STUDY PROTOCOL

PROTOCOL TITLE:
Extensive Peritoneal Lavage after Curative Gastrectomy for Gastric Cancer: a Randomized Controlled Trial (EXPEL Study)

PROTOCOL NUMBER:
EXPEL Trial

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1. BACKGROUND AND RATIONALE

Gastric cancer is the second most common cause of cancer death worldwide. Surgery is the mainstay treatment for cure. Peritoneum is a common site of recurrence and the prognosis in patients with peritoneal recurrence is dismal. Hence, prevention is essential to patient's outcomes. In patients with serosal invasion, about half experience peritoneal recurrence within first 2 years after surgery, even after curative surgery. Peritoneal metastasis is caused by the implantation of free cancer cells in the peritoneal cavity exfoliated from the primary tumor before or during curative surgery. It is well known that cancer cells spillage could occur during surgery due to manipulation or even after lymph node dissection. If we can remove these free exfoliated cancer cells on the peritoneal lining, we may reduce the risk of tumor recurrence.

Recently, a study has demonstrated a dramatic reduction of peritoneal recurrence with extensive peritoneal lavage in patients who underwent curative resection of gastric cancer. Extensive peritoneal lavage was performed after the curative operation. The peritoneal cavity was washed with normal saline which is then followed by the complete aspiration of the fluid. This procedure was done 10 times using 1 liter of normal saline. The method was based on the 'limiting dilution theory' in which the method can dilute the number of free cancer cells to minimal hence reduce the risk of tumor implantation. In this study, among patients with microscopic peritoneal metastasis, peritoneal recurrence developed in 40% of patients with extensive peritoneal lavage and surgery, compared to 89.7% in patients with surgery alone. Extensive peritoneal lavage carries minimal risk to patients. It is simple and inexpensive, and it is not time consuming. Hence, it may be an effective strategy for treatment of gastric cancer.

1.1. General Introduction

Gastric cancer is the second most common cause of cancer death worldwide. Surgery is the mainstay treatment for cure. Peritoneum is a common site of recurrence and the prognosis with peritoneal recurrence is dismal. Hence, any measure that can prevent peritoneal relapse will significantly improve treatment outcomes. There is recent evidence suggesting that extensive peritoneal lavage with large volume of normal saline after surgery before abdominal closure can reduce risk of peritoneal recurrence and enhance overall survival.

1.2. Rationale and justification for the Study

Significance: Because of the simplicity of this technique, the outcome of this study can change clinical practice in surgery for gastric cancer in the future

Hypothesis: Extensive peritoneal lavage improves the overall survival of patients with gastric cancer who undergo gastrectomy by reducing the risk of peritoneal recurrence.

a. Rationale for the Study Purpose

Peritoneum is a common site of recurrence and the prognosis with peritoneal recurrence is dismal. We performed a study of the outcomes of our patients who received radical gastrectomy for cancer in our prospective gastric cancer database. Out of 273 patients, recurrence was developed in 83 patients (30%) in which 20% were at the peritoneum. Among patients with serosal invasion, 30% of patients developed peritoneal recurrence during follow-up. Hence, peritoneal recurrence is a major clinical problem.

b. Rationale for Study Population

The study population are patients with T3 or T4 gastric cancer based on clinical staging. These groups of patients have highest risk of peritoneal recurrence

c. Rationale for Study Design

This is a randomized controlled study to evaluate the benefits of extensive peritoneal lavage as a prophylactic strategy for preventing peritoneal recurrence in patients with gastric cancer.

2. HYPOTHESIS AND OBJECTIVES

To compare the outcomes between extensive peritoneal lavage and standard treatment for patients with curative gastrectomy for gastric cancer.

2.1. Hypothesis

Extensive peritoneal lavage significantly improve the overall survival of patients by reducing the risk of peritoneal recurrence.

2.2. Primary Objectives

Overall survival

2.3. Secondary Objectives

Disease free survival
Peritoneal recurrence rate

2.4. Potential Risks and benefits:

a. End Points - Efficacy

The primary endpoint of the study is overall survival. Secondary endpoints are disease-free survival and the frequency of peritoneal recurrence.

b. End Points - Safety

Safety Data will be monitored. Complications of peritoneal lavage are rare and includes
- Injury to the viscera during lavage
- Intra abdominal bleeding.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

The total target number of enrollment is 800 research subjects by 23 centres in the region (refer to table 1 below for recruitment projection) There are no restrictions based on gender and race. There may be a doctor-patient relationship but the rejection to participate in the study of not allowing the research team to perform the peritoneal lavage will not compromise with the treatment rendered to the patient. The patient will still receive the standard of care should they not allow the excess peritoneal lavage for the research. The study will involve inpatients and outpatients subjects.

Table.1 All participating sites for EXPEL trial

Country	Site	Recruitment Target
China	Nanfang Hospital, Southern Medical University	78
	Peking University Cancer Hospital	150
Hong Kong	PWH, Chinese University of Hong Kong	5
	QMH, University of Hong Kong	35
Japan	Aichi Cancer Centre Hospital, Japan	12
	Fukushima Medical University, Japan	8
	Gifu University Hospital, Japan	12
	Kanagawa Cancer Centre, Japan	12
	National Cancer Centre East Hospital, Japan	12
	Niigata Cancer Center Hospital, Japan	12
	Shizuoka Cancer Centre, Japan	65
Korea	Ajou University, Korea	74
	Gyeongsang National University Jinju Hospital, Korea	10
	National Cancer Centre, Korea	10
	Seoul National University Bundang Hospital, Korea	60
	Seoul National University Hospital, Korea	130
	Seoul St Mary's Hospital-The Catholic University of Korea	23
	The Catholic University of Korea Uijeongbu St. Mary Hospital, Korea	5
	Yonsei University College of Medicine, Korea	23
Malaysia	National University of Malaysia	14
	University Malaya Medical Centre (UMMC) Kuala Lumpur, Malaysia	10
Singapore	Tan Tock Seng Hospital, Singapore	8
	National University Hospital, Singapore	32
Sub-total	**All Centres**	**800**

3.2. Criteria for Recruitment

Potential subjects will be identified by study team. Clinicians from the study team will make the first contact with subjects. The clinician will assess patient suitability for study and inform patient about this clinical trial. The research nurse will recruit the potential subjects by a face-to-face contact when they come for their prospective regular clinic visits.

3.3. Inclusion Criteria

1. Patients who have T3 (subserosal) or T4 (serosal) disease based on CT TAP scan and intra-operative inspection with any N staging and M0 gastric cancer.
2. Patients planned for open or laparoscopic gastrectomy.
3. Patients undergoing gastrectomy with curative intent.
4. Lower age limit of research subjects 21 years old and upper age limit of 80 years old.
5. Ability to provide informed consent
6. Ability to come back for study visits throughout the 5 years duration after surgery
7. Patients are local residents

3.4. Exclusion Criteria

1. Patients who undergo a palliative gastrectomy.
2. Patients who undergo a gastrectomy as emergency.
3. Vulnerable persons under age of 21.
4. Patients receiving neoadjuvant therapy.
5. Patients presented with life-threatening bleeding from tumour
6. ASA score of 4 & 5
7. Patients with another primary cancer within last 5 years
8. Patients with gross peritoneal and liver metastasis at surgery.

3.5. Withdrawal Criteria

Study closure due to DSMB review.

3.6. Subject Replacement

Subjects who drop out will not be replaced.

4. TRIAL SCHEDULE

The length of time of the subject's direct involvement in the study coincides with clinical visits. The subject will be followed up post operatively during routine outpatient clinical visits for 5 years to assess survival and spread of cancer or recurrence after surgery.

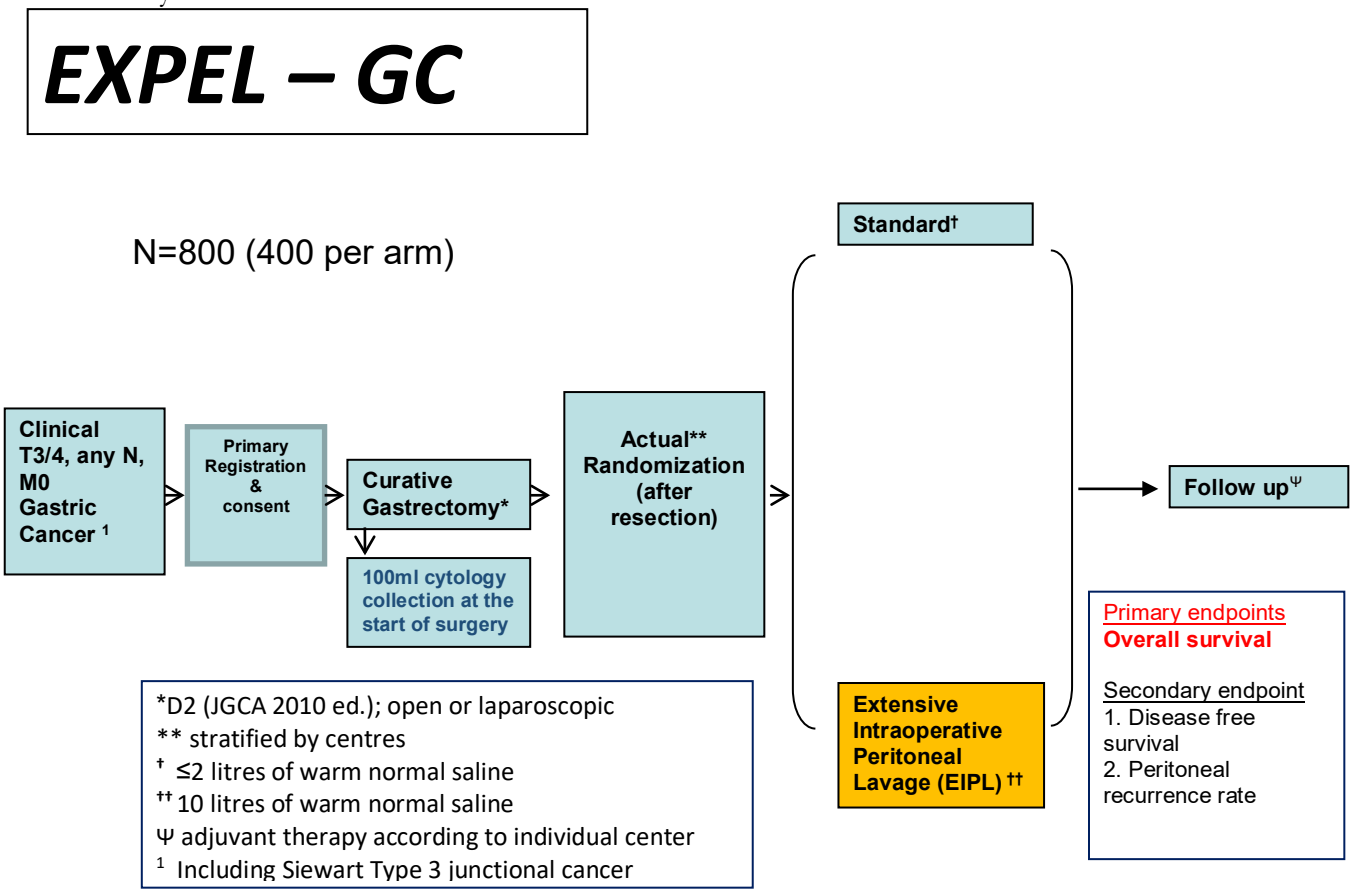
1. There will be 4 visits each in the first year & second year (Every 3 monthly)
2. Follow by half-yearly by the 3rd year
3. Yearly at the 4th and 5th year

5. STUDY DESIGN

It is a multi-center randomized controlled study. Patients with locally advanced gastric cancer (clinically T3 or T4, M0 disease) who are undergoing radical gastrectomy with curative intent will be recruited. After gastrectomy and before abdominal wall closure is performed, patients who had consented will be randomized into 2 arms: a study arm in which the peritoneal cavity will be washed with 10 liters of normal saline (1 liter each cycle for 10 cycles); and a control arm in which ≤ 2 liters of lavage will be performed. The surgery time for patients in the study arm will be approximately 20 minutes longer than patients in the control arm. Patients will be followed up as per routine practice. The primary endpoint is overall survival. Secondary endpoints are disease-free survival and frequency of peritoneal recurrence.

5.1. Summary of Study Design

Briefly describe the study design and indicate, in general terms, how the design will fulfil the intent of the study.



6. METHODS AND ASSESSMENTS

It is a multi-centre randomized controlled study. Patients with locally advanced gastric cancer (clinically stage T3 or T4 and M0 based on AJCC 7th edition) who underwent radical gastrectomy with curative intent will be recruited. Before abdominal wall closure after the curative gastrectomy is performed, patients will be randomized into 2 arms: a study arm in which the peritoneal cavity will be washed with 10 litres of normal saline; and a control arm in which standard surgery with ≤ 2 litres of lavage will be performed. Patients will be followed up at as per routine practice. The primary endpoint is overall survival. Secondary endpoints are disease-free survival and frequency of peritoneal recurrence.

Randomisation and Blinding

Study participants will be randomized to study arm and control arm using computer generated code. The patients will be stratified according to individual study site. Potential subjects are identified based on prospective imaging. Primary registration and study consent will be obtained from the potential subjects. Patients with clinical T3 or T4 gastric cancer on inspection at surgery will be formally recruited into the study. The randomisation code will be disclosed to the surgeon only at the end of gastrectomy. Extensive or standard lavage will then be performed according to the randomisation code. The abdomen will then be closed as per standard.

6.1. Contraception and Pregnancy Testing

Not Applicable

Schedule of Events

	Visit window*	Informed Consent	Medical History	Physical Examination	CT TAP Scan	Inclusion/ Exclusion	Randomisation	Peritoneal Lavage	Adjuvant Therapy	AE/SAE reporting**	Documentation
Screening Baseline	+/- 14 days	**X**	**X**	**X**	**X**	**X**				**X**	Fill registration form **(section A)** & on-study form **(section B)**
Surgery	+/- 7 days			**X**		**X**	**X**	**X**		**X**	Complete registration form **(section A)** & OT form **(section C)**,
Post-op visit week 2	+/- 7 days			**X**						**X**	Surgery treatment form **(section D)**
Study visit 1	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 2	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 3	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 4/ **1st year follow up**	+/- 60 days			**X**	**X**				**X**	**X**	Complete follow-up form **(section E)**
Study visit 5	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 6	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 7	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 8/ **2nd year follow up**	+/- 60 days			**X**	**X**				**X**	**X**	Complete follow-up form **(section E))**
Study visit 9	+/- 30 days			**X**					**X**	**X**	Complete follow-up form **(section E)**
Study visit 10/ **3rd year follow up**	+/- 60 days			**X**	**X**				**X**	**X**	Complete follow-up form **(section E)**
Study Visit 11 / **4th year follow up**	+/- 180 days			**X**	**X**				**X**	**X**	Complete follow-up form **(section E)**
Study Visit 12 / **5th year follow up**	+/- 180 days			**X**	**X**				**X**	**X**	Complete follow-up form **(section E)**

*Filing of protocol deviation form **(section G)** is mandatory if any of the above visit fails to occur within the visit window; however, should the visit day fall short within acceptable range of 1-2 weeks outside the visit window due to scheduling difficulties, no protocol deviation filing is required.

** Reporting of AE/SAE events should be done through the AE/SAE form **(section H)**

7. SURGICAL TREATMENT

Potential candidates will be given the same treatment option as other gastric cancer patients. At the start of surgery, 100ml of normal saline will be infused into patient's peritoneal cavity. The saline containing cells will then be collected by suction for cytological examination A standard D2 lymph node dissection based on Japanese gastric cancer classification will be performed on candidates. Techniques for lymph node dissection may involve diathermy, energy sealing, mechanical clips or suture ligation. After reconstruction, prior to wound closure, suitable patients will then be randomized to undergo either a standard peritoneal lavage (<2l) or extensive peritoneal lavage (10l). Following peritoneal washing the rest of the operation would proceed as per routine.

Patients with intraoperative staging of T3/T4, any N, M0 stage will be included in to the study even if histopathology turned out to be T1/T2 or M1. They will be put under intention to treat group. It will be considered as screen failure if patient is found to be non-T3/T4 stage or have metastasis during operation.

Patients undergoing completion gastrectomy will be included in to the study if the partial gastrectomy is for benign ulcer or was done more than 5 years ago.

8. SAFETY MEASUREMENTS

8.1. Definitions

Serious Adverse Event

What is a Serious Adverse Event?

An adverse event is considered **serious** if it results in any of the following outcomes:

- Death due to any cause
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Hospitalization (inpatient admission or overnight stay) or prolongation of hospitalization.
- An immediately life-threatening adverse event (the occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization readmission within 30 days post procedure may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition .

Additional Guidance For Hospitalizations

Hospitalization is not a SAE; it is an action due to an adverse event (AE), serious adverse event (SAE) or unanticipated problem or experience. Hospitalization for an elective procedure or surgery for a pre-existing condition that has not worsened is not a serious adverse event; however, is must be reported as an adverse event (AE).

It requires reporting of all hospitalizations including elective admissions and all deaths even if unrelated to investigational treatment.

Unanticipated Adverse Effects
An unanticipated adverse effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)

SAE Reporting in Long-Term Follow–Up Studies
Reporting of hospitalizations is not necessary for subjects enrolled in long-term follow-up studies in which the subjects are receiving no investigational treatment. Other hospitalizations that are part of the disease process do not have to be reported unless they have increased in severity or frequency or if requires notification.

Deaths
All deaths within 30 days post-surgery must be reported, regardless of relationship to study intervention or disease progression to the respective ethics committee. The research team should report any death, regardless of the time point, as soon as they become aware of the event to the main study site

Serious Adverse Events Review
The DSMB reviews all serious adverse events.

Requirement of Reporting Form
All local subjects (e.g., those followed by our investigators) unexpected adverse events, unanticipated problems, or serious adverse events must be reported to EXPEL Study Team.

The File number, the protocol title, the Principal Investigator's name and the name of the person submitting the report must be included. The report must also provide the subject identification number, a statement that the PI has reviewed the information and the PI's signature. A copy of the adverse event or serious adverse event form(s) may be provided as supplemental information.

8.2. Safety Monitoring Plan

The purpose of the Data and Safety Monitoring Plan is to ensure the safety and well-being of study subjects, and the integrity of the data collected for the study. A Data Safety Monitoring Board (DSMB) would be appropriate way to monitor data as this is a large study population with multiple study sites. This includes a combination of the Principal Investigator and experts within the institution, Dr Kenichi Nakamura (National Cancer Centre, Tokyo, JCOG Operations) A/Prof Mikael Hartman (NUS SPH), Dr Chan Yiong Huak (NUS Medicine Dean's Office)

The review of the adverse events/ serious adverse events data will be monitored to study the safety and compliance of the trial. UPIRTSO Reporting will be done according to the DSRB guidelines.

The stopping criteria for the research study will based on futility that the study question will not be answered when the study is completed.

The route of dissemination of any data and safety information can be communicated to the study sites via regular emails and at ad-hoc meetings, the person/team responsible for doing so will be initiated from the Principal PI and the sites PI.

8.3. Complaint Handling –

Complaints will be handled at the individual hospital and any conflict regarding the design of trial will be discussed with the overall PI.

9. DATA ANALYSIS

9.1. Data Quality Assurance

The PI, study coordinator and the biostatistician in the study team will ensure the quality of the data. Annual interim analysis will be conducted out every year from external party. Onsite monitoring services engaged from commercial company will be done for sites with high volume subjects. Web randomization system will undergo audit as well.

9.2. Data Entry and Storage

The study team would store all research data within the institution. The research data (hardcopy) will be stored and the location storage is secured (data stored in research team office location with lock and key access. Storage of records are locked in file cabinets) There is limited access to the study data. Only the PI and study coordinator will have access to the research data.
According to SGGCP ant the NHG research policy recommends, the essential documents should be retained a minimum storage until 6 years after the completion of the clinical trial.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1. Determination of Sample Size

We have estimated the sample size by regarding overall survival as the primary endpoint of interest. We assume survival of 60% in the control arm, and 70% in the intervention arm (ie. HR=0.7) based on a power of 80%, a two sided level of significance of 5% and equal allocation between the two treatment arms. This suggests a minimum sample size of 800 in total, or 400 per arm

10.2. Statistical and Analytical Plans

The data will be analysed as intention-to –treatment basis. Survivals are calculated using Kaplan-Meier method. Peritoneal recurrence is based on clinical and radiological findings. A p-value <0.05 is considered as statistically significant.

An interim analysis was performed on 350 subjects with 6 month follow up data. Data Safety Monitoring Committee recommended that at least another 200 subjects to be recruited. Hence the original target recruitment of 600 subjects is being changed to 800 subjects in this protocol.

11. ETHICAL CONSIDERATIONS

11.1. Informed Consent

Informed consent will be obtained from potential Research Participants before enrolment into the study. Only study team members or research assistants who have been delegated by the PI can obtain consent from the subjects. This should be documented in the Study Responsibility Log. It is the responsibility of the PI to ensure that the study staffs who are delegated to obtain consent have received proper training (e.g. CITI, SGGCP, PCR course).

Subjects should be approached in a quiet and conducive environment. The consent process will be carried out by the research nurse in a quiet room in the outpatient clinic in the absence of the attending doctor and his medical team. Alternatively, if the patient is warded, the consent will be carried out by the bedside with the curtains drawn to maintain the privacy of the patient and also in the absence of the doctor and his medical team. The research nurse will conduct the consent process with the potential research participant to reduce any possibility of coercion or undue influence by the attending doctor. The patients will be given sufficient time to take the consent document for discussion with their family members before coming to any decision after the research nurse has explained the study to the patient.

All Research Participants will be given a copy of the Informed Consent Form. The study can enrol non English speaking subjects. The possible languages that will be understood by the prospective participant or the legally acceptable representative includes Chinese, Malay and Tamil. The consent will be communicated in the language that is understood by them. The non-English consent will be documented using the English Informed Consent Form with DSRB translated short consent form.

11.2. IRB review

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by the IRB / NHG DSRB.

11.3. Confidentiality of Data and Patient Records

Research data will be coded to protect the Study Subject's confidentiality, and the links between the Subject's identifiers and the codes will be stored separately from the research data. The key to the code is located in another physical location.

12. PUBLICATIONS

A writing committee (P.I. of each centre & chief statistician) will write the paper on behalf of the EXPEL trial group; sequence of authors will be determined based on the number of patients contributed to the total target recruitment; study P.I. is the corresponding author

Each centre is required to contribute **at least 20** cases to be included into writing committee

The 1st author will be allocated to the site PI of the centre with the highest recruitment number and he/she is responsible for drafting the manuscript within 3 months from completion of study.
The 2nd author to the second last author: in decreasing number of recruitment starting from the site with the 2nd highest number of recruitment. Last and corresponding author is the overall PI of the study.

13. RETENTION OF TRIAL DOCUMENTS

The study team would store all research data within the institution. The research data (hardcopy) will be stored and the location storage is secured (data stored in research team office location with lock and key access. Storage of records are locked in file cabinets) There is limited access to the study data. Only the PI and study coordinator will have access to the research data.
According to SGGCP ant the NHG research policy recommends, the essential documents should be retained a minimum storage until 6 years after the completion of the clinical trial.