

Study Protocol

Combining surgery and extensive intraoperative peritoneal lavage versus surgery alone for locally advanced gastric cancer (SEIPLUS study): A randomized controlled trial

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Study Team Roster

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Participating Study Centers

Anhui Provincial Hospital

Anqing Municipal Hospital

Jiangsu Cancer Hospital

Jiangxi Provincial Cancer Hospital

The Second Affiliated Hospital of Zhejiang University School of
Medicine

The First Affiliated Hospital of Wannan Medical College

Lishui Municipal Central Hospital

The First Affiliated Hospital of Anhui Medical University

Tianjin Medical University Cancer Institute and Hospital

Sun Yat-sen University

Yuebei People's Hospital

Study Protocol

Study Title

Combined surgery and extensive intraoperative peritoneal lavage versus surgery alone for locally advanced gastric cancer (SEIPLUS): A randomized controlled trial

Study Status

Study Start: March 2016

Study Completion: March 2020

Background

Gastric cancer has been one of the most common cancers and remains the third leading cause of death among malignant tumors all over the world. Surgery has always been considered as the most effective treatment. While surgical technique and perioperative management have dramatically improved the survival of patients with advanced gastric cancer, patients with T4 stage or serosal-positive gastric cancer often suffer from recurrence as peritoneal dissemination, and the prognosis of those patients is extremely poor. Despite curatively resected, peritoneal

metastasis is completed by the implantation of peritoneal free cancer cells exfoliated from serosa invasive tumors. Therefore, things need to be done to eliminate the free exfoliated cancer cells on the peritoneal lining in order to reduce the risk of peritoneal recurrence.

A multi-institutional prospective, randomized Phase III trial has been done by Kuramoto recently. The trail was intended to demonstrate the superiority in overall survival of addition of Extensive Intraoperative peritoneal Lavage (EIPL) to standard treatment in patients with \geq stage T3 carcinoma of stomach. Based on the ‘limiting dilution theory’, after total or distal gastrectomy with D2 lymphadenectomy, the peritoneal cavity is extensively rinsed 10 times with 1 L physiological saline at a time, followed by complete aspiration of the fluid. In total ,10 L saline is to be used. In this study, the EIPL-IPC group had a significantly lower incidence of peritoneal recurrence. Furthermore, the 5-year overall survival rate of the patients in the EIPL-IPC group (43.8%) was significantly better than that of the IPC group (4.6%) and the surgery-alone group (0%). All in all, EILP is easy to carry out, safe and inexpensive. Therefore, gastrectomy with EIPL will be a new standard treatment of gastric cancer.

Objectives

Our study aims to explore the potential function of EIPL in improving the overall survival and progression-free survival for locally advanced gastric cancer after curative resection.

Outcomes

Primary End Point

3-year overall survival

Secondary End Points

3-year disease free survival, postoperative complications and short-term mortality

Statistical Considerations

We calculated that 254 patients were needed in each group in order to detect a difference in 3-year overall survival of 60% for surgery alone group and 71% for EIPL group, with the use of the log-rank test, a two-sided alpha level of 0.05 and a power of 80%.

The differences between groups were compared by using chi-square tests and t test. All P values calculated in the analysis were two-sided. P

values less than 0.05 were considered as statistically significant. Statistical analysis was performed using SPSS software, version 17.0 (IBM Corporation, Armonk, NY, USA).

Arms and Interventions

Experimental:

Extensive Intraoperative Peritoneal Lavage (EIPL): The peritoneal cavity will be washed with 10 L of warmed normal saline (1 L per cycle for 10 cycles). Every time, the peritoneal cavity was stirred and washed sufficiently, and the fluid was aspirated completely.

No Intervention:

Standard Treatment (surgery alone): The peritoneal cavity will be washed with 3 liters or less of warmed normal saline.

All patients were recommended to undergo eight 3-week cycles of oral S-1 (40 mg/m² twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (100 mg/m² on day 1 of each cycle) postoperatively. Dose reductions or interruptions were used to manage potentially serious or life-threatening adverse events.

Selection and Enrollment of Participants

Inclusion Criteria

Preoperative Inclusion Criteria

1. Age older than 18 and younger than 80 years
2. ECOG PS 0 or 1
3. Written informed consent
4. Open surgery
5. cT3/4NanyM0 at preoperative evaluation according to AJCC Cancer Staging Manual, 7th Edition

Intraoperative inclusion criteria:

1. cT3/4NanyM0 according to the macroscopic appearance of exploratory laparotomy
2. R0 surgery

Exclusion Criteria

1. Previous neoadjuvant chemotherapy or radiotherapy
2. Peritoneal dissemination, distant lymph nodes, ovary, liver, lung, brain, and bone metastases
3. Massive ascites or cachexia

4. Participating in any other clinical trials currently
5. Severe cardiovascular, respiratory, kidney, liver and mental disease and diabetes
6. poor compliance

Participant Rights and Confidentiality

Institutional Review Board (IRB) Review

The study protocol and the informed consent document for all clinic sites will be reviewed and approved by the Cancer Center of Sun-Yat Sen University. Individual site protocols will also be submitted for review and approval by the site local IRBs.

Consent Forms

Consent forms will be obtained from each participating provider. The consent form will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, and compensation for participation.

Participant Confidentiality

Data will be recorded with the Crybyter protected web sites (<https://crabyter.sinyoo.net/>) to a data warehouse and transferred over secure network protocol. Only study investigators will have access to a list of study ID codes that will be traceable back to actual subject contact identifiers for clinicians.

Quality Assurance

Quality Control

Sponsor shall appoint monitors to conduct systematic monitoring for the study in accordance with Good Clinical Practice (GCP) principles to ensure the study is carried out according to the protocol and the case report form is identical with original data. The monitors should also assess compliance corresponding to the regulations and protocol. Investigators must ensure the integrity of the medical files. All study files will be reviewed by the sponsor and monitors. Monitors should ensure the following: the rights of the subjects should be protected; original data should comply with GCP and protocol requirements.

Ethics Committee

Before study initiation, the study director must submit the study protocol, informed consent form and other related study documents to the Ethics Committee to obtain its approval for conducting the clinical trial. After receiving the application, the Ethics Committee will convene a meeting to review, discuss and issue written comments attached with the list of participants, professional information and signature of primary investigator. During the study, the sponsor or contract research organization appointed by the sponsor should promptly report serious adverse events, including risks to subjects and other issues. Any modification to the protocol should be approved and recorded by the Medical Ethics Committee.

Training

Sponsor must ensure that all staff involved in the study have been trained by the sponsor or the organization designated by sponsor before the study starts. An investigators' meeting should be convened for all investigators to be familiar with the protocol as well.

In the present study, all hospitals perform >100 D2 gastrectomy per year, and surgeons have sufficient experience for the surgery. Before the start of the study, standard operating procedures were predefined and

given to all surgeons as text and figures. During the study, we made some SOP (standard operating procedure) cards for all centers to ensure the quality of procedures.

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