PROTOCOL

TITLE: A Phase II study of cytoreduction, gastrectomy, and hyperthermic intraperitoneal chemoperfusion (HIPEC) in patients with gastric adenocarcinoma and carcinomatosis or positive cytology

PROTOCOL TYPE: Standard Clinical

PROTOCOL PHASE: II

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ABBREVIATIONS

BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CT	Computed Tomography
CI	Confidence Interval
ECOG	Eastern Cooperative Oncology Group
EUS	Endoscopic Ultrasound
Gy	Gray
H & P	History and Physical
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PET	Positron Emission Tomography
RBC	Red Blood Cells
SOP	Standard Operating Procedure
TNM	Tumor Regional Nodes and Metastases
WBC	White Blood Count

1.0 OBJECTIVES

Primary: To assess overall survival from the date of diagnosis in subjects with stage IV gastric or gastroesophageal cancer and positive cytology or carcinomatosis after cytoreduction, gastrectomy, and hyperthermic intraperitoneal chemotherapy administration.

Secondary:

1) To assess the safety of cytoreduction, gastrectomy, and hyperthermic intraperitoneal chemotherapy administration for subjects with gastric or gastroesophageal cancer and positive cytology or carcinomatosis.

2.0 BACKGROUND

Peritoneal carcinomatosis and microscopic peritoneal disease represents an aggressive mode of spread for gastric cancer which ultimately results in death. In most cases progression of the intraperitoneal disease precedes distant metastasis and results in complications that hasten the death of the patient. Obtaining cytotoxic concentrations of chemotherapy within the peritoneal and abdominal cavity may be difficult. A regional technique to treating peritoneal spread of tumor is appealing as a theoretical approach to deliver high concentrations of chemotherapy directly to the tumor while limiting systemic toxicity. Heated regional peritoneal chemotherapy has been demonstrated to be effective in mesothelioma and appendiceal tumors.[1, 2] In addition, intraperitoneal chemotherapy has been found to improve survival in select populations of patients with gastric cancer.[3-5]

In one of our first reports highlighting the incidence and outcome of patients with peritoneal disease, we identified 381 patients with gastric or gastroesophageal adenocarcinoma at M. D. Anderson Cancer Center without metastatic disease on radiologic imaging whom underwent diagnostic laparoscopy for further staging prior to consideration for neoadjuvant treatment.[6] Eighty-three patients had carcinomatosis on laparoscopy while 39 had positive cytology in the absence of carcinomatosis. Carcinomatosis and positive cytology are classified as metastatic or Stage IV disease according to the American Joint Commission on Cancer Staging Manual (7th edition).[7] However, this population of 122 patients had stage IV disease that could be described as a local effect from serosal invasion and peritoneal spread rather than hematologic or lymphatic spread, and therefore are good candidates for local chemotherapy administration. The population of patients with isolated peritoneal disease are also good candidates for a clinical trial as traditional treatment regimens yield dismal survival rates. Median OS (overall survival) for patients with positive peritoneal cytology and no visible metastatic disease at laparoscopy was 12.8 months while median OS was 10.2 months for patients with carcinomatosis.[6] For the patients with positive peritoneal cytology and no visible metastatic disease, use of neoadjuvant therapy (most often induction 5-FU and oxaliplatin followed by chemoradiation therapy with 45 Gy) resulted in a 3-year OS rate of 12% versus 0% for patients treated as having incurable stage IV disease. For the patients with carcinomatosis at laparoscopy, outcomes were worse with 0% 3-year OS. For the 122 patients with

carcinomatosis at laparoscopy or positive cytology, only 8 (6.7%) underwent resection. The proposed trial will focus on the combined population of patients with carcinomatosis or positive cytology at laparoscopy.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a surgical technique for combining hyperthermia and chemotherapeutic agents to the peritoneal surface via a heated perfusion circuit.[8] Support for the concept of combining heat with chemotherapy is provided through in vivo and in vitro laboratory studies that have established the selective lethal effects of heat on human and murine neoplastic cells.[9] Hyperthermia may work through a direct antitumor effect, augmenting the cytotoxic effects of chemotherapy, or increasing the depth of penetration of chemotherapy into tissues and tumor nodules.

Over the last 2 decades, intraperitoneal chemotherapy has been found to have activity for select subgroups of patients with carcinomatosis from colon, ovarian, appendiceal, and recently, gastric origins. There have been 13 randomized trials on adjuvant intraperitoneal chemotherapy for gastric cancer with a recent meta-analysis demonstrating improved overall survival. Collectively, these studies displayed a 40% improvement in survival (hazard ratio = 0.60, 95% CI 0.43-0.83) for patients treated with hyperthermic intraperitoneal chemotherapy.[4] A more recent meta-analysis on adjuvant hyperthermic intraperitoneal chemotherapy for patients undergoing gastrectomy with serosal invasion demonstrated an improvement in survival (risk ratio = 0.73, 95% CI 0.64-0.83) and peritoneal recurrence (risk ratio = 0.45, 95% CI 0.28-0.72).[5] While these findings are encouraging, there are a number of problems with these studies. First, there were no studies from Western centers which make these studies difficult to interpret given the historically improved outcomes of gastric cancer associated with reports from Eastern centers. Second, the intraperitoneal chemotherapy regimens and technique varied among institutions. Third, combining gastrectomy, cytoreduction, and HIPEC likely results in increased morbidity and mortality compared to gastrectomy alone as shown in a recent systematic review reporting 30-day morbidity and mortality rates of 22% and 5%.[10] In addition, few reports include patients treated with a neoadjuvant or laparoscopic approach to HIPEC.

There are many theoretical benefits to adding a neoadjuvant laparoscopic approach to HIPEC in gastric cancer. Patients would not be subjected to the risks of gastrectomy with HIPEC unless they demonstrated a response to laparoscopic HIPEC. Performing a laparoscopic HIPEC would also allow for clear visualization of the response to treatment as a diagnostic laparoscopy with peritoneal washings should be performed at the intitiation of the procedure. There is also data to suggest that performing laparoscopic HIPEC without cytoreduction and gastrectomy is a low risk procedure. A recent systematic review of laparoscopic hyperthermic intraperitoneal chemotherapy suggests this is a safe procedure with no mortalities and < 10% morbidity in 183 patients. Of note, however, is that only 5 patients in this series underwent this procedure as part of a neoadjuvant approach prior to cancer treatment.[11]

Our group is now finishing our initial Phase II trial of laparoscopic HIPEC for patients with gastric cancer and radiologically-occult carcinomatosis or positive cytology (2013-0989). This novel trial has demonstrated the feasibility and safety of laparoscopic preoperative HIPEC, and our early

results regarding survival are encouraging. Nineteen patients were enrolled and treated with 36 laparoscopic HIPEC procedures. Median age was 51 (range 29-69). Six patients had positive cytology only and 13 had carcinomatosis. All patients were treated with systemic chemotherapy prior to enrollment with a median of 8 cycles (range 3-12). Twelve patients were also treated with chemoradiation therapy. Post-HIPEC major morbidity rate was 3% with no mortalities. Median length of stay was 3 days (range 3-6). Five patients have gone on to gastrectomy. Median follow-up was 15.1 months. The OS rate at 2 years was 90.9% (95% CI: 75.4% -100%).

However, only 1 of the 5 patients that has undergone gastrectomy had carcinomatosis. The LS HIPEC procedure is associated with survival beyond that expected from previous reports for patients with carcinomatosis, but has not been effective at eradicating carcinomatosis to allow for gastrectomy. Due to the limitations in penetration of intraperitoneal chemotherapy, cytoreduction will need to be added to the HIPEC procedure in patients with carcinomatosis to pursue gastrectomy. We now seek to incorporate the many lessons we have learned from our previous trial, create a trial focused on cytoreduction with HIPEC, and expand the inclusion criteria to include patients with radiologically-evident carcinomatosis. Therefore, the purpose of this clinical trial is to determine the efficacy and safety of cytoreduction, gastrectomy, and hyperthermic intraperitoneal chemotherapy with Mitomycin C and Cisplatin in patients with stage IV gastric cancer limited to the peritoneum after treatment with systemic chemotherapy.

3.0 Eligibility: (List All Criteria)

Inclusion:

1) Age 18 years and above. There will be no upper age restriction.

2) ECOG performance status ≤ 2. (See Appendix A –ECOG Performance Status Scale).

3) Cytologic or histologic proof of adenocarcinoma of the stomach or gastroesophageal junction.

4) Adequate renal, and bone marrow function:

   a. Leukocytes >= 3,000/uL

   b. Absolute neutrophil count >= 1,500/uL

   c. Platelets >= 60,000/Ul

   d. Serum creatinine <= 1.5 mg/dL

5) Distant metastatic disease of peritoneum may be visualized on imaging:

   a. Positive peritoneal cytology

   b. Carcinomatosis on diagnostic laparoscopy or laparotomy.

6) Completion of preoperative systemic chemotherapy and preoperative laparoscopic HIPEC.

Exclusion:

1) Distant metastatic disease not limited to peritoneum:

a. Solid organ metastases (liver, central nervous system, lung).

2) Infections such as pneumonia or wound infections that would preclude protocol therapy.

3) Women with a positive urine or serum pregnancy test are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months) must agree to refrain from breast feeding and practice adequate contraception as specified in the informed consent. Adequate contraception consists of oral contraceptive, implantable contraceptives, injectable contraceptives, a double barrier method, or abstinence.

4) Subjects with unstable angina or New York Heart Association Grade II or greater congestive heart failure.

5) Subjects deemed unable to comply with study and/or follow-up procedures.

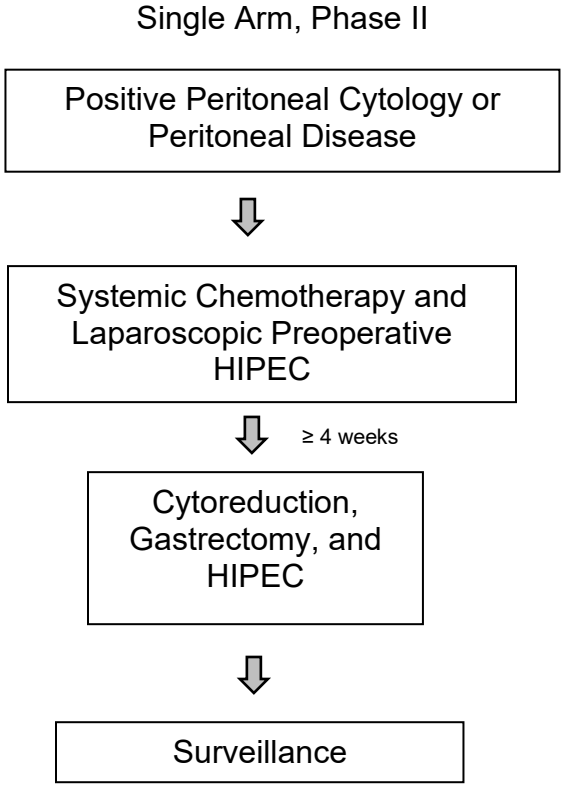
6) Subjects with a known hypersensitivity to protocol systemic chemotherapy that was life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity.

4.0 DESIGN AND METHODS

1) Subjects with gastric and gastroesophageal adenocarcinoma and positive peritoneal cytology or carcinomatosis that have completed treatment with systemic chemotherapy and laparoscopic HIPEC will be offered participation in the study. Type and duration of systemic chemotherapy will be left to the discretion of the treating medical oncologist. Patients may also receive treatment with chemoradiation therapy. Duration and frequency of preoperative laparoscopic HIPEC procedures will be left to the discretion of the treating surgical oncologist. Subjects may be inpatients or outpatients. Subjects should have a contrast CT scan, MRI, or PET/CT scan within 6 weeks (42 days) of enrollment. Patients will have completed standard systemic therapy and laparoscopic HIEPC administration prior to enrollment. Enrollment will occur within 30 days of treatment initiation. This will occur after chemotherapy, and often, chemoradiation therapy. Lack of imaging evidence of solid organ metastatic disease will be defined based on radiologic (CT scan, MRI, or PET/CT) imaging. Evidence of carcinomatosis or positive cytology will be based on clinical criteria (see eligibility criteria). HIPEC will be administered as defined by the protocol. Gastrectomy and cytoreduction will be performed according to standard of care. Patients will undergo treatment as displayed in Figure 1. The HIPEC procedure will consist of Mitomycin C 30 mg

and Cisplatin 200 mg in 3-7 liters of infusate circulated using an extracorporeal circulation device at a flow rate of 700-1500 mL/minute for 60 minutes, performed no sooner than 4 weeks after completion of any previous therapy (systemic chemotherapy or laparoscopic HIPEC procedures). After completion of study–related treatment, subjects will be followed until recurrence and/or death for up to five years.

Figure 1.



Study Calendar

	STUDY CALENDAR				
	Pre-Treatment Evaluation ≤ 30 days	Treatment Initiation	Post-Treatment (Post-operative) Inpatient Evaluation	Post Gastrectomy Evaluation ≤4 Weeks after Discharge	Survival Follow-up Q 6 months (+/- 3 months) [G]
H&P & Concurrent Meds	X			X	X
Consent	X				
Vital Signs[a]	X	X		X	
ECOG Performance Status	X				
Serum Chemistries[b]	X				
CBC[c]	X				
Pregnancy Test (urine or serum)	X				
Imaging[d]	X				X
Postoperative Morbidity [e]		X	X	X	
Cytoreduction, Gastrectomy, & HIPEC[f]		X			
Tissue for correlative studies		X			

*See the Study Calendar Footnotes

Study Calendar Footnotes:

a. Vital signs: blood pressure and pulse rate.
b. Serum Chemistries: BUN, chloride, CO2, creatinine, glucose, potassium, sodium,].
c. Complete Blood Count (CBC): Hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts such as: neutrophils, lymphocytes, monocytes, eosinophils, basophils).
d. Imaging can include CT Chest/Abdomen/Pelvis, Abdominal/Pelvis MRI, or PET/CT scan and may be within 6 weeks of enrollment or pre-gastrectomy evaluation.
e. All postoperative complications occurring 30 days post HIPEC procedure(s) will be recorded.
f. Performed no sooner than 4 weeks after completion of preoperative therapy.
g. Follow up assessements may be done by telephone contact and outside imaging may be utilized.

Informed Consent will be obtained.

Type of Study: Prospective phase II, single institution clinical trial.

Procedures and Treatment Plan

1. HIPEC: Mitomycin C 30 mg and Cisplatin 200 mg in 3-7 liters of infusate will be administered using a rolling pump with hyperthermia for 60 minutes.

Surgery:

1. Cytoreduction, Gastrectomy, & HIPEC: Cytoreduction will be obtained of any suspicious lesions and gastrectomy will be performed according to standard surgical principles. Subtotal or total gastrectomy will be performed according to standard surgical technique. Extent of lymph node dissection will be left to the discretion of the operating surgeon. Once the cytoreduction and gastrectomy portion of the procedure are concluded, inflow and outflow catheters will placed. Crystalloid perfusate will be circulated using an extracorporeal circulation device at a flow rate of 700-1,500 mL/minute. Once the heated perfusion is established per standard of care, Mitomycin 30 mg and Cisplatin 200 mg will be instilled. Although there is variability in the perfusate temperature during the operation, target inflow temperature will be 41-42ºC with target outflow of 39-40ºC. Manipulation of the inflow temperature will be allowed to maintain an esophageal probe temperature level of < 39ºC. The Perfusion will be performed for 60 minutes and all perfusate will be removed. Perfusate volume will be maintained to moderately distend the abdomen. Physical manipulation of the abdomen will be maintained for 60 minutes to assure even distribution of the perfusate. The cannulas will be removed and remaining perfusate aspirated. Abdominal washout will then be performed with crystalloid solution. Post-operative hydration will include maintenance intravenous fluids and urine output will be maintained and monitored as per standard of care.

   Sodium thiosulfate: A loading dose and 12 hour continuous infusion of sodium thiosulfate will be administered to limit the systemic toxicity of cisplatin. A loading dose of 7.5 gm/M^2 of sodium thiosulfate will be diluted in 20 ml/kg of 0.9% normal saline up to 500 mL. The total loading dose is not to exceed 12.5 grams. This loading dose will be infused over 20 minutes prior to or during addition of cisplatin to the peritoneal perfusion circuit. Then a maintenance infusion of sodium thiosulfate 25.56 gm/M^2 will be delivered by continuous infusion pump over approximately 12 hours as per standard of care, until the infusion is complete.

Pathology

Esophageal, gastric, or duodenal margins will be evaluated per standard of care. Recorded on permanent section will be tumor stage, margin status, and lymph node status.

Pretreatment Evaluation

Within 30 days Prior to Study Enrollment the following procedures will be performed:

a) (Complete blood count: hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils). ;

b) Serum chemistries (BUN, chloride, CO2, creatinine, glucose, potassium, sodium).

c) Pregnancy test - conducted prior to study enrollment to meet eligibility criteria.

d) A history and physical exam.

e) ECOG Performance status.

f) Concurrent medications.

g) Vital signs will also be collected during the pre-treatment evaluation.

h) Within 6 weeks subjects must have undergone staging radiographic studies (CT chest, abdomen and pelvis, Abdominal/Pelvis MRI, or PET/CT scan). These studies are considered standard of care in the evaluation and treatment of patients with gastric cancer.

Post-treatment (Post-operative) Evaluation

After cytoreduction, gastrectomy, & HIPEC, patients will be monitored during their inpatient postoperative stay with standard of care postoperative laboratory analysis and daily vital signs.

Post-resection Outpatient Evaluation

Within 4 weeks of hospital discharge after gastrectomy, the subject will have:

1. History and physical and concurrent medications will be collected.
2. Vital signs (blood pressure and pulse rate) on days of clinic evaluation.
3. Standard of care postoperative laboratory analysis.

Survival

1. The primary endpoint in this study is overall survival, as measured from the time of diagnosis of stage IV disease. Patterns of tumor recurrence and survival will be assessed by reviewing routine surveillance imaging. Patient contact may be by telephone.
2. After completion of the treatment, all subjects will be followed with imaging approximately every 6 months for five years. This may include outside imaging.

Criteria for Removal from Study:

1. Inability of subject to comply with study requirements
2. Determination by the investigator that it is no longer safe for the subject to continue therapy

Follow-up

Patients will be followed for survival as shown in the study calendar.

Data Collection

Data collection will include:

- Patient age and gender
- Initial diagnosis date and stage IV diagnosis date
- Tumor grade, signet ring, lauren classification (if recorded), tumor location, and presence of linitis plastica.
- CT and EUS findings at diagnosis
- Type and duration of systemic chemotherapy
- Laparoscopic HIPEC findings
- Type and dose of chemoradiation therapy, if given
- Operative details of cytoreduction, gastrectomy, & HIPEC such as length of operation, estimated blood loss, gastrectomy type, extent of lymphadenectomy, need for resection of adjacent organs, and drain placement.
- Perioperative morbidity and mortality
- Primary tumor TNM stage and pathologic details.
- Dates and sites of disease recurrence and/or progression
- Date of last follow-up and vital status

Correlative Studies: Tissue Banking

All tissue samples will be collected according to MD Anderson Tissue Protocol LAB01-543 SOPs. An IRB approved protocol in standard format is on file with the IRB (PI: Jaffer A. Ajani, M.D.). Patients are consented prior to any endoscopic procedures performed at MD Anderson. Per the protocol and consent, if the patient requires surgery as part of his/her treatment, a portion of the remaining tissue will be stored. No additional surgical maneuvers or procedures are necessary for the collection of study tissues, since all tissue samples will be collected from tissue that has already been removed as part of standard care. When feasible, tissue adequate for preparation of 50 slides (5 mm thick) will be stored from each collection. In brief, the objectives of this protocol are to:

1. To collect and store, both prospectively and retrospectively, tissue, blood, body fluids and information for the sole purpose of banking pre-malignant and malignant lesions of the gastrointestinal tract. An IRB approved Informed Consent in standard format is on file with the IRB.

2. To collect, store, and analyze, both prospectively and retrospectively, data on disease characterization, treatment and outcomes for patients with suspected premalignant and malignant lesions of the gastrointestinal tract at the University of Texas M. D. Anderson Cancer Center (UTMDACC).

3. To collect, store, and analyze data on patients with gastrointestinal malignancies of the University of Texas M. D. Anderson Cancer Center (UTMDACC) from patients' primary physicians or other treatment centers prior to, during and after the patients' visits at UTMDACC.

4. To collect, store or discard residual tissue, blood and other body fluids obtained during the performance of research activities for which consent and authorization have been obtained from the participant.

5.0 STATISTICS AND JUSTIFICATION OF SAMPLE SIZE

This is a single-center, single arm phase II trial of cytoreduction, gastrectomy, and HIPEC in patients with gastric cancer metastatic to the peritoneum. The primary endpoint in this study is overall survival, as measured from the time of diagnosis of stage IV disease. A maximum of 30 patients will be enrolled into this study at an expected accrual rate of 1 to 2 patients per month.

Sample size and power

The primary endpoint is overall survival. A retrospective study showed that median OS is 11 months for patients with positive peritoneal cytology or gross metastatic disease at laparoscopy.[6] For the futility monitoring of overall survival (OS), we have therefore assumed a median OS of 11 months for historical treatment and a median of 15 months (i.e., 4 months improvement) with the experimental therapy, based on reports from other centers that utilize cytoreduction and HIPEC in the treatment of metastatic gastric cancer.[12]

The study will be continuously monitored for the primary endpoint, OS, using the method of Thall, Wooten, and Tannir.[2] It is assumed that the OS for each patient is exponentially distributed with a median of λ_E among patients who receive the experimental treatment and a median of λ_H for the historical treatment. Further, λ_H was assumed to follow an inverse gamma distribution, i.e., $\lambda_H \sim IG(60, 649)$, which has a mean of 11 months and variance of 2.09. To reflect the little prior knowledge of λ_E we assumed an inverse gamma prior distribution with the same mean of 11 months and a much larger variance of 121, i.e., $\lambda_E \sim IG(3, 22)$. The trial will be stopped early if $Pr(\lambda_E > \lambda_H + \delta \mid data) < pL$, where δ = 4 months and pL=0.02 and this monitoring rule will be first applied when 3 patients have been enrolled. A maximum of 30 patients will be enrolled into this study at an expected accrual rate of 1 to 2 patients per month. Patients will be followed up for an additional 5 years after the enrollment has been completed. The trial will be conducted using the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct/) maintained by the Department of Biostatistics at MDACC.

The operating characteristics of the design, based on an overall assumed accrual rate of 1.5 patients per month with 5000 simulated trials per scenario, are given in the following table:

Scenario	True Median (months)	Pr(Stopped Early)	Mean No. patients	Average Trial Duration (months)
1	7	0.839	18.2	72.0
2	9	0.560	22.8	74.9
3	11	0.306	25.9	76.9
4	13	0.148	27.9	78.1
5	15	0.078	28.8	78.6

One-Arm Time-to-Event Simulator (version 3.0.1) was used to run the simulations and generate the OC table.

Justification of Sample Size:
If we assume an exponential distribution for the overall survival time and an uniform distribution for the censoring time, then with sample size of 30 patients, the estimated 95% confidence interval for median OS will range from 8.5 months to 25.2 months when the true median OS is 15 months. Alternatively, if the true median OS is 11 months, then the estimated 95% confidence interval will be 6.4 to 18.1 months. The sample size justification was based on 1000 simulations.

Statistical Analysis:
All patients who received treatment will be included in the analysis for efficacy and safety. Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. Overall survival time will be estimated using the Kaplan-Meier method. Patients who drop out of the study will be included in the time to event data as “censored data”. The two-sided log-rank test will be used to assess the differences of time to events between groups. As a secondary analysis, we will also analyze overall survival, using surgery date as the start time.

6.0 Monitoring for early death

Death within 30 days from surgery will be monitored. A recent series of patients undergoing this procedure reported a postoperative mortality rate of 5%.[12] Denote the probability of early death rate by $T_{deathD30}$. We assume T_{LE} ~ beta (0.05, 0.95). We will monitor for early mortality in cohort size of 10, starting from the 10^{th} patient, and we will stop the enrollment if $Pr(T_{deathD30} > 0.05 \mid data) > 0.9$. That is, we will stop the trial early if at any interim assessment in cohort sizes of 10 we determine that there is more than 90% chance that the rate of death within 30 days is more than 5%. The corresponding stopping boundaries are to stop the trial if (number of patients died within 30 days from surgery / number of patients) ≥2/10, 3/20. The trial will be stopped if 2 patients die within the first 10 patients. The operating characteristics are listed in table 2.

Table 2: Operating Characteristics (OCs) for early death monitoring

True Prob (death within 30	Pr(stop the trial early)	Average # Pts treated

days from surgery)		
0.01	0.005	29.9
0.05	0.120	27.9
0.10	0.391	23.5
0.15	0.649	18.9
0.20	0.826	15.5

Multic Lean Desktop version 2.1.0 was used to generate the stopping boundaries and OC table for the monitoring of early death.

7.0 AUDITS AND INSPECTIONS

Regulatory authorities or the Institutional Review Board (IRB) may perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

8.0 TRAINING OF STAFF

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). Dr Badgwell will ensure that appropriate training relevant to the study is given to all study staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

A Site Initiation Visit will be conducted at MD Anderson Cancer Center for study staff.

9.0 CHANGES TO THE PROTOCOL

Study procedures will not be changed without approval from the IRB. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be approved by the MD Anderson IRB, and if applicable, by the local regulatory authority, before implementation. Local and federal (Food and Drug Administration [FDA]) requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB and study sponsor is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to the sub-investigators and staff involved with the study.

10.0 ETHICS

Ethics Review:

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by the MD Anderson IRB. The principal investigator is responsible for

informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually.

Ethical Conduct of the Study:

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Written Informed Consent:

The principal investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Written Informed Consent Form in the subject's medical record as well as his/her study subject file. A copy of the signed Written Informed Consent Form must be given to the subject. The consent process will be documented in the subject's medical records.

Subject Data Protection:

The Written Informed Consent Form will explain that for data verification purposes, a regulatory authority, and the IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

11.0 EMERGENCY PROCEDURES

Procedures in Case of Medical Emergency:

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study.

Procedures in Case of Overdose:

There is currently no known antidote for the systemic chemotherapy in this study. The treatment of AEs associated with overdose should be supportive for the underlying adverse symptoms.

Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose. Overdose, with or without associated symptoms should be handled in the same way as a deviation and sent to IRB. Signs or symptoms of an overdose that meet the criteria of serious should be reported as a SAE in the appropriate timeframes and be documented as clinical sequelae to an overdose.

12.0 DATA SAFETY MONITORING PLAN

The principal investigator and all research staff associated with this trial have received training and certification in human subject protections research and are ultimately responsible for monitoring the safety of this trial.

The PI will continuously monitor this trial and more frequently safety related data. This trial will also be reviewed periodically by physicians and research staff at the Gastric Cancer Multidisciplinary Group meeting.

Monitoring will be provided by the MD Anderson Clinical Research Center for this clinical trial. The monitor will assure that the rights and well – being of human subjects are protected and the data are accurate, complete and verifiable from source documents and the trial is conducted in compliance with currently approved protocol/amendments, with good clinical practice (GCP) and the applicable regulatory requirements.

The monitor will be familiar with the protocol, the informed consent form, any other information provided to the subjects, the standard operating procedures (SOP), GCP and applicable regulatory requirements.

Monitors will have access to subject medical records and other study-related records. The principal investigator agrees to cooperate with the monitor (s) to ensure that any problems detected in the course of these monitoring visits are resolved. Personal contact between the monitor and the investigator will be maintained throughout the clinical trial to assure that the investigator is fulfilling his obligations and the facilities used in the clinical trial remain acceptable.

Investigational Products:

The systemic chemotherapy in this study is the current standard of care for the treatment of gastric cancer.

Monitoring Report:

After each monitoring visit a separate monitoring report will be generated and submitted to the principal investigator and project manager. This report will include significant findings related to deficiencies and deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements and actions taken to prevent recurrence of the detected deviations. The report will make recommendations for actions to be taken to secure compliance.

Continuing Review:

An annual report will be compiled and sent to the IRB to report on number of subjects enrolled in the study and safety events and accrual schedule.

13.0 DATA QUALITY ASSURANCE AND DOCUMENTATION

CRF’s should be filled by qualified personnel, reviewed, dated and signed by the investigator. The forms have to be completed in a neat and legible manner with black or blue ballpoint pen. No entries should be erased or over written or correction fluid or white out be used. Corrections can only be crossed out with a single line and should have the date and initials of the person making the change.

Source Documents are defined as original documents with original observations and information about the clinical investigation. All electronic source documents should be 21 CFR 11 compliant. Source documents will include progress notes, computer print outs, laboratory data and all recorded data from automated instruments. Monitor will review CRF's against source documentation for accuracy of the information. Subject Confidentiality will be maintained. CRFs will not include any personal identification information such as name etc. Subjects will be identified with Initials and subject study number only.

Non-safety related data analysis will be collected retrospectively by the investigator and study team. This information will be transcribed into an excel database maintained by the investigator on a password protected computer in the surgical oncology department.

14.0 RETENTION OF RECORDS

All documentation related to this trial will be retained for 2 years after the investigator is complete.

15.0 REFERENCES

1. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol* 2012; 30(20):2449-56.
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