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

Informed Consent Form

Research Sponsor: The Affiliated Hospital of Qingdao University

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INFORMED CONSENT FORM

Protocol Title: Prehabilitation for Gastric Cancer Patients Receiving Neoadjuvant Chemotherapy: A Randomized Trial
Protocol Version No.: 1.0 2024-7-27
Informed Consent Form Version No.: 1.0 2024-7-27
Research Institution: Department of Gastrointestinal Surgery, The Affiliated Hospital of Qingdao University
Patient Name: _____
Patient Address: _____
Patient Phone: _____
Dear _____ (Mr./Ms.)

We are inviting you to participate as a subject in a clinical trial. This informed consent form provides you with information to help you decide whether to participate. Please take time to read it carefully. If you have any questions or do not understand something, please discuss it with the investigating physician.

Your participation in this study is entirely voluntary. This study has been reviewed and approved by the Ethics Committee of The Affiliated Hospital of Qingdao University.

1. Research Background:

1.1 Epidemiology of Gastric Cancer

Gastric cancer is one of the most common malignant tumors worldwide. Statistics from the WHO and GLOBOCAN show it ranks 5th in incidence and 4th in mortality. China has about 400,000 new cases and approximately 290,000 deaths annually, 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. 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 radical resection (R0 resection), and over 50% of those resected having a poor prognosis. 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. in 1982, it was first applied to gastric cancer by Wilke et al. in 1989. NACT can reduce tumor size and stage, improving overall survival (OS) and progression-free survival (PFS). Japanese studies JCOG001, JCOG0405, JCOG1002 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 (ECF regimen: epirubicin, cisplatin, fluorouracil) and the French FNCLCC/FFCD9703 trial (PF regimen: cisplatin,

fluorouracil) showed similar benefits (tumor downstaging, increased R0 resection, prolonged OS). Our center participated in the RESOLVE study, confirming the non-inferiority of the SOX regimen to Capox, providing good disease-free survival 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. first used cardiopulmonary exercise testing (CPET) to show NACT is associated with reduced physical fitness and shortened 1-year OS. Sinclair et al. and West et al. 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. 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, 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, Academician Jieshou Li first applied ERAS to gastrointestinal surgery in 2007. With development, our research 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 (C-reactive protein, procalcitonin) differed significantly on postoperative days 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, contributing to the recovery and prognosis of advanced gastric cancer patients.

1.4 Preoperative Prehabilitation

Facing the challenges of NACT, prehabilitation has been integrated into clinical practice. Preoperative prehabilitation involves preoperative interventions to improve physiological and psychological state, enhancing the response to surgical stress. Introduced in the early

21st century, Professor Carli from Canada proposed a multimodal intervention centered on exercise (aerobic, anaerobic, breathing). Later, Topp et al. introduced prehabilitation in ICU. Given the impact of cancer on quality of life, prehabilitation is needed in oncology. Since Kehlet's Fast-Track surgery concept in 1989 was introduced to surgical oncology, evolving into Enhanced Recovery After Surgery (ERAS), it has become essential for improving outcomes in cancer patients.

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 (reduces AKI, mortality, readmission). ② Preventive analgesia (e.g., NSAIDs, COX-2 inhibitors) reduces pain, chronic pain risk, analgesic doses. ③ Preoperative frailty assessment (e.g., Clinical Frailty Scale, CFS) and intervention reduces mortality. ④ Preoperative exercise: Assess tolerance and create a plan to improve functional capacity; reduced activity is an independent risk factor for poor outcomes. ⑤ Preoperative cognitive assessment (e.g., MMSE, MoCA) and intervention if needed; impairment increases complication/mortality risk. ⑥ Preoperative inflammation control: Consider steroids to reduce pain, inflammation, fatigue. ⑦ Preoperative psychological intervention: Assess with Hospital Anxiety and Depression Scale (HADS), provide support. 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. Use PN if oral/enteral inadequate. Duration typically 7-10 days; longer for severe cases.

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. 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 Procedures:

(1) After obtaining your consent and signing this form, the researcher will submit your information for screening. If eligible, you will proceed per protocol. If not, you will exit the study.

(2) After screening, the prehabilitation and chemotherapy plans will be explained.

(3) Postoperative recovery and adjuvant therapy are the surgeon's responsibility.

(4) Surgery will be performed according to permitted protocols. Surgery outside protocol leads to study exit.

4. What is Required of You:

For the success of this study, please:

● Comply with screening for inclusion/exclusion criteria.

● Do not change your current treatment or start new treatments before confirming with the research doctor.

● Implement the prehabilitation plan during NACT as guided by your doctor/research team.

● If discontinuing study treatment early, please complete the final evaluation.

● Adhere to the follow-up schedule (outpatient, phone, online).

● Report any adverse reactions, clinic visits, or hospitalizations to your doctor/research team.

● Inform your doctor/research team if you change your mind about participation.

● You must sign this ICF if you decide to participate.

5. Risks and Discomforts of Participation:

Risks are primarily related to NACT, surgery, and anesthesia, including:

● NACT adverse reactions (fatigue, weakness, sweating, fever, pain, hepatorenal toxicity, etc.)

● Respiratory complications (pneumonia/atelectasis/pleural effusion/respiratory failure, etc.)

● Cardiovascular complications (arrhythmia/pericardial effusion/heart failure, etc.)

Additionally, you may experience anesthesia/surgery-related discomfort like wound pain, postoperative fever, bloating, abdominal pain, acid reflux, nausea, etc. A minority may experience gastrectomy complications like intestinal obstruction, anastomotic leak, abdominal bleeding, wound issues, thromboembolic disease, etc. Most resolve with conservative treatment.

Rarely, disease may progress, leading to loss of surgical/curative opportunity.

You may experience none, some, or all adverse reactions, of mild, moderate, or severe intensity. Your doctor/team will manage any events promptly.

6. Benefits of Participation:

You may, but are not guaranteed to, receive direct medical benefit.

Potential benefits include:

① Potential improvement in your condition, accelerated recovery, better prognosis.

② Potential reduction in postoperative infections/antibiotic use, shorter hospital stay, lower costs, improved quality of life.

③ Scientific guidance for your disease and close medical monitoring.

④ Close follow-up may detect recurrence/metastasis early, allowing better treatment.

We hope information from this study will benefit future patients with similar conditions.

7. Alternative Treatments:

For neoadjuvant therapy, alternatives include:
(1) Other preoperative therapies: Chemotherapy, Chemoradiotherapy, Immunotherapy, etc.
(2) Other surgical approaches: Open surgery, Local resection, etc.
Please discuss these and other options with your doctor.

8. Costs Related to Participation:
No extra fees are required for participation. Routine costs (tests, surgery, medications) are your responsibility.

9. Compensation:
There is no monetary compensation for participation.

10. Indemnity:
If you suffer injury or serious adverse events related to this study during participation, you are entitled to compensation according to Chinese laws and regulations.

11. Right to Refuse or Withdraw:
You can choose not to participate or withdraw at any stage without reason, without affecting your medical care/rights. Data processed before withdrawal is lawful. Integrated pre-withdrawal data may continue to be used, protecting your privacy, if removal is impractical.
Once you decide to participate, please sign this ICF. Screening will confirm eligibility.

12. Privacy and Confidentiality:
During the study, identifiable information (name, gender, etc.) will be coded/numbered and kept strictly confidential. Only relevant doctors know your identity. Your privacy will be protected. Results may be published but will not identify you. If you consent, your medical data may be reviewed by the sponsor, relevant authorities, or the independent Ethics Committee to ensure proper conduct. Signing implies consent for such review.

13. How to Get Help During the Study:
You can inquire about study information/progress. For study-related questions, contact _____ or _____.
For questions about participant rights, contact the Ethics Committee of The Affiliated Hospital of Qingdao University at Tel: _____.

INFORMED CONSENT SIGNATURE PAGE

If you fully understand this research project and agree to participate, please sign this Informed Consent Form in duplicate. The investigator and the subject (or legal representative) will each retain one copy.

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

To be signed by the subject or their legal representative:

Consent Statement:

1. I confirm I have read and understood this ICF. Potential problems and solutions during the research have been explained, and I had the opportunity to ask questions.
2. I understand participation is voluntary, and refusing will not harm my interests.
3. I am aware that the investigating physician, the responsible personnel at The Affiliated Hospital of Qingdao University overseeing this work, and its Ethics Committee have the right to review research records and case data. I agree to allow the aforementioned parties direct access to my research records, understanding this information will be handled confidentially.
4. I agree to participate in this study.

Subject's Full Name: Year Month Day

Legal Representative's Full Name: Year Month Day

Relationship to Subject: _____ (If a non-close relative authorized representative, is there a Power of Attorney from the subject: Yes No)

To be completed by the physician obtaining informed consent:

Investigator's Declaration: I confirm that I have explained the nature, purpose, requirements, and potential risks of this study to the patient, discussed alternative treatment options, and ensured the subject has received a copy of this Informed Consent Form.

Investigator's Full Name: : Year Month Day