.” Journal of internal medicine vol. 287,2 (2020): 153-170.
27. Aglio, Linda S et al. “Preemptive analgesia for postoperative pain relief in thoracolumbosacral spine operations: a double-blind, placebo-controlled randomized trial.” Journal of neurosurgery. Spine vol. 29,6 (2018): 647-653.
28. Hall, Daniel E et al. “Association of a Frailty Screening Initiative With Postoperative Survival at 30, 180, and 365 Days.” JAMA surgery vol. 152,3 (2017): 233-240.
29. Ripollés-Melchor, Javier et al. “Committed to be fit. The value of preoperative care in the perioperative medicine era.” Minerva anestesiologica vol. 84,5 (2018): 615-625.
30. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. “Postoperative delirium in older adults: best practice statement from the American Geriatrics Society.” Journal of the American College of Surgeons vol. 220,2 (2015): 136-48.e1.
31. de la Motte, Louise et al. “Preoperative methylprednisolone enhances recovery after endovascular aortic repair: a randomized, double-blind, placebo-controlled clinical trial.” Annals of surgery vol. 260,3 (2014): 540-8; discussion 548-9.
32. Levett, D Z H, and C Grimmett. “Psychological factors, prehabilitation and surgical outcomes: evidence and future directions.” Anaesthesia vol. 74 Suppl 1 (2019): 36-42.
33. Weimann, Arved et al. “ESPEN practical guideline: Clinical nutrition in surgery.” Clinical nutrition (Edinburgh, Scotland) vol. 40,7 (2021): 4745-4761.
34. Minnella, Enrico M et al. “Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial.” JAMA surgery vol. 153,12 (2018): 1081-1089.
35. Kang, Yoon-Koo et al. “PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1

for Resectable Advanced Gastric Cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 39,26 (2021): 2903-2913.
36. Kang, Yoon-Koo et al. "PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 39,26 (2021): 2903-2913.
37. Al-Batran, Salah-Eddin et al. "Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial." The Lancet. Oncology vol. 17,12 (2016): 1697-1708.
38. Zhu, Xiao-Dong et al. "XELOX doublet regimen versus EOX triplet regimen as first-line treatment for advanced gastric cancer: An open-labeled, multicenter, randomized, prospective phase III trial (EXELOX)." Cancer communications (London, England) vol. 42,4 (2022): 314-326.
39. Liu, Z., Qiu, T., Pei, L., Zhang, Y., Xu, L., Cui, Y., Liang, N., Li, S., Chen, W., & Huang, Y. (2020). Two-Week Multimodal Prehabilitation Program Improves Perioperative Functional Capability in Patients Undergoing Thoracoscopic Lobectomy for Lung Cancer: A Randomized Controlled Trial. Anesthesia and analgesia, 131(3), 840–849.
40. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002). ATS statement: guidelines for the six-minute walk test. American journal of respiratory and critical care medicine, 166(1), 111–117
41. Kondrup, J., Allison, S. P., Elia, M., Vellas, B., Plauth, M., & Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN) (2003). ESPEN guidelines for nutrition screening 2002. Clinical nutrition (Edinburgh, Scotland), 22(4), 415–421.
42. Sun Zhenxiao, Liu Huaxia, Jiao Linying, et al. Reliability and Validity Study of Hospital Anxiety and Depression Scale [J]. Chinese Journal of Clinical Physicians: Electronic Edition,2017, 2): 4Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., Filiberti, A., Flechtner, H., Fleishman, S. B., & de Haes, J. C. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute, 85(5), 365–376.
43. Bennett, J. A., Riegel, B., Bittner, V., & Nichols, J. (2002). Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. Heart & lung : the journal of critical care, 31(4)
44. Clavien, P. A., Barkun, J., de Oliveira, M. L., Vauthey, J. N., Dindo, D., Schulick, R. D., de Santibañes, E., Pekolj, J., Slankamenac, K., Bassi, C., Graf, R., Vonlanthen, R., Padbury, R., Cameron, J. L., & Makuuchi, M. (2009). The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery, 250(2), 187–196.
45. Li Ziyu, Wu Zhouqiao, Ji Jiafu. Expert Consensus on the Diagnosis and Registration Norms for Postoperative Complications of Gastrointestinal Tumor Surgery in China

(2018 Edition)[J] Chinese Journal of Practical Surgery,2018,38(6):7.