Abbreviated Title: Metastatic Gastric Cancer

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Prospective Randomized Trial Comparing Gastrectomy, Metastasectomy plus Systemic Therapy versus Systemic Therapy Alone: GYMSSA Trial

Principal Investigator: Udo Rudloff, M.D., PhD[1]

Lead Associate Investigator: Prakash Pandalai, M.D.[1]

Associate Investigators: Udai S. Kammula, M.D.[1]
David Schrump, M.D.[1]
King Kwong, M.D.[1]
Austin Duffy, M.D.[2]
Daniel Zlott, PharmD[4]
Martha Quezado, M.D.[3]
Aradhana Venkatesan, M.D.[5]
Melissa Walker, R.N.[1]
Carole Webb, R.N.[1]
Mary Ann Toomey, R.N.[1]
Seth M. Steinberg, Ph.D.[6]

[1]Surgery Branch, CCR, NCI
[2]Medical Oncology Branch, CCR, NCI
[3]Laboratory of Pathology, CCR, NCI
[4]NIH Clinical Center Pharmacy
[5]Diagnostic Radiology Department, NIH Clinical Center
[6]Biostatistics and Data Management Section, CCR, NCI

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PRECIS

Background:

- The standard of care for metastatic gastric cancer (MGC) is systemic therapy resulting in median survival of 6-12 months and rare survivors of up to three years.
- For patients with limited MGC, retrospective studies have shown improved overall survival following gastrectomy and/or metastasectomy plus systemic therapy (e.g. median survival after liver resection for metastatic gastric cancer of 15-37 months, with a five year survival rate of 25%).
- This prospective randomized trial for patients with MGC and limited metastases is designed to compare two therapeutic approaches: gastrectomy with metastasectomy plus systemic therapy (GYMS) vs. systemic therapy alone (SA) and to evaluate outcome in light of selection criteria to define those patients who may benefit from the more aggressive approach.

Objectives:

Primary Objective:

- To compare two therapeutic approaches: GYMS vs. SA in terms of overall survival in patients with limited MGC.

Secondary Objectives:

- To analyze selection criteria for patients who might benefit from the GYMS approach.
- To determine progression-free survival in both arms.

Eligibility:

- MGC with limited metastatic disease thought to be resectable to no evidence of disease.
- 18 years old or greater with an ECOG 0-2
- Laboratory and physical examination parameters within acceptable limits by standard of practice guidelines prior to surgery

Design:

- Patients will be randomized to receive gastrectomy and metastasectomy followed by systemic chemotherapy (GYMS) or systemic chemotherapy (SA) alone and will be stratified based on sites of metastatic disease, previous therapy and disease free interval (Appendix 3, trial schema).
- Patients in both arms will receive the FOLFOXIRI regimen (5-FU, leucovorin, oxaliplatin and irinotecan)
- No cross over will be allowed.
- Survival analysis will be done in intention to treat fashion from time of randomization.
- Based on estimated 12 and 20 months overall survival for the SA and the GYMS arms respectively, 68 patients per arm (power=0.80, 0.05 two-tailed log-rank test) will be enrolled. Patients will be recruited over 6 years and followed for an additional 2 years from the date of entry of the last patient.

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1. Introduction:

1.1. Study Objectives

1.1.1. Primary Objective:

- To determine whether a therapeutic approach that includes gastrectomy and/or metastasectomy plus systemic therapy is superior to the standard of care approach that includes systemic therapy alone in terms of overall survival for patients who present with limited metastatic gastric cancer (MGC).

1.1.2. Secondary Objectives:

- To compare progression-free survival (PFS) between the two study arms
- To analyze prognostic factors and generate potential selection criteria for patients who present with limited gastric cancer metastases that might benefit from gastrectomy and/or metastasectomy plus systemic therapy.
- To analyze prognostic factors and generate potential selection criteria for patients who present with limited gastric cancer metastases that will not benefit from gastrectomy and/or metastasectomy.
- To determine if surgical resection impacts the dosing and duration of subsequent chemotherapy administration
- To compare quality of life (QOL) parameters between the two study groups. We will use tools specifically developed for assessment of QOL in gastric cancer patients: FACT-Ga, EORTC QLQ-STO22 and the SROTC QLQ-C30[1-4].
- To determine and compare patterns of disease recurrence between the two therapeutic approaches and their clinical implications.

1.2. Background and Rationale

Gastric cancer is the fourth most common cancer world-wide with approximately 930,000 people diagnosed each year and an annual mortality close to 700,000[5]. In the United States, in 2008 approximately, 21,500 people will develop gastric cancer and an estimated 10,880 individuals will die from the disease[6]. Overall, gastric cancer is the 14th most common cancer in the United States, and accounts for 1.5% of all new diagnoses and 5.2% of all cancer deaths[6]. The annual age-adjusted incidence rate is 8 in 100,000 with an annual death rate of 4.1 in 100,000[7]. The lifetime risk for developing gastric cancer is 0.89% or 1 in 113 men and women born in the United States today[7]. At the time of diagnosis, 4-14% of patients will present with metastases to the liver [8,9,10] and 0.1% with metastases to the lung[45, 46]. At the time of initial surgical intervention for locally advanced disease,15-50% of patients will have metastases to the peritoneum[38] This study seeks to define the role of metastasectomy in patients with gastric cancer who present with metastases to the liver, peritoneum, or lung.

Hepatic Disease

At the time of diagnosis 35% of patients present with evidence of distant metastases with 4-14% having metastatic disease to the liver [8,9,10]. A study from Memorial Sloan-Kettering Cancer Center (MSKCC) described patterns of recurrence in completely resected gastric adenocarcinomas (NED) in a large series of patients (n=1172) and found liver specific recurrence rates at 37%[11]. In a study analyzing 643 patients enrolled in 5 separate chemotherapy trials by the Japanese Clinical Oncology Group, (JCOG) 5-year survival for patients with liver only metastases treated with systemic therapy alone was 1.7%[12]. There have been no large prospective studies detailing the natural history of metastatic gastric carcinomas and long term survival. However, two small randomized trials compared best supportive care with combination chemotherapy and found that no patients treated with supportive care lived for longer than 1 year [13,14,15]. Palliative chemotherapy has been widely used as the treatment of choice, but only minimal improvements have been observed with median survival increasing from 3 months to 7-12 months[13-17].

Over the past several decades, hepatic resections have evolved into a common operative procedure performed safely at large centers throughout the world. Improvements in the understanding of anatomy, physiology, perioperative care, and surgical technique have reduced operative mortality for liver resections to less than 4%[18]. In most tertiary referral cancer centers, liver resection carries mortality of less than 2%. For hepatic colorectal metastases, retrospective studies spanning thousands of patients show that surgical resection can yield 5-year survival between 35 – 62 %[19]. Similar results have been observed following resection of hepatic metastases from primary neuroendocrine tumors with resection now considered the standard treatment. Initial reports of liver resections for metastatic gastric cancers have been encouraging but are limited by being retrospective and consisting of only a small number of patients.

Resection of liver metastases from gastric cancer is not widely performed; however a thorough review of the literature (Kerkar and Avital et al., in preparation) identified 19 studies reporting survival rates on a total of 358 patients receiving hepatic resections for gastric adenocarcinomas. The in-hospital mortality rate was 3.7%. Median overall survival for the reporting studies was 18 months and median 5-year actuarial survival was 24.5% (range: 0 -60%). Although follow up was limited in several studies, 13.4% of patients were still alive at 5 years (Table 1). The presumed aggressive biology, high incidence of peritoneal dissemination, and lack of sufficient data from single studies reporting on patients undergoing metastasectomy for metastatic gastric cancer to the liver have made it difficult to highlight the benefits of operative management for these patients.

Although the data certainly represents a highly selected group of patients and bias of surgeons, evidence that long term survival can be achieved in individuals with metastatic gastric cancer to the liver is nonetheless encouraging. Furthermore, analyzing the characteristics of individuals surviving for greater than 5 years shows that potential ‘cures’ exist, as evidenced by 7 (4%) patients living for greater than 10 years (Table 2).

Patient selection is critical when considering liver resection but delineating conclusive prognostic factors from several retrospective studies may be less than ideal. Analyzing the data presented in these studies may help in identifying factors that can be prospectively analyzed in a clinical trial such as this. Prognostic factors identified as being significant on univariate analysis in at least one study included the number of liver metastases (solitary vs. multiple nodules), negative resection margins, synchronous vs. metachronous presentation, certain primary tumor characteristics such as depth (serosal invasion), venous and lymphatic invasion, histologic grade, lymphocytic infiltration and fibrous pseudocapsule along with metastatic tumor characteristics such as disease free interval, size and distribution of metastases (unilobar vs. bilobar). Factors identified as significant on multivariate analysis in at least one study included the number of liver metastases (solitary vs. multiple), negative resection margins, serosal/lymphatic/venous invasion of primary tumor, and synchronous vs. metachronous presentation. Although two studies did show a significantly worse outcome for patients undergoing synchronous hepatic resections, the detailed analysis of 29 long term survivors shows that 17 patients (59%) had synchronous disease.

Considering the pattern of distant failure of gastric metastases, we believe that the majority of the study population will include patients with hepatic gastric metastases. Based on the data presented here regarding liver resection for hepatic gastric metastases and data from colorectal cancer metastatic to the liver, we propose the following selection criteria for this trial: Patients eligible for this trial may include patients with synchronous or metachronous gastric liver metastases, and liver disease (bilateral or unilateral) limited to ≤ 5 lesions and/or ≤ 15cm.

Peritoneal Disease

The next most common mode of failure is locoregional-peritoneal disease. Sugarbaker et al. categorized gastric peritoneal disease into four distinct categories defined below[37]:

Peritoneal Staging (adapted with modifications)

P0	No peritoneal seeding
P1	Adjacent peritoneal involvement only; seeding limited to the upper abdomen only, all resectable to ≤ 0.5mm
P2	Few scattered metastases to distant peritoneum; small-volume seeding throughout the abdomen, resectable to ≤ 0.5mm
P3	Extensive peritoneal spread or not resectable to ≤ 0.5mm

Patterns of failure after curative resection showed that up to 50% of patients undergoing gastric resection developed locoregional recurrences 1-3 years after surgery. There is a strong theoretical basis for the use of perioperative intraperitoneal chemotherapy with debulking to NED. The tumor cell entrapment hypothesis suggests that manipulation of the primary tumor at surgery result in free peritoneal cancer cells (Figure 1). These cells become fixed in fibrin and later results in peritoneal recurrence.

This represents only one of several theoretical considerations. The use of adjuvant intraperitoneal chemotherapy for patients presenting with advanced primary gastric cancer has been examined in several randomized controlled trials (Table 3). Individually, these trials were not powered to definitively highlight the role of adjuvant intraperitoneal chemotherapy. However, a meta-analysis in the Annals of Surgical Oncology in 2007 concluded that patients with advanced gastric cancer treated with adjuvant hyperthermic intraoperative intraperitoneal chemotherapy experienced statistically improved overall survival[38].

Another report in 2008 in the Journal of Surgical Oncology pooled together expert opinions for the interpretation of the previous randomized trials and meta-analysis in regard to intraoperative intraperitoneal chemotherapy as an adjuvant treatment modality[39]. All the experts agreed that patients who have undergone a curative gastric resection and who have peritoneal washings with positive cytology should be treated with intraperitoneal chemotherapy. Eighty-three percent recommended intraperitoneal chemotherapy for patients with T3 and T4 primary lesions[39]. However, due to the heterogeneity of the randomized studies, a consensus for patient selection criteria and chemotherapy regimen still remains unclear.

Patients who present with locally advanced disease are typically found to have peritoneal metastases during surgical exploration[38] (15 -50%). For these patients (with peritoneal dissemination resectable to no visible disease [NED] and no evidence of other distant metastases) the majority of the experts (83%) recommended peritonectomy followed by hyperthermic intraoperative intraperitoneal chemotherapy, although 92% of the experts believed a large randomized trial needed to be conducted to make this treatment standard of care[39].

A large percentage (31%) of the patients with gastric cancer in the United States presents with stage IV disease, including P1-P2 disease. After analyzing 20 years of data from multiple studies of patients receiving a 'palliative' gastric resection for stage IV gastric cancer with peritoneal dissemination, Sugarbaker et al. concluded that gastric resection in the presence of peritoneal metastases improved quality of life and survival[37]. Furthermore, 4 separate small studies concluded that complete removal of both the gastric primary and all visible peritoneal disease combined with intraperitoneal chemotherapy was associated with improved survival[40-43]. For patients not treated with intraperitoneal chemotherapy, Ouchi et al. showed that overall survival was improved with total gastrectomy performed for patients with peritoneal disease[44]. However, they also reported that patients with >P2 disease had significantly worse outcomes compared to those with P0 or P1 metastases. Patients with >P2 disease are excluded from this study.

Therefore, based on the data presented regarding gastric peritoneal disease, we propose the following eligibility criteria: Patients with gastric peritoneal metastases of $\leq$ P2 disease, synchronous or metachronous, limited extrabdominal disease and disease resectable to NED.

Pulmonary Disease

The incidence of lung metastases from gastric cancer is reported to be extremely low. Kanemitsu et al. reported an incidence of 0.1% (4/3076)[45, 46]. The following represents the sum of our knowledge regarding lung metastases from gastric cancer: Once considered the *sine qua non* for surgically unresectable disease, advances in anesthesia, thoracic surgery, and postoperative care have made pulmonary metastasectomies for other intestinal malignancies such as colorectal cancer an essential part of treatment of metastatic disease. A review of over 5,000 patients who underwent pulmonary resections for malignancies of various histologies showed that after complete metastasectomy long term survival of 36% at 5 years, 26% at 10 years, and 22% at 15 years are possible in selected patients[47]. Despite these promising but biased statistics, pulmonary resection of malignant gastric metastases is not routine. Autopsy series of patients with gastric cancer demonstrate pulmonary metastases in 22-52% of patients[45,48]. The incidence of clinically apparent pulmonary metastases ranges from 0.5-14%[45,49]. Anywhere from 0.3-6% of patients will have purely isolated pulmonary metastases from their primary gastric adenocarcinoma[45,49]. Pulmonary metastases treated with chemotherapy alone have traditionally been associated with poor outcomes, with survival measured in a few months[50].

A thorough review of the literature identified case reports and several limited case series which report on 45 patients who have undergone resection of pulmonary metastases following curative resections of primary gastric malignancies (Kemp and Avital et al[51], in preparation) (Table 4). Resections included wedge excisions, segmental resections, and lobectomies. No patients underwent pneumonectomy. Mean survival in case series is 13.8-24.3 months[45,52]. Several authors report survival of greater than 5 years and one study reported on a long term survivor alive 7 years after metastasectomy [53-56]. This translates into overall survival up to 15 years from the initial resection of the primary gastric cancer[54]. In addition, repeated pulmonary resections, combinations of pulmonary and hepatic and pulmonary and adrenal lesions, as well as resection of primary lung cancer along with metastatic gastric cancer have all been reported, with long term survival a possibility in selected patients[50,54,55,57,58].

Despite these promising reports of long term survival among highly selected patients who undergo resection of pulmonary metastases from gastric cancer, metastasectomy has not been scientifically studied as a potential routine practice in the management of this disease. Furthermore, no studies have adequately addressed this topic in a prospective, randomized fashion comparing metastasectomy to best alternative care of systemic chemotherapy. While considering the retrospective nature, inherent biases and limited experience from these studies, clearly there is a potential group of highly selected patients that might benefit significantly from aggressive approach to pulmonary gastric metastases. This study is designed to answer the question: What are the characteristics of patients who might benefit from the GYMS approach for metastatic gastric cancer, including metastases to the lung.

The rational for using FOLFOXIRI in this trial:

Metastatic gastric cancer remains a therapeutic challenge due to poor prognosis and optimum chemotherapy regimen for this disease has not been established. Several randomized phase III trials comparing combination chemotherapy such as 5-fluorouracyl (5-FU), doxorubicin, and mitomycin or 5-FU, doxorubicin and high dose methotrexate with best supportive care have demonstrated significantly prolonged overall survival (OS) of 8-10 months for chemotherapy group as compared with 3-5 months in the best supportive care alone group[59,60]. Since then, various combination chemotherapy regimens were tested in phase II or phase III trials in metastatic gastric cancer without significant improvement in overall survival. A recent phase III trial comparing docetaxel-cisplatin-5-FU (DCF) to the reference arm of cisplatin-5FU (CF) showed a modest improvement in OS (9.2 vs. 8.6 months), time to progression (5.6 vs. 3.7 months), and response rate (37% vs. 25%) for the DCF arm[61]. These results represent one of the best improvements in treatment of metastatic gastric cancer. However, DCF was associated with high rates of grade 3 and 4 toxicities, and as a consequence the regimen has not yet been widely accepted.

Irinotecan, a camptothecin analog, acts as an anti-tumor agent by inhibiting the eukaryotic enzyme DNA topoisomerase I. Irinotecan has demonstrated high activity as a monotherapy in gastric cancer patients with response rates from 18% to 43%[62,63]. Phase II studies with irinotecan plus 5-FU and leucovorin (FOLFIRI) showed a response rate of 40% with median survival time between 10.7 and 12.6 months[64-66]. A phase II study of modified FOLFIRI in gastric cancer patients who had failed taxane/cisplatin chemotherapy reported a response rate of 21% with low toxicity profile[67].

Oxaliplatin, an alkylating agent, inhibits DNA replication by forming DNA adducts between two adjacent guanines or guanine and adenine molecules. Oxaliplatin has shown a notable activity against colorectal cancer in combination with 5-FU and leucovorin, which has led to several phase II trials in gastric cancer. The oxaliplatin/5-FU/leucovorin regimen yielded response rates in the range of 38% to 54% with a survival time from 8 to 11 months with favorable toxicity profile[68].

In an attempt to develop a more active and efficacious chemotherapy regimen, irinotecan and oxaliplatin, have been combined with or without 5-FU and leucovorin in a few phase I trials, which have shown safe toxicity profiles in patients with advanced solid tumors[69]. Preclinical studies reported synergistic anti-tumor activities between irinotecan and oxaliplatin in several tumor cell lines[70]. A phase II study of irinotecan, oxaliplatin plus continuous infusion of 5-FU/leucovorin without chronomodulation in 32 colorectal cancer patients produced very promising activity with a response rate of 72%[71]. Another phase II study of FOLFIRINOX in advanced pancreatic cancer patients also yielded response rate of 26% with manageable toxicity[72].

On the basis of these encouraging results, several phase II studies were recently executed in order to assess the efficacy and safety of the modified FOLFOXIRI as a frontline chemotherapy in patients with metastatic gastric cancer[73,74]. Results from these trials are among the best ever reported in gastric cancer: Overall response rate of 63-66%

(CR 2-4% and PR 60-65%), median survival 12-15 months, and median time to progression 7-10 months. The most common grade 3/4 toxicities were: neutropenia (12-49% of all cycles), emesis (8-42% of all cycles), grade 2 neuropathy (10%), grade 3 diarrhea (10%), and stomatitis (4%). No grade 4 non-hematologic toxicities were observed.

The role of surgery in early and/or locoregional solid organ cancers is relatively well defined. When solid organ cancers, including gastrointestinal cancers, are diagnosed in an early stage and found to be resectable to NED, surgical resection with or without adjuvant systemic therapy can result in high cure rates. However, the role of surgery in patients with metastatic solid organ cancers continues to be controversial. Generally, the alternative, systemic therapy, on average, achieves only a single digit improvement in median survival and five year survivors are rare with few exceptions. In some cancers, such as colorectal, sarcoma, endocrine and breast cancers with metastases to the liver and the lung, metastasectomy is relatively an acceptable practice in specialty centers. Although considered "systemic disease", in selected patients, surgery plus systemic therapy resulted in dual digit 5-year survivals. This practice is not based on prospective randomized trials but instead on multiple retrospective reports. It took >30 years to compile enough retrospective data to establish these practices, i.e. liver and lung resection for colorectal and neuroendocrine cancers. As a strategy for the next 5 to 7 years, one of the aims the Surgery Branch is to ask the following question in a scientific fashion: What is the role of surgery plus systemic therapy in metastatic gastrointestinal and breast cancers? This study is the first trial resulting from this strategy.

In light of the retrospective data presented here suggesting that metastasectomy plus systemic therapy might improve outcomes in metastatic gastric cancer, the purpose of the current study (the GYMSSA Trial) is to answer the question: What is the role of surgery plus systemic therapy in patients with gastric cancer who present with limited metastases to the liver, lung and peritoneum (≤P2 disease). In addition, we will be monitoring the safety of this combined modality treatment in light of previously conducted studies [80, 81]. The study will be conducted as a random-assignment phase III trial. After thorough staging, including laparoscopy and peritoneal washings, patients will be stratified and randomized to one of two arms: GYMS (gastrectomy and/or metastasectomy plus systemic therapy) vs. SA (systemic therapy alone.) The primary objective is to define the overall survival in the two study groups. Importantly, this study will try to define the characteristics of patients with gastric metastases who might benefit from gastrectomy and/or metastasectomy plus systemic therapy. The Surgery Branch in collaboration with the Medical Oncology Branch of the NCI aim to answer these questions in a scientific manner.

2. Eligibility Assessment and Enrollment:

2.1. Eligibility Criteria

2.1.1. Inclusion Criteria

a. Histologically or cytologically confirmed gastric adenocarcinoma

b. Metastatic disease must be measurable by CT and/or MRI

or

There must be a history of positive peritoneal washings or carcinomatosis

c. All disease should be deemed resectable to negative margins (NED) based on imaging studies e.g.:

- Esophageal invasion <4cm that does not require thoracotomy (Seiwert II and III lesions)
- Hepatic metastases (unilateral or bilateral ≤ 5 lesions, ≤ 15 cm total diameter)
- Primary peritoneal metastases (small disease load ≤ P2 disease) without massive ascites or intestinal obstruction
- Para-aortic lymph node metastases (stations 16 a1 and/or b2, see appendix 5)
- Lung metastases (≤3 unilateral/bilateral, 9 cm total diameter)
- Patients who present with both hepatic and peritoneal metastases must have no evidence of extensive para-aortic/retro-pancreatic lymph node metastases

Note: Patients with both pulmonary and peritoneal metastases will be enrolled at the discretion of the PI

d. Greater than or equal to 18 years of age

e. Must be able to understand and sign the Informed Consent Document

f. Clinical performance status of ECOG ≤2

g. Life expectancy of greater than three months

h. Patients of both genders must be willing to practice birth control during and for four months after receiving chemotherapy

i. Hematology:

- Absolute neutrophil count greater than 1500/mm^3 without the support of Filgrastim.
- Platelet count greater than 75,000/mm^3.
- Hemoglobin greater than 8.0 g/dl.

j. Chemistry:

- Serum ALT/AST less or equal to 5 times the upper limit of normal; except in the presence of obstructive liver metastases where ALT/AST may be up to 10 times the upper limit of normal
- Serum creatinine less than or equal to 1.5 mg/dl unless the measured creatinine clearance is greater than 60 mL/min/1.73 m^2
- Total bilirubin less than or equal to 2 mg/dl, except in the presence of obstructive metastases
- PT within 2 seconds of the upper limit of normal (INR≤1.8)

k. No history of prior/other malignancies within the 2 years prior to enrollment with the exception of basal cell carcinoma

2.1.2. <u>Exclusion Criteria</u>

a. Prior treatment with FOLFOXIRI (treatment with any of the components as separate regimens is allowable)

b. Inability to tolerate any of the chemotherapeutic agents
c. Grade 2 or greater neuropathy
d. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the chemotherapy on the fetus or infant.
e. Active systemic infections, coagulation disorders or other major medical illnesses of the cardiovascular, respiratory or immune system, myocardial infarction, cardiac arrhythmias, obstructive or restrictive pulmonary disease.
f. Brain metastases or a history of brain metastases
g. Childs B or C cirrhosis or with evidence of severe portal hypertension by history, endoscopy, or radiologic studies
h. Weight less than 40 kg
i. Significant ascites, greater than 1000cc in the absence of peritoneal disease
j. History of congestive heart failure and/or an LVEF < 40%
Note: Patients at increased risk for coronary artery disease or cardiac dysfunction (e.g., >65yo, diabetes, history of hypertension, elevated LDL, first degree relative with coronary artery disease) will undergo full cardiac evaluation and will not be eligible if they demonstrate significant irreversible ischemia on stress thallium or an ejection fraction <40%.
k. Significant COPD or other chronic pulmonary restrictive disease with PFT's indicating an FEV1 less than 50% or a DLCO less than 40% predicted for age
Note: Patients who have shortness of breath with minimal exertion or who are at risk for pulmonary disease (e.g., chronic smokers) will undergo pulmonary function testing and will not be eligible if their FEV1 is < 50% of expected.
l. Concomitant medical problems that would place the patient at an unacceptable risk for a major surgical procedure or for the administration of FOLFOXIRI

2.2. Research Eligibility Evaluation

2.2.1. **Within 6 weeks prior to treatment:**

- Complete physical examination including vital signs, height and weight as well as ECOG assessment.
- HIV, Hepatitis B surface antigen and Hepatitis C antibody
- UGT1A1genotyping (selected patients)
- 12 lead EKG
- Patients will undergo pulmonary function tests as indicated in section 2.1.2 i.
- Cardiac evaluation with possible stress test for patients with history of cardiac disease will be performed as indicated in section 2.1.2h
- Thoracic oncology consult for patients with pulmonary metastatases
- Pathology will be confirmed by the NCI Laboratory of Pathology.

- Radionuclide bone scan, when clinically indicated.
- MRI Brain when indicated.
- PET-CT when indicated.
- EGD-EUS when indicated.
- Female patients will undergo pelvic ultrasound and/or MRI if indicated.

2.2.2. **Within 4 weeks prior to treatment:**

- Baseline imaging: CT scan of chest, abdomen and pelvis (CT C/A/P) with triphasic 1mm cuts as per the liver scan protocol. For patients with evidence of hepatic disease, a baseline MRI-L will be performed. Note: If the screening CT and MRI of the liver are consistent indicating that CT is an accurate reflection of hepatic disease, then CT may be used for baseline and subsequent evaluations.
- Randomization (**Note:** patients should begin treatment as soon as feasible following randomization)
- *Helicobacter pylori* IgG Antibody
- Patients who test positive for *H. pylori* will receive:
  - Omeprazole 20 mg po daily x 10 days
  - Clarithromycin 500 mg po twice daily x 10 days
  - Amoxicillin 1000mg po twice daily x 10 days

    OR
  - Omeprazole 20 mg po daily x 10 days
  - Clarithromycin 500 mg po twice daily x 10 days
  - Metronidazole 500 mg po twice daily x 10 days

2.2.3. **Within 3 – 6 weeks prior to treatment (one week prior to randomization):**

All patients will have a definitive staging laparoscopy and peritoneal washings. Pathology results of peritoneal washings must be completed before randomization. (**Note**: patient should be randomized as soon as feasible following laparoscopy)

2.2.4. **Within 2 weeks prior to treatment:**

- Laboratory evaluation
  - CBC with platelets
  - Chem-20 (Sodium (Na), Potassium (K), Chloride (Cl), total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, total CK, Uric acid
  - Ferritin, Prealbumin,
  - PT/PTT & INR,
  - Urinalysis
  - iron levels, B12 levels, c-reactive-protein
  - tumor markers (CEA, CA19-9, AFP, CRP, CA 15-3, CA 27-29 and CA125)

- Anesthesia consult – for patients randomized to the surgery arm

2.2.5. **Within 2-3 days prior to chemotherapy**

- Complete physical examination including vital sign measurements, weight and ECOG assessment should be conducted within 3 days prior to treatment. This can be performed by home oncologist if patient decides to undergo systemic therapy at home.
- Serum beta-HCG on all females of child bearing potential or urine pregnancy test within 2 days prior to treatment.

2.2.6. **On Study within 1 week of surgical treatment:**

- Physical examination including vital sign measurements, weight and ECOG assessment.
- Laboratory evaluation: CBC, platelets, Chem-20 (Sodium (Na), Potassium (K), Chloride (Cl), total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, total CK, Uric acid, PT/PTT & INR, Urinalysis.
- Base line tumor markers, Prealbumin and Ferritin.

2.3. Patient Registration, Stratification, and Randomization

Registration of patients onto this study will take place within 10 days of the patient signing the consent by faxing a completed eligibility checklist to the Central Registration Office (CRO) at 301-480-0757 between 9:00 and 5:00 Monday through Friday. Following laparoscopy, patients will be stratified and then randomized by the CRO to receive gastrectomy and/or metastasectomy plus systemic therapy (GYMS arm) or standard therapy (SA arm). The CRO will notify the Study Coordinator of the results of randomization.

Note: As soon as the patient has signed the informed consent, the patient's referring oncologist (or Dr Duffy or his designee for those patients being treated at the NCI) will be notified of the expected date of randomization and potential start dates for the chemotherapy. Immediately following randomization the referring oncologist will be notified. Subjects who are randomized to receive chemotherapy only must begin chemotherapy treatment within 14 days following randomization.

Stratification will be done according to the following factors:

- Site of metastases (liver, lung, and peritoneal disease). Note: positive peritoneal washings will be stratified as peritoneal disease.
- Time to development of first metastases (earlier than 1 year vs. later than 1 year)
- Previous systemic therapy specifically given for gastric metastases vs. no therapy for metastatic disease. (**Note**: patients who have received adjuvant chemotherapy will be stratified to the *no therapy for metastatic disease* group)

3. Study Implementation:

Study Design (See appendix 3 for trial schema)

Experimental Design:

- This is a prospective randomized trial comparing the effects of two therapeutic approaches, gastrectomy and/or metastasectomy plus systemic therapy (GYMS) to systemic therapy alone (SA) on the overall survival of patients with limited gastric cancer metastases.
- Patients who are newly diagnosed as well as those who have received prior systemic treatment for gastric metastases will be eligible. Both groups will be randomized to surgery plus chemotherapy or chemotherapy alone.
- Candidate patients for this trial will undergo all or part of the following staging elements before randomization and/or if indicated medically: pathologic confirmation of gastric cancer as feasible, H&P, laboratory evaluations, imaging studies and other studies as medically indicated.
- Patients who enroll and are willing to have tissue collected for research purposes will be enrolled on protocol 09-C-0079.
- All patients found eligible will undergo staging laparoscopy with peritoneal lavage prior to randomization.
- Patients will be randomized following staging laparoscopy and after the results of the peritoneal washings are available.
- Stratification will adjust for site of metastases (liver, peritoneal and lung), disease-free interval (DFI), and previous systemic therapy for gastric metastases. Note: positive peritoneal washings will be stratified as peritoneal disease.
- Patients randomized to the GYMS approach and who have peritoneal disease will undergo, as an integral part of their treatment, complete peritonectomy and peritoneal perfusion (CHPP).
- Patients who present with intrabdominal disease without peritoneal involvement will undergo CHPP with limited peritonectomy as described in section 3.2.6
- All patients randomized to the GYMS arm will undergo gastrectomy, modified D2 lymph node dissection and/or appropriate metastasectomy followed by systemic therapy.
- *H. pylori* infection will be tested and treated following the recommendations of the American College of Gastroenterology guideline on the management of *H. pylori* infection[75] (Appendix 2). This treatment should not delay surgery.
- Patients randomized to the systemic therapy arm (SA) will receive systemic therapy preferably by their home medical oncologist or by the NCI Medical Oncology Branch.
- Systemic therapy: Since there is no definitive standard of care in metastatic gastric cancer and oxaliplatin and/or irinotecan were shown in phase III trials[76] to be equally effective to other common regimens in gastric cancer, patients will receive the FOLFOXIRI regimen as described by Masi et al from the GONO group[77].
- Patients in the SA arm who develop metastases synchronous to the primary gastric cancer will be eligible for palliative gastrectomy for pain, bleeding, obstruction and/or if deemed in the best interests of the patients.
- Palliative gastrectomy will include tumor resection (R0 when possible) and a bypass. As per standard of care, no adjacent organ resection (with the exception of obstructing lesions) will be performed.

- During follow up, all patients will undergo H&P laboratory evaluation and imaging studies and tumor markers as indicated. The timing of all follow up evaluations will be based on the date of randomization.
- Progression will be measured by a radiologist blinded as to the treatment arm.

3.1. Staging Laparoscopy

3.1.1. Patients who meet eligibility criteria will be taken to the operating room for staging laparoscopy and peritoneal washings. At laparoscopy biopsies of the peritoneum will be done and used later to confirm status of peritoneal disease (not as a part of the staging procedure but as part of the study).

- Any suspicious lesions that might preclude resection to NED will be biopsied as well.
- Liver ultrasound to confirm axial imaging findings will be done.
- Randomization and stratification will be done after laparoscopy and only after the results of the peritoneal washings are known (within one week of laparoscopy).

3.1.2. Patients will then be randomized to receive gastrectomy and/or metastasectomy plus systemic therapy (GYMS arm) or systemic therapy alone (SA arm).

- Patients randomized to receive the standard of care (SA arm) will receive systemic therapy (as described in Section 3.5). **Note:** Patients may undergo palliative gastrectomy if indicated but must begin chemotherapy within 6 weeks of gastrectomy (8 weeks following randomization).
- Patients randomized to receive gastrectomy and/or metastasectomy plus systemic therapy (GYMS arm) will be taken to the operating room within 1-2 weeks of randomization (as soon as feasible). Patients may undergo surgery only at the NCI. Subsequently, patients will receive systemic therapy within 4 to 16 weeks after surgery and/or when fully recovered from surgery. Patients who do not recover within 16 weeks will be taken off treatment and followed for survival. (**Note:** patients who undergo thoracotomy for pulmonary metastases must be able to receive systemic therapy within 24 weeks of their initial surgery.) This is an intent-to-treat phase III trial.

3.2. Gastrectomy, Metastasectomy, Peritonectomy and Intraperitoneal Therapy

Surgical Guidelines:

Note: The following guidelines are for the purpose of promoting consistency in the surgical procedure, and peri-operative care where possible. Physician discretion will be exercised as necessary to ensure that the specific needs of the patient are met. Details pertaining to surgical and perioperative management will be recorded in the patient medical record but will not be captured on the CRFs.

3.2.1. **Preoperative Patient Management**

- Patients will receive standard preoperative care as appropriate to the planned surgical intervention and the patient's underlying health status which may include:
    - The day prior to surgery: anti-embolism stockings (TEDS), Sequential Compression Devices (SCDS), incentive spirometry and appropriate bowel preparation regimen
    - The night before operation: Hibiclens® shower

Note: For patients undergoing hepatic resection, no anticoagulation will be given prior to operation.

3.2.2. **Patient Management in the Operating Room:**

- Patients will receive broad spectrum antibiotics in the recovery room before moving into the operating theater.
- Epidural catheters should be considered in all patients. Decisions will be made by the anesthesiologist and the operating surgeon in full collaboration.
- TEDS will be placed and SCDs will be "on" before induction of anesthesia.
- A central venous line, arterial line, and large bore catheters will be placed if blood loss is anticipated to be >500cc.
- In cases where liver resection is anticipated, fluid administration will be tightly coordinated with the operating surgeon. Before the liver parenchyma is transected administered crystalloids should be limited to <500ml when possible. During parenchymal transection the CVP should be kept under 4 and preferably at 0-1 using Trendelenburg position and vasodilators; urine output of 25 cc per hour will be considered sufficient.

3.2.3. **Choice of Gastric Resection:**

General Guidelines:

- The overall goal for surgical therapy is to render the patient NED and to obtain negative margins whenever technically feasible.
- All patients will receive an intraoperative ultrasound of the liver regardless of the preoperative imaging or laparoscopic ultrasound to determine if hepatic metastases exist even if preoperative imaging fails to show evidence of disease.
- Hand sewn anastomosis with PDS and a G-J tube placement for patients undergoing CHPP and gastrectomy will be preferred.
- A resection of surrounding organs will be allowed if the operating surgeon observes local invasion.
- The drainage procedure after gastric resections will consist of either a Billroth II or preferably, Roux-en-Y gastrojejunostomy when possible.

Type of resection

- Lesions of the gastric body or antrum: a "radical subtotal gastrectomy" will be performed: this will include an approximate 70-90% distal gastrectomy, and if technically feasible, ligation of the right gastric, right gastroepiploic, and left gastric arteries at their origin with removal of associated lymphoid tissues. The lesser and greater omentum will be removed if considered resectable.

- Proximal lesions: a total gastrectomy with 2-4 cm esophageal margins will be done when possible.
- Lesions of the cardia or fundus: a total gastrectomy will be performed where possible. Tumors extending < 4 cm into the esophagus will also be resected through the abdominal incision with the intention of gaining 2-4 cm negative margins on the esophagus.
- Distal lesions: a proximal subtotal gastrectomy (as opposed to total gastrectomy) with high ligation of the left gastric artery, removal of the gastrosplenic ligament, lesser omentum and surrounding lymphoid tissue will be done when possible

3.2.4. **Lymph node dissection:**

- Perigastric lymph nodes (stations 1, 3 and 5) and greater curvature lymph nodes (stations 2, 4 and 6) are grouped as N1 (D1 range); the nodes around the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9) and splenic artery (stations 10 and 11) are grouped as N2 (D2 range). More distant nodes such as para-aortic nodes (N3 and N4) are regarded as distant disease (M1).
- All visible perigastric lymph nodes will be removed along with technically feasible resections of lymph nodes along the following named arteries: 1) Right Cardiac, 2) Left Cardiac, 3) Left Gastric, 4) Celiac, 5) Splenic Artery, 6) Hepatic Artery, 7) Suprapyloric, 8) Infrapyloric, 9) and low paraesophageal according to the extent of gastrectomy.
- A modified D2 lymph node resection will be carried out to include removal of the omental bursa along with the posterior leaf of the transverse mesocolon, anterior leaf covering the pancreas, and lymph node stations 1-11 without obligatory splenectomy or distal pancreatectomy.
- The extent of a D2 resection will be determined by the operating surgeon depending on tumor characteristics and whether nodal regions can be accessed safely while sparing the spleen and pancreas. However, if the tumor is adherent to the spleen or invading the gastrosplenic ligament, a splenectomy will be performed

  Note: Patients at risk for splenectomy (proximal T3-T4 lesions) may receive triple vaccination (Pneumococcal, Meningococcal, *Haemophilus influenzae*) prior to surgery.

3.2.5. **Hepatic metastasectomy:**

- Intraoperative ultrasound will be performed on all patients to detect disease not witnessed on preoperative imaging. Unexpected findings will be recorded in the patients chart.
- The goal of hepatic metastasectomy is to render the patient NED with at least 1 cm negative margins when possible.
- The preferred modality of hepatic metastasectomy is anatomical segmental resection. For single lesions, when possible, segmentectomy should be performed. For more than a single isolated lesion, a secterectomy or partial hepatectomy should be performed if feasible. In all cases, the surgeon should strive to obtain negative margins.

- A non-anatomic wedge resection shall be performed only for small superficial lesions deemed resectable to negative margins by intra-operative ultrasound and preoperative imaging.
- In selected cases, intraoperative RFA and/or microwave ablation may be used at the discretion of the operating surgeons if deemed in the best interests of the patient.
- Portal vein ligation/embolization should be considered in selected patients to preserve post-operative liver function.
- A formal hepatic lobectomy will be done for large lesions spanning more than two sectors, or multiple lesions within a single hepatic lobe.
- In all cases of hepatic gastric metastasis undergoing liver resection, the surgeon should perform portal and hepatic artery lymph node dissection whenever possible.

3.2.6. **Peritoneal metastasectomy (cytoreductive surgery):**

- If there is evidence that the extent of disease is beyond the ability to be debulked such that the largest residual tumor nodule is less than or equal to 0.5 cm, patients will be considered ineligible and removed from treatment.
- For patients with primary peritoneal metastases (small disease load; P0-P2 disease) without massive ascites or intestinal obstruction, all visible disease will be resected if technically feasible.
- Complete peritonectomy for patients with peritoneal disease includes the following: the right and left sub-diaphragmatic peritoneum, the falciform ligament, lesser and large omentum, anterior, right and left abdominal wall down to the paracolic gutters and the pelvic peritoneum.
- Partial (limited) peritonectomy for patients with intra-abdominal disease without peritoneal disease includes (i.e., liver metastases without peritoneal disease): peritoneal attachment of the hepatic left lateral segment and the spleen, 2 cm along the incision at the anterior abdominal wall and the falciform ligament (Appendix 1).

3.2.7. **Para-aortic lymph-node metastases:**

- To be considered eligible for CHPP and debulking with “positive” para-aortic lymph nodes, patients will have no evidence of metastatic disease outside of para-aortic lymph nodes on preoperative imaging and no evidence of hepatic or peritoneal metastases on intraoperative examination.
- Stations 16a1 and/ or b2 will be resected when technically possible.

3.2.8. **Lung metastases:**

- Timing of resection will be in the best interest of each individual patient. The decision will be made by the thoracic surgeon and the GI surgeon. It can either be performed at the same time as the gastric resection or at a later time point, with a delay of no more than 16 weeks in cases of synchronous disease. **Note:** patients must begin chemotherapy within 24 weeks of randomization.
- Lung metastasectomy will follow the standard of care and as defined by the inclusion/exclusion criteria.

3.3. Intraperitoneal Chemotherapy CHPP

3.3.1. **Perfusion**

- Two large bore catheters will be inserted through the abdominal wall, one over the right lobe of the liver and one in the pelvis. The abdominal fascia will be closed, and the catheters connected to a perfusion circuit.
- The perfusate passes from a reservoir through a roller pump, heat exchanger, and then into the abdominal cavity.
- Efflux from a second catheter is then recirculated through the reservoir and pump.
- The perfusion flow rate will be maintained at 2.0 L/min and a perfusate volume will be maintained which moderately distends the abdominal cavity correlating with intra abdominal pressures of 5 to 15 mm Hg (2.0 L/m^2). Stable perfusion parameters are obtained and the peritoneal cavity is warmed to a minimum of 41° C prior to starting the clock for perfusion time.
- The perfusion will be continued for 35 minutes.
- During the perfusion, constant physical manipulation of the abdomen (shaking) will be maintained for the entire 35 minutes to assure even distribution of the perfusate.
- The heater coil will be maintained at 46-48°C. Peritoneal temperature will be measured continuously by three probes placed immediately beneath the peritoneal surface on either side of the abdomen and in the pelvis.
- The patient's core temperature will be measured with an esophageal probe (which correlates well with pulmonary artery temperatures) and maintained at less than 41°C using a cooling blanket and ice packs around the legs and head.
- At the end of the perfusion, the abdomen will be re-opened and the perfusate irrigated from the abdominal cavity.

3.3.2. **Medications**

All intraperitoneal drug dosages will be calculated on ideal body weight (IBW). Ideal body weight will be calculated based upon the following formula:

IBW (male, in kg) = {(Height in inches – 60) x 2.3} + 50
IBW (female, in kg) = {(Height in inches – 60) x 2.3} + 45.5

- **5-FU (patients randomized to surgery arm)**

  Due to pH incompatibility, 5-FU cannot be mixed with oxaliplatin inside the peritoneal cavity; therefore, it will be administered IV, to bath the tumor and healthy tissue to potentiate oxaliplatin activity. Prior to the beginning of CHPP patients will receive:

  - Fluorouracil (5-FU) 400 mg/m^2 IV in 50 cc over 5 minutes
  - Leucovorin 20 mg/m^2 IV in 50 cc over 5 minutes

- **Oxaliplatin (patients randomized to surgery arm)**
  - Oxaliplatin 460 mg/m^2 diluted in 2.0 L/m^2 of D5W via the perfusion circuit

3.4. Postoperative Care

3.4.1. Patient Monitoring

- The patients will be monitored in the Intensive Care Unit for no less than 12 hours after surgical resection.
  - Routine ICU monitoring of vital signs will be performed according to the patient's clinical status.
  - While in the ICU, an attempt to keep urine output greater than 100 cc/hour will be made when physiologically feasible.
  - Patients will be transfused as appropriate to maintain a hemoglobin greater than or equal to 8.0 g/dl, and platelet count greater than 25,000 mm^3
- Patients will be discharged from the ICU at the discretion of the treating surgeon and in accordance with the institution policies.
- Following discharge from the ICU, vital signs (blood pressure, temperature, pulse, respirations) will be taken per routine (every 2-6 hours and as clinically indicated).

3.4.2. Continued Postoperative Management:

- Patients will receive routine postoperative care; early ambulation will be encouraged.
- Laboratory evaluations will include:
  - CBC, platelets, and acute panel daily x 4 days and then every third day or as clinically indicated until discharge.
  - Tumor markers for new baseline will be obtained on the day of discharge.
- Patients undergoing CHPP who develop post operative thrombocytopenia and neutropenia will receive standard supportive care as needed.
- X-rays and scans as clinically indicated.

3.4.3. Discharge:

- Total hospitalization may be approximately 7-21 days.
- Patients who are discharged within this time frame should be able to tolerate an oral diet. Patients who have a prolonged hospitalization but are able to tolerate a diet may be discharged with home rehab/physical therapy.
- Within 5 days prior to discharge the following tumor markers should be drawn: AFP, CEA, CRP, CA 19-9, CA 125, CA 15-3, and CA 27-29

3.4.4. Post Discharge

- Patients will have CBC with differential and Chem 20 drawn weekly until values are less than or equal to grade 2 or baseline. This may be done through the patient's referring physician with the results faxed to Dr. Rudloff or his designee.

- Patients will return to clinic approximately 4-6 weeks following surgery for their 1st post operative visit. Subsequent follow up is detailed in section 3.9.

3.5. Systemic Chemotherapy Therapy

3.5.1. Guidelines

Patients who randomize to receive systemic chemotherapy alone (SA) will begin treatment within 14 days of randomization; patients who undergo palliative gastrectomy will begin chemotherapy within 6-8 weeks of randomization. Patients who randomize to surgery plus chemotherapy (GYMS) will begin treatment approximately 6-8 weeks following surgery (24 weeks for patients requiring sequential thoracic and abdominal surgery). **Note:** patients must meet eligibility requirements prior to beginning chemotherapy. Patients who do not recover from the surgical procedure within the stated timeframe will be removed from treatment and followed for survival.

Systemic therapy may be administered by the patient's local oncologist in collaboration with the PI or at the NCI by the Medical Oncology Branch. Systemic therapy will follow the guidelines for the FOLFOXIRI regimen[77]. Chemotherapy and supportive care will be administered in accordance with each institution's policies for the administration of chemotherapeutic agents.

During treatment, the treating oncologist will be asked to fax the following information (Appendix 8) to the research nurse (noted below) at the conclusion of every other cycle (4 weeks):

- chemotherapy administration sheets including dose reductions and reason for dose reduction
- laboratory test results
- other clinically relevant information

The patient will be asked to maintain a diary to be faxed to the research nurse every 4 weeks:

Melissa Walker RN
301-451-6933

All systemic chemotherapy will be administered based on actual body weight if within 20% above or below the ideal body weight. If actual weight is not within 20% of ideal body weight, then ideal body weight will be used to calculate systemic chemotherapy doses.

Ideal body weight will be calculated based upon the following formula:

IBW (male, in kg) = {(Height in inches – 60) x 2.3} + 50
IBW (female, in kg) = {(Height in inches – 60) x 2.3} + 45.5

3.5.2. Treatment Schedule FOLFOXIRI

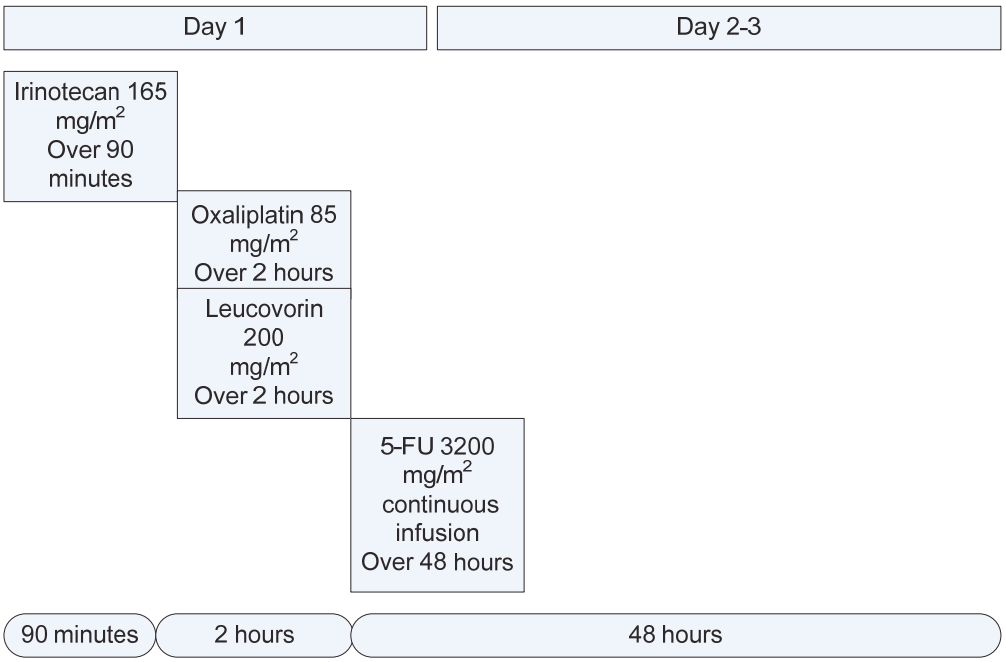
Systemic chemotherapy will be administered every other week (one treatment every 14 days), and repeated for 12 cycles (approximately 6 months). Patients in the systemic chemotherapy alone (SA) arm who are responding may continue chemotherapy beyond 12 cycles at the discretion of the PI. Refer to Section 8 for further administration guidelines.

Day 1: Irinotecan will be administered IV over 90 minutes followed by leucovorin IV and oxaliplatin IV given concomitantly over 2 hours, followed by 5-FU given via continuous infusion (CIV) over 48 hours.

Dose Level

Agent	Starting Dose	Dose level -1 (25% reduction)	Dose level -2 (50% reduction)
Irinotecan	165mg/ m^2 IV	123 / m^2 IV	82 /m^2 IV
Leucovorin	200 mg/m^2 IV	200 m^2 IV	200 mg/m^2 IV
Oxaliplatin	85 mg/m^2IV	63 mg/m^2 IV	42 mg/m^2 IV
5-FU	3200 mg/m^2 CIV	2400 mg/m^2 CIV	1600 mg/m^2 CIV

Cycle 1
Week 1



3.5.3. **Treatment Modifications FOLFOXIRI**

Treatment will be continued for up to 12 cycles (4 cycles = 1 course) unless one of the following events occur: disease progression, unacceptable adverse effects, or withdrawal of patient consent. Dose modification will be based on toxicity profiles and adverse effects based upon the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

The dose levels for oxaliplatin, irinotecan, leucovorin and 5-FU are noted above; the dose modification table is attached as Appendix 4.

NOTE: Patients for whom peripheral neuropathy would pose significant hardship (e.g., musicians, jewelers, dentists) may receive the standard FOLFIRI regimen as noted below.

FOLFIRI			
Agent	**Starting Dose**	**Dose level -1 (25% reduction)**	**Dose level -2 - 50% reduction**
Irinotecan	180 mg/ m^2 IV	150 / m^2 IV	120 /m^2 IV
Leucovorin	200 mg/m^2 IV	200 m^2 IV	200 mg/m^2 IV
5-FU bolus	400 mg/m^2IV	320 mg/m^2 IV	240 mg/m^2 IV
5-FU infusion (over 46 hours)	2400 mg/m^2 CIV	2000 mg/m^2 CIV	1600 mg/m^2 CIV

Day 1: Irinotecan will be administered IV over 90 minutes followed by leucovorin IV over 2 hours followed by 5-FU bolus injection, followed by 5-FU given via continuous infusion (CIV) over 46 hours. Dose reductions will follow appendix 4; all evaluations will follow the same schedule as outlined for FOLFOXIRI.

3.6. Treatment Evaluation During Chemotherapy:

- Laboratory evaluation weekly or according to the standards of the treating physician, to include: CBC with differential and Chem 20: (Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid).
- Physical examination and toxicity assessment every 2 weeks or according to the standards of the treating physician

3.7. Evaluation of Response and QOL Assessment

- CT scan of the chest/abdomen/pelvis will be performed within 4 weeks prior to the first chemotherapy treatment and then every 8 weeks (+/- 1 week) during chemotherapy (at the end of each course).
- Response will be determined using RECIST criteria
- Quality of Life Questionnaires as described in Section 3.11.

3.8. Off Treatment Criteria

- Completion of systemic chemotherapy regimen
- Voluntary withdrawal from treatment
- Inability to follow the treatment regimen
- Unacceptable toxicity
- Radiographic or clinical disease progression
- Unwilling or unable to undergo surgical resection for progressive disease
- If the physician deems it is in the patient's best interest not to receive further treatment
- Completion of chemotherapy

3.9. Post Treatment Follow up (Both Arms)

Patients will be evaluated every 12 weeks (+/- 2 weeks) for the first 2 years, following completion of chemotherapy, every 6 months for the next 3 years and yearly thereafter. At any stage between these follow-ups additional evaluations will be conducted as clinically indicated. At each evaluation patients will undergo:

- Physical examination
- Laboratory tests to include CBC with differential and CHEM 20
- Tumor markers as appropriate
- CT scan of the chest, abdomen and pelvis and other imaging as appropriate
- Completion of QOL measures

Patients who are unwilling or unable to return for follow up evaluation will be followed by phone contact. The following information may be obtained:

- Summary of treatment received since the previous contact
- Estimation of ECOG status
- Request for imaging studies, physical exam and laboratory reports to be sent to the PI

Note: The CT of chest/abdomen and pelvis, done within 2 weeks of randomization, will be used as the base line study for assessment of disease progression. In special cases MRI-L (liver MRI) will be used to assess liver disease or PET scan when indicated.

Patients randomized to the GYMS arm who progress during the follow up period will be offered further debulking/metastasectomy if deemed in the best interest of the patient. No additional chemotherapy will be given as a part of this protocol; however, patients may be referred to other NCI treatment protocols or back to their treating oncologist.

3.10. Off Study Criteria

- Death

- Unwillingness to participate in study specified follow up (including phone contact)
- If the physician deems it is no longer in the best interest of the patient to remain on study

Note: As the objective of this study is overall survival, every attempt will be made to follow patients for life.

Patients will be officially taken off study by contacting the CRO.

3.11. Measurement of Health Related Quality of Life

Baseline Quality of Life Questionnaires (QOL) will be completed prior to randomization, prior to cycle 9 of chemotherapy and then every 12 weeks (+/- 2 weeks) for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. (Note: patients who begin chemotherapy >5 weeks following randomization will be asked to complete the QOL prior to the first cycle of chemotherapy.

Patients will be informed of the details of the QOL part of this study and reassured that their decision to participate will not affect their participation in the either of the treatment arms of this protocol. Once enrolled, the patient has the right at any time to elect not to continue completing the questionnaires. In the event a patient goes off study prior to completion of the follow up time points, the data gathered from their completed QOL questionnaires will be included in the final analysis.

To QOL parameters and quality of life adjusted survival between the two study groups, we will use tools specifically developed for assessment of QOL in gastric cancer patients: FACT-Ga, ; Blazeby JM, Eur J cancer 2004 (Appendix 6). Measures will be initially administered by the Associate Investigator Research Nurse or designee prior to randomization. The Research Nurse will assess the patient's ability to read, and if the patient is unable to read, it will not be administered. The Research Nurse or designee will administer the questionnaires providing a firm surface at a table or a clipboard and a pencil. The patients will be directed to complete the questionnaires using the following instructions:

We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities, and how you rate your health while you are participating in this research study. To help us better understand these things about you and other persons participating in this study, please complete these two questionnaires about your quality of life. Both questionnaires should not take longer than 15 minutes to complete.
The questionnaires are simple to fill out. Be sure to read the instructions on the top each questionnaire. Remember, this is not a test and there are no right or wrong answers. Choose the response that best represents the way you feel. I will quickly review the questionnaires when you are done to make sure that all the items have been completed. Please answer all the items with the response that is most applicable.

You should answer these questions by yourself. Your husband/wife or other family members or friends should NOT assist you in completing the questionnaires. Please fill out the questionnaires now. Return the questionnaires to me when you have completed them. We will be asking you to complete these again during some of your follow up visits. If you have any questions, please ask.

Once the patient has completed the questionnaires, the Research Nurse or designee, will review them for completeness and thank the patient for their cooperation. Subsequent measurements will be administered by the Associate Investigator Research Nurse, or designee, when the patient returns for follow-up visits as specified in section 3.9.

The Research Nurse or designee will request that the patient complete the questionnaires prior to seeing the physician, as the interaction between the patient and physician may influence the patient's answers to the questionnaires. In the event a patient is taken off study, patients will be asked to complete one last set of questionnaires (as appropriate to the point of withdrawal) and the data will be included in the analysis. Patients who are only being followed for length of survival will be asked to continue to participate in completing the measures at the set intervals (every 6-12 months) through the mail. Patients will be phoned prior to the scheduled date of measurement and asked to complete the questionnaire; the FACT-Ga will then be mailed to the patient with a self-addressed return envelope and a cover letter with the script above as directions. If the questionnaires are not returned within 2 weeks, patients are phoned again.

4. <u>Supportive Care:</u>

During the post-operative period patients will receive all standard of care supportive measures including nasogastric tube drainage and bowel rest for ileus, pulmonary toilet teaching and incentive spirometry to prevent atelectasis, transfusions, and antibiotics as indicated.

During the administration of systemic chemotherapy patients will receive all necessary supportive care as per the guidelines of the treating physician and institution. This may include:

- Blood transfusions and growth factor support as necessary for the management of myelosuppression. Filgrastim 5 mcg/kg/day subcutaneously may be administered for ANC less than 1000 mm^3 or as per the guidelines of the treating institution. **Note:** Filgrastim will not be administered prophylactically during systemic chemotherapy.
- Neutropenic fever will be treated with broad-spectrum antibiotics pending culture results.
- Renal dysfunction (very rare) from oxaliplatin will be managed with supportive measures such as avoidance of renal toxic drugs, maintenance of good renal perfusion (hydration), and diuretics as necessary.
- Diarrhea will be managed with medication such as diphenoxylate/atropine or loperamide.

- Mucositis will be treated with bicarbonate rinses or anesthetic mouth wash.
- Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended during systemic chemotherapy.

5. Data Collection and Evaluation:

5.1. Data Collection

Data will be collected using the NCI C3D web based data collection system. Quality of life will be assessed using questionnaires as specified in section 3.11.

5.2. Response Criteria

5.2.1. **Surgery + chemotherapy arm**

Because of the nature of peritoneal imaging and because cytoreductive surgery will likely eliminate all imageable disease, response can only be measured in terms of radiographic or symptomatic disease-free survival and overall survival. Patients will be followed with CT scans at predetermined intervals as described in Section 3.9. At any time point when there is evidence of progressive disease (imageable tumor nodules or increasing ascites persistent on CT scans as interpreted by the official interpretation of the imaging studies) the patients will be scored as progressive disease. In some cases this may require successive scans, but the time of recurrence will be retrospectively defined at the point the first scan demonstrated imageable disease. Patients who have symptoms of peritoneal tumor recurrence will be followed closely with serial scans and where necessary, laparoscopy (GYMS arm) in order to confirm disease status.

5.2.2. **Systemic chemotherapy alone arm**

Lesions will be evaluated using the RECIST criteria as described below.

Evaluation of target lesions*

- Complete Response (CR): Disappearance of all target lesions
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.
- Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

* All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Evaluation of non-target lesions**

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
- Non-Complete Response: Persistence of one or more non-target lesions
- Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions

** All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present" or "absent."

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Confirmatory Measurement/Duration of Response Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

5.3. Toxicity Criteria

This study will utilize the CTCAE version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 3.0.

5.4. Statistical Section

The primary objective of the trial is to determine if there is a difference in overall survival among patients with limited gastric cancer metastases who are randomized to receive either systemic therapy alone or gastrectomy, metastasectomy and systemic therapy.

Based upon results in the literature, patients who would be eligible for this trial and who receive systemic therapy alone would be expected to have an estimated 12-month median overall survival from the date of randomization. The goal of this study will be to determine if the use of gastrectomy, metastasectomy and systemic therapy will result in an 8-month increase in overall survival, to a median of 20 months. Patients will be randomized between systemic therapy alone or gastrectomy, metastasectomy and systemic therapy and followed for overall survival. Kaplan-Meier curves and a two-tailed log-rank test will be the primary analysis methods. Assuming exponential overall survival curves, the hazard rate for the systemic therapy is 0.0578, or approximately a 5.8% probability of death each month when the median survival is 12 months. If we assume that the surgery plus systemic therapy arm has a median overall survival of 20 months, this corresponds to a hazard rate of 0.0347, and the resulting hazard ratio for the comparison of the two overall survival curves would be 1.67. To compare these curves and detect a difference with a 0.05 two-tailed log-rank test, a total of 68 evaluable subjects per arm (136 total) will need to be enrolled over a 6-year period and followed for an additional 2 years from the date of entry of the last patient, with 121 total deaths, in order to have 80% power to compare the curves.

Patients will be stratified for site of metastases (liver, peritoneal, or lung), disease-free survival and prior systemic therapy for gastric metastases.

Progression-free survival will also be evaluated using Kaplan-Meier curves, and a two-tailed log rank test, as a secondary endpoint. In addition, a prognostic factor evaluation using Cox proportional hazards modeling will take place after the study has concluded in order to identify if there are factors which can be identified that are associated with survival or progression free survival in patients randomized to treatments on this trial; this will also be interpreted as a secondary endpoint.

The study will be monitored by the NCI/CCR Data Safety and Monitoring Board on an annual basis to evaluate the safety of the two arms. The SAEs (typically grade 3 toxicities, or greater) will be reported according to type of toxicity, and maximal grade noted per patient, for toxicities with at least a possible attribution to the therapy provided on that arm. Comparisons will be made between the two arms using Cochran-Armitage tests for trend, or other appropriate methods, to determine if there is increased toxicity associated with either arm.

In addition, at the first Data Safety and Monitoring Board (DSMB) meeting held following the point at which half of the required total subjects have been enrolled (68 total), a single evaluation for futility will be undertaken. Evaluations for better than expected efficacy will also be made annually, beginning after half the subjects have been enrolled.

The futility evaluation will be performed as follows: based on the full data available at the time, a conditional power analysis will be performed to determine if the trial is unlikely to find an effect at the 0.05 two-tailed significance level with continued accrual based on an overall survival endpoint. Median survivals of 12 and 20 months correspond to 12-month survivals of 50% and 66% respectively. Using these as the values under the alternative, and using the actual proportions alive at 12 months, based on the observed fractions and the expected sample sizes at 12 months, the conditional power of the trial will be determined assuming accrual of the remaining patients to achieve a total of 136 patients. If the conditional probability of finding a difference at the two-sided 0.05 level at the conclusion of the trial is less than 20%, then it will be reasonable to recommend that no further patients will be enrolled.

The evaluation for better than expected efficacy will be performed as follows. Beginning at the first annual DSMB meeting after 68 patients have been randomized, annual interim evaluations will be performed to determine if there is sufficient evidence to terminate accrual because of a better than expected improvement in overall survival. An alpha spending function approach to monitoring will take place using an O'Brien-Fleming interim evaluation boundary [79]. It will be assumed that a total of 121 deaths would take place over a total of 8 years of accrual plus monitoring, and that monitoring would begin after approximately 40-45 deaths have been noted. The information fraction used to compute the interim boundary at each annual evaluation will be calculated as the number of patients who died /121.

Quality of life evaluations will be compared between the two study arms, with comparisons at multiple individual time points, as well as with respect to changes from baseline. Wilcoxon rank sum tests will likely be used. The evaluation will be considered secondary, and p-values resulting from the analysis will be presented without adjustment for multiple comparisons, but in the context of the number of tests evaluated.

It is expected that 24 patients per year can be accrued onto this trial, and thus accrual will be completed in approximately 6 years. Allowing for a very small number of inevaluable patients, the accrual ceiling will be set at 140 patients.

5.5. Safety and Monitoring Plan

Careful evaluation to ascertain the toxicity and clinical response will be performed. The principal investigator will monitor the data and toxicities to identify trends quarterly. The principal investigator will be responsible for revising the protocol as needed to maintain safety. The NCI IRB will review submitted adverse events

monthly to also evaluate trends and will require a follow up plan from the principal investigator whenever a trend is identified.

The trial will be monitored at least annually by the NCI/CCR DSMB. Interim outcome results will not be revealed to the investigators of the trial; results will be presented to the investigators prior to final accrual to the trial only if the DSMB recommends early termination of the trial. Until 68 patients have been randomized, only toxicity and adverse events will be examined at each review. Once 68 patients have been randomized, interim evaluations to determine whether there is sufficient evidence to terminate accrual because of a better than expected improvement in overall survival, will be performed as detailed in Section 5.4. At the first such review of outcomes, a single evaluation for futility will also be performed.

5.6. Clinical Trial Monitoring Plan

Harris Orkand Information Services (HOIS) provides study auditing/monitoring services under contract with the Center for Cancer Research, NCI. The number of patient records monitored is based on actual accrual. Below is a tabular summary of monitoring evaluations:

Time of year	Evaluation	# of records monitored	%data verification
1st quarter (Jan.- March)	Compare CRFs to source documentation, verify subject registration with Drug Accountability Records	3-4 study patients	100%
2nd quarter (April – June)	Compare CRFs to source documentation, verify subject registration with Drug Accountability Records	3-4 study patients	100%
3rd quarter (July – Sept.)	Compare CRFs to source documentation, verify subject registration with Drug Accountability Records	3-4 study patients	100%
4th quarter (Oct. – Dec.)	Compare CRFs to source documentation, verify subject registration with Drug Accountability Records	3-4 study patients	100%

*Based on expected accrual, 25% of enrolled patients will be monitored.

6. Human Subject Protection:

6.1. Rational for Subject Selection

The investigational nature and objectives of this trial, the procedure and the treatments involved, the attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the patient in the clinic setting and in the hospital prior to treatment and prior to obtaining a signed Informed Consent. This is particularly important for this study because of the relatively unique nature by which the treatment is given. That is to say, the patients must subject themselves to a major operative procedure with the attendant risks and complications associated with it in order to receive treatment without any assurance of benefit from the treatment.

6.2. Evaluation of Potential Benefits and Risks

The potential benefit to patients undergoing this therapy would be palliation in terms of preventing or delaying intra-abdominal tumor progression and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend progression free and overall survival. The risks for this protocol include the risks associated with any abdominal surgery. This includes postoperative bleeding, intra-abdominal infection, enterocutaneous fistulas, anesthetic mishap and perioperative death. In addition, the toxicities of chemotherapy place the patients under risk. A combination of surgery and chemotherapy may decrease healing at a time when healing of abdominal wounds and bowel anastomosis is essential for recovery. All attempts will be made to avoid enterotomies or a bowel resection where feasible. In the case of intraabdominal catastrophe after surgery, patients may require reoperation.

6.3. Risks/Benefit Analysis

Patients dying of peritoneal carcinomatosis suffer with recurrent bowel obstructions, nausea, vomiting, crampy abdominal pain and incapacitating ascites. This clinical scenario justifies aggressive treatment strategies as a means of palliation and survival benefit. In Phase I and II trials we have seen long-term remissions after CHPP in patients who were otherwise terminal with no other therapeutic options available.

The potential benefit is great for these patients if a regional response is obtained. Therefore, this protocol involves greater than minimal risk, but presents the prospect of direct benefit to individual subjects.

6.4. Consent Process

All patients are thoroughly screened prior to initial consultation at the NIH. This usually involves a telephone conversation between the patient and a physician or nurse associate investigator. During the initial consultation the patient, along with family members, is presented a forthright and detailed overview of the treatment option available to them at the NIH. The experimental nature of the treatment, its theoretical advantages and disadvantages, and an overview of the operative procedure and anticipated convalescence are presented. The fact that the patient may undergo an operative procedure in order to receive therapy without any assurance of benefit, the aggressive nature of the treatment, and the likelihood of serious or potentially life-threatening complications are presented. The Informed Consent document is given to the patient and they are asked to review it, make notes and follow-up with a phone call to the physician or nurse investigator to have any additional questions answered prior to considering treatment on protocol.

When the patient is admitted to the Clinical Center for treatment, an associate physician investigator responsible for the care of the patient presents the previously described information in detail. The research nurse or Principal Investigator, or designee is responsible for obtaining consent from the patient upon admission. The patient is reassured that participation on the trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. In fact, the

investigators assure the patient that if alternate therapies are preferred that we will do all that we can to facilitate obtaining consultation and treatment from the appropriate medical center. The signed consent will be verified by the physician responsible for the care of the patient. The patient is asked to participate in completing the self-administered questionnaires measuring health related quality of life during this study. They are assured that their eligibility to participate in the perfusion portion of this study is not dependent upon their willingness to complete the quality of life questionnaires.

7. Data Reporting:

7.1. DEFINITIONS

7.1.1. Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 6.1.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

7.1.2. Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3. Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4. Serious

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,

- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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 this definition.

7.1.5. Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.6. Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.7. Protocol Deviation (NIH Definition)

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

7.1.8. Protocol Violation (NIH Definition)

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

7.1.9. Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2. Routine Data Reporting

7.2.1. Following randomization, all adverse events will be described in the source documents, reviewed by the designated research nurse, and captured in C3D.

- All chemotherapy dose reductions and the reason for the reduction will be captured in C3D
- During the follow up period (more than 30 days following the last treatment), only those events that are serious, unexpected, and related to the treatment will be captured in C3D.

7.2.2. Laboratory events will be captured as follows:

- During hospitalization for surgical resection, only the admission labs, first morning labs drawn after 4am, and labs that support the diagnosis of a reportable event will be uploaded into C3D.
- During systemic chemotherapy regimen, for laboratory values obtained at sites other than the NIH Clinical Center: only the following values (highest grade per cycle) will be captured in C3D:
  - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count
  - PTT, PT or INR
  - Creatinine, ALT, AST, Bilirubin (total and direct),
  - Any unexpected laboratory abnormality ≥ grade 2 possibly, probably or definitely related to the research

7.3. <u>Exclusions to Routine Data Reporting:</u>

The following Adverse Events will be captured only in the source documents and will not be reported in C3D

7.3.1. <u>For</u> the duration of the study:

- Laboratory values that do not support the diagnosis of a reportable event
- All grade 1 events

7.3.2. During hospitalization for surgical resection

- Grade 2 events
- Grade 3 and 4 events which resolve during the first 72 hours following surgery

7.3.3. Post operative recovery phase (following discharge)

- Grade 2 events

7.3.4. During systemic chemotherapy administration

- Grade 1 and 2 events that are listed in the package insert of any of the agents
- Grade 3 events that are listed in the package insert of any of the agents and do NOT require hospitalization. Events that initiate dose reduction will be captured as described in Section 7.1.1

Note: Events that result in a hospitalization for convenience will not be reported.

7.3.5. Concomitant medications:

Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured in C3D. {Thus onetime medications, PRN medications, and medications given to treat adverse events will not be captured in C3D.}

7.4. NCI-IRB REPORTING

7.4.1. NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.4.2. NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

- All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported

8. Pharmaceutical Information:

8.1. Oxaliplatin

8.1.1. **Source:**

Oxaliplatin is commercially available (manufacturer: Sanofi-Winthrop, France) and will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

8.1.2. **Toxicities:**

Predominant dose-limiting toxicity: sensory peripheral neuropathy. Fifty-six percent of patients with this combined therapy experienced an acute, reversible primarily peripheral sensory neuropathy that is of early onset, occurring within hours or one or two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2 % of patients is characterized by subjective sensations of dysphagia or dyspnea, with laryngospasm or bronchospasm. In 48% of

patients receiving this combination, a persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysethesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception) has occurred. Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. If patients experience unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, the agent should be discontinued until further pulmonary investigation excludes pulmonary fibrosis or interstitial lung disease. Other effects: nausea, vomiting, diarrhea, mucositis, transaminase elevations, and alopecia. Myelosuppression is minimal with the agent alone but may be significant when given in combination with 5-FU/LV; severe nephrotoxicity not reported. Extravasation of oxaliplatin may result in local pain and inflammation that may be severe and lead to complications, including necrosis. Injection site reaction, including redness, swelling and pain have been reported.

8.1.3. **Formulation and Preparation:**

Oxaliplatin is supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg as a sterile, preservative-free lyophilized powder for reconstitution, containing lactose monohydrate as an inactive ingredient (450mg or 900 mg respectively). For IV administration, the appropriate dose is reconstituted in a parenteral solution of 250 mL of 5% Dextrose Injection, USP (D5W). For CHPP administration, Oxaliplatin 460 mg/m^2 [is] diluted in 2.0 L/m^2 of D5W and administered via the perfusion circuit. Reconstitution of final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.

8.1.4. **Stability/Storage:**

Oxaliplatin is stable when stored under normal lighting conditions at room temperature of 25°C (77°F).After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration (2-8°C (36-46°F). After final dilution with 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hour under refrigeration [2-8°C (26-46°F)]. Oxaliplatin is not light sensitive.

8.1.5. **Administration:**

Oxaliplatin will be administered in a 250 mL solution of 5% Dextrose Injection, USP (D5W) as a 2 hour infusion on day one of each cycle concurrently with leucovorin in different IV lines. Oxaliplatin is incompatible in solution with alkaline medications or media and must not be mixed with these or administered simultaneously through one infusion line. The infusion line should be flushed with D5W prior to administration of any concomitant medication.

8.2. <u>Leucovorin Calcium (Injection)</u>

8.2.1. **Source:**

Leucovorin calcium injection will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

8.2.2. **Toxicity:**

Allergic sensitization has been reported following both oral and parenteral administrations of folinic acid.

8.2.3. **Formulation and Storage:**

Leucovorin calcium is supplied as 350 mg/vial dry powder and will be reconstituted with sterile water for injection, USP, to a concentration of 20mg/ml. Intact vials of leucovorin need to be stored at controlled room temperature (25 degrees C) and protected room light.

8.2.4. **Stability:**

Leucovorin has been administered extensively with FUDR and dexamethasone as a 2 week intra-arterial infusion in patients with colorectal cancer and loses less than 10% of its activity in solution with these agents at more than 60 days of incubation.

8.2.5. **Administration Procedures:**

Leucovorin will also be administered on day 1 of each cycle at a dose of 200 mg/m^2 intravenously over 2 hours concomitant with oxaliplatin. Doses will be based on actual body weight if patient's weight is within 20% of the ideal body weight. If the patient's weight is 20% above or below the ideal body weight, then ideal body weight will be used to calculate systemic chemotherapy doses. Leucovorin will be diluted in 5% Dextrose Injection, USP (D5W).

8.3. 5-Fluorouracil

8.3.1. **Source**:

It will be purchased commercially by the NIH Clinical Center Pharmacy Department.

8.3.2. **Toxicities:**

The most common adverse reactions include stomatitis, esophagopharyngitis, diarrhea, anorexia, nausea, emesis, dermatitis, and alopecia. Hand-foot syndrome (palmar-plantar erythrodysesthesia) has been observed with 5-FU administration. Bone marrow suppression may occur at high doses with the lowest counts expected between the 9th and 14th day of treatment. Leukopenia is the most common hematologic toxicity associated with fluorouracil (5-FU) with the nadir typically between 9 and 14 days after treatment. The white blood cell count usually returns to normal after stopping treatment. Ischemic chest pain and myocardial ischemia or signs of electrocardiogram changes may occur with fluorouracil administration. Onset of chest pain in many cases occurs within hours of receiving a second or third dose but may be associated with the first dose. Anginal attacks often recur upon rechallenge, but may or may not be prevented with vasodilators such as nitrates or calcium channel blockers. Death has occurred secondary to cardiogenic shock. Most commonly, these effects occur when the drug is administered as a continuous infusion and within several hours from the start of the infusion. Patients with pre-existing coronary artery disease (CAD) appear to be at greater risk; however, most reported cases are in those with no previous history of CAD. Neurological effects reported by the manufacturer include nystagmus, headache, disorientation and euphoria. Of 25 patients receiving low-dose leucovorin (20 mg/m^2) and fluorouracil (425 to 600 mg/m^2), 15 (65%) developed hypocalcemia, and two each had tetany or hiccups.

Calcium levels should be monitored in patients receiving this regimen, and calcium supplementation should be provided if calcium levels are low. The manufacturer reports that visual changes and photophobia have occurred with 5-fluorouracil use.

8.3.3. **Formulation and Preparation:**

5-FU (Fluorouracil) is supplied as a sterile, nonpyrogenic injectable solution for administration. Each 10-cc contains 500 mg in a colorless to faint yellow aqueous solution. The pH is adjusted to 9.2 with sodium hydroxide.

8.3.4. **Stability/Storage:**

Fluorouracil solutions should be stored at room temperature and protected from light. Solutions may discolor slightly but potency and safety are not adversely affected. Any precipitate which forms may be resolubilized by heating and agitation. The stability of aqueous fluorouracil 50 mg/mL was studied in portable infusion pumps under simulated infusion conditions. The drug was found to be stable for 7 days at 37 °C. Fluorouracil solution maintained 98% to 100% potency over 48 hours after dilution and storage in syringes or ethylene vinyl acetate infusion-pump reservoirs.

8.3.5. **Administration:**

Intravenous administration (Intra-operative)

Each 10 ml ampoule contains 500 mg of fluorouracil, and the appropriate amount is diluted in a parenteral solution of 5% Dextrose Injection, USP (D5W). 5-FU will be administered on days 1 and 2 of each cycle of systemic chemotherapy at a dose of 3200 mg/m^2 via continuous intravenous infusion over 48 hours. Doses will be based on actual body weight if patient's weight is within 20% of the ideal body weight. If the patient's weight is 20% above or below the ideal body weight, then ideal body weight will be used to calculate systemic chemotherapy doses. See Section 3.2.2 for the calculation for ideal body weight.

8.4. Irinotecan

8.4.1. **Source:**

Irinotecan is commercially available and will be purchased by the CC Pharmacy Department.

8.4.2. **Adverse effects:**

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, increased bilirubin, interstitial lung disease, and alopecia. Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of irinotecan) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimination, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated

promptly with loperamide. Patients with diarrhea should be carefully monitored and given fluid, and electrolyte replacement if they become dehydrated, or antibiotic therapy if they develop ileus, fever, or severe neutropenia.

8.4.3. **Formulation and preparation:**

Irinotecan is supplied as 20 mg/mL solution (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid in single-dose amber 2mL (40 mg) and 5mL (100 mg) vials. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Solutions should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL using 100 to 500 mL of 5% Dextrose Injection, USP.

8.4.4. **Stability/Storage:**

Store at controlled room temperature 15º to 30ºC (59º to 86ºF). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use. Admixtures are physically and chemically stable for up to 24 hours at room temperature (approximately 25ºC) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2º to 8ºC), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing irinotecan stock solutions and irinotecan admixtures may result in precipitation of the drug and should be avoided.

8.4.5. **Administration:**

Doses will be diluted in 100 to 250 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and infused over 90 minutes.

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10. Figures, Tables and Appendices

Table 1: Long-term survival for patients who underwent liver resection for metastatic gastric adenocarcinoma

Authors	Country	Year	Number of patients	Median survival in months	Mean survival in months	1 year survival in %	3 year survival in %	5 year survival in %	Number of patients alive at 5 years	Number of treatment related deaths
Morise et. al.[20]	Japan	2008	18	13	-	56	27	27	3+	0
Thelen et. al. [21]	Germany	2008	24	-	-	53	22	15	2	1
Cheon et. al. [22]	S. Korea	2008	22	17	-	77	30	23	3	1
Ueda et al.*[23]	Japan	2008	15	-	-	80	60	60	3	0
Sakamoto et.al[26]	Japan	2007	37	31	-	-	-	11	2	0
Koga et. Al[24]	Japan	2007	42	34	-	76	48	42	8	2
Roh et al.[25]	S. Korea	2005	11	19	-	73	38	38	1	0
Shirabe et al.[27]	Japan	2003	36		-	64	26	26	4	0
Okano et al.[28]	Japan	2002	19	21	-	77	34	34	3	0
Saiura et al.[29]	Japan	2002	10	25	27	50	30	20	2	3
Zacherl et al.[30]	Austria	2002	15	9	16	36	29	-	0	1
Ambiru et al.[31]	Japan	2001	40	12	-	-	-	18	6	0
Imamura et al.[32]	Japan	2001	17	-	-	47	22	0	0	0
Fujii et al.[33]	Japan	2001	10	16	-	60	20	10	1	1
Elias et al.[34]	France	1998	11	-	-	90	35	-	4	-
Ochai et al.[35]	Japan	1994	21	-	-	-	-	-	4	0
Bines et al.[36]	USA	1993	10	-	-	45		30	2	3
Total		-	**358**	-	-		-	-	**48**	**12**

* 3 patients received microwave ablation therapy

\+ Alive at 4 years at time of follow up

Table 2: Profile of Long Term Survivors (> 5 years)

Study		Age	Sex	Histology	T	N	# Mets	Synch	Surgery	Survival
Koga et. al.	1.	75	F	Poorly		1-2	1	1	Y	Lobectomy	Alive at 85 months
	2.	56	M	Poorly		1-2	1	1	N	Wedge	Alive at 84 months
	3.	65	M	Well		1-2	0	1	N	Lobectomy	Alive at 86 months
	4.	61	M	Mod		1-2	3	1	Y	Wedge	Alive at 77 months
	5.	52	M	Well		1-2	2	1	Y	Wedge	Alive at 78 months
	6.	52	F	-		1-2	1	1	Y	Wedge	Alive at 65 months
	7.	67	F	Mod		1-2	1	1	N	Wedge	Alive at 61 months
	8.	61	F	Mod		3	1	1	Y	Lobectomy	Died at 71 months
Ueda et. al.	1.	54	M	-		2	0	1	Y	R lobectomy	Alive at 136 months
	2.	58	M	-		2	1	1	Y	Wedge	Alive at 107 months
	3.	74	F	-		3	2	1	Y	L lobectomy	Alive at 71 months
Roh et. al.	1.	69	F	Mod		1	2	1	Y	Wedge	Alive at 102 months
		64	M	Well		3	2	1	N	Segmentectomy	Alive at 102 months
Shirabe et. al.	1.	-	-	Mod-Well		3	1	1	Y	-	Alive at 63 months
	2.	-	-	Mod-Well		1	1	1	N	-	Died at 75 months(lung ca)
	3.	-	-	Mod-Well		3	1	1	N	-	Alive at 84 months
	4.	-	-	Mod-Well		1	1	1	Y	-	Alive at 207 months
Saiura et al.	1.	59	M	Mod		3	0	3	N	-	Alive at 67 months
	2.	60	F	Mod		2	0	10	Y	-	Alive at 68 months
Okano et. al.	1.	61	M	Well		2	1	1	N	Wedge	Alive at 138 months
	2.	75	F	Well		3	2	1	N	Segmentectomy	Alive at 96 months
	3.	69	M	Well		2	0	1	N	Wedge	Alive at 81 months
Fuji et. al.	1.	41	M	Poorly		4	1	1	Y	Wedge	Alive at 245 months
Ochiai et. al	1.	55	M	Well		2	1	1	Y	Segmentectomy	Alive at 218 months
	2.	52	F	Well		2	1	1	N	Limited Resection	Died at 77 months
	3.	49	M	Well		2	0	6	Y	Segmentectomy	Alive at 86 months
Bines et. al.	1.	51	M	Poorly		-	1	1	Y	L Lobectomy	Alive at 120 months
	2.	60	M	Well		-	1	1	Y	L Lobectomy	Alive at 156 months
	3.	70	F	Variable		-	-	1	N	Trisegmentectomy	Died at 74 months

Table 3: Eight Reports of Adjuvant Treatment with Perioperative Intraperitoneal Chemotherapy in Gastric Cancer [37]

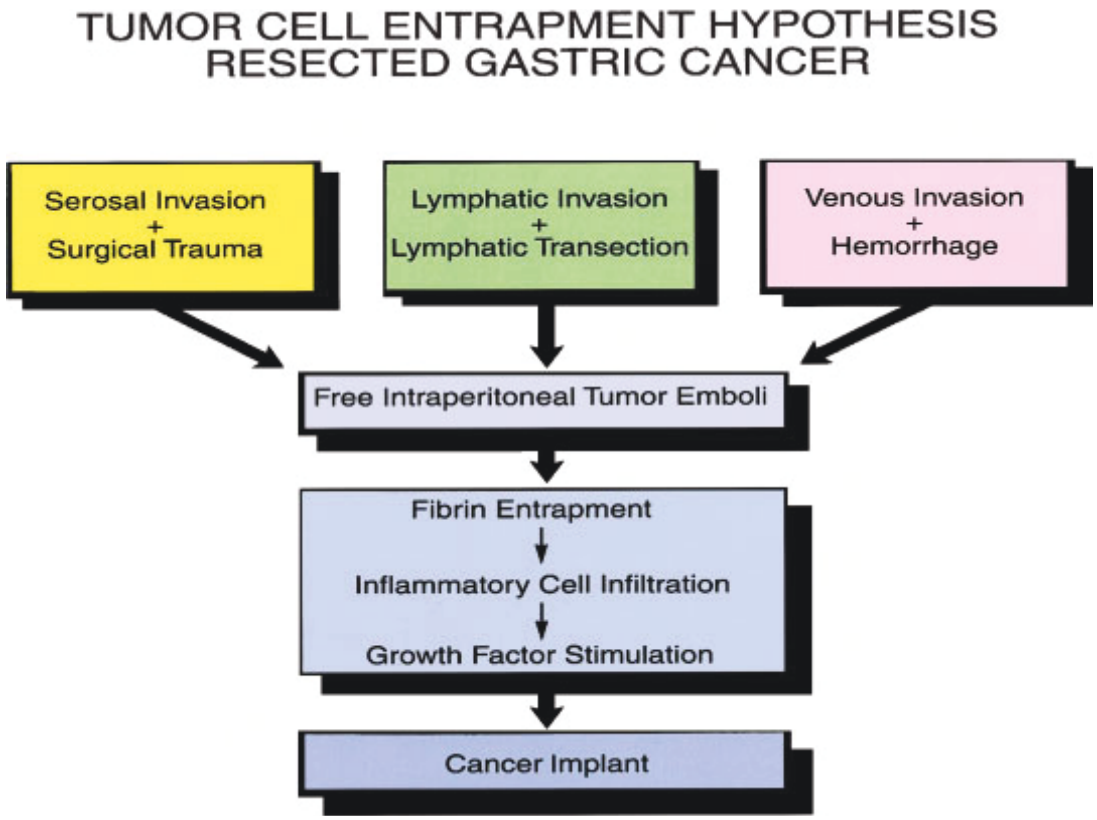
Reference	Location	No. of patients study/control	Survival rates % study/control	*P*	Study/control morbidity %	Study/control mortality %
Koga et al. [18]	Yonago	26/21	2.5-year 83/67.3	NS	3.1/7.1	NA
Hamazoe et al. [19]	Yonago	42/40	5-year 61.3/52.5	0.02	4.8/7.50	0
Fujimura et al. [20]	Kanazawa	22/18	3-year 68/23	0.01	36/NA	0
Yonemura et al. [21]	Kanazawa	79/81	3-year 55/38	0.052	3/2.5	3/2.5
Ikeguchi et al. [22]	Yonago	78/96	5-year 51/46	NS	1.2/2.08	1.2/2.08
Yu et al. [23]	Taegu	125/123	5-year 54.1/38.1	0.0278	28.8/20.3	6.4/1.6
Fujimoto et al. [24]	Chiba	71/70	5-year 69/55	0.0362	2.81/2.85	0
Kim et al. [25]	Seoul	52/51	5-year 34.6/31.4	NS	NA	NA

*Negative margins of excision and absence of disseminated disease.
NA, not available; NS, not significant.

Table 4: Lung Resections for Gastric Cancer

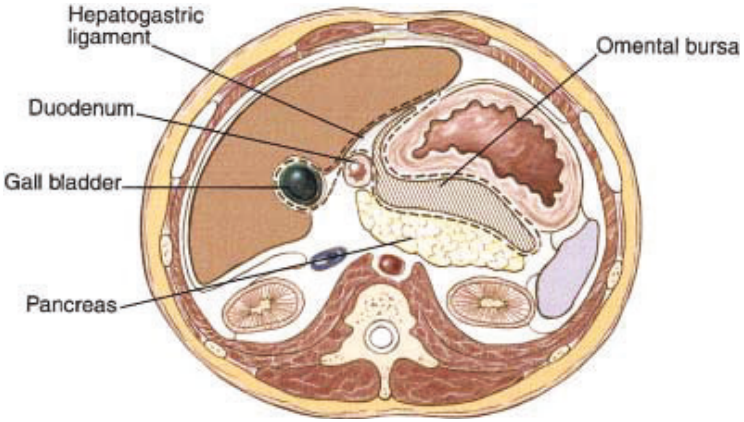
Year	Author	Patients	Pathology	Operation	Follow up
1975	Siono Y	1	adenocarcinoma		
1984	Mai M	1	adenocarcinoma	Lobectomy	
1988	Tomita M	1	adenocarcinoma	Lobectomy	Died 9 months after resection
1989	Raute M	1	adenocarcinoma		
1989	Umehara Y	2	adenocarcinoma		
1995	Konno, H	1	adenocarcinoma	Lobectomy	NED at 4 years
1996	Piltz, S	1	adenocarcinoma		
1996	Urabe M	2	adenocarcinoma	Lobectomy/Wedge resection	1 patient died at 3y, 5mo, 1 patient alive at 3 years, 3 mo
1998	Kamiyoshihara, M	3	adenocarcinoma	Lobectomy/Wedge resection	Mean survival: 22 months, 67% 1 year survival
1998	Kanemitsu, Y	4	adenocarcinoma	Lobectomy	Mean survival 24.3 months
1998	Tsumatori G	5	adenocarcinoma		1 survivor > 5 years
2000	Tanaka T	1	adenocarcinoma	Lobectomy	
2001	Kobayashi, O	1	adenocarcinoma		
2001	Kobayashi, O	1	adenocarcinoma		
2002	Inage, Y	1	leiomyosarcoma	Lobectomy	
2002	Tamura M	4	adenocarcinoma		Mean survival: 13.8 months
2002	Inoue Y	1	adenocarcinoma	Lobectomy, Wedge resection	Alive 15 years after gastrectomy (7 years after first resection)
2004	Nakahashi, C	1	adenocarcinoma	Lobectomy, Wedge resection	Alive 7 years after initial gastric resection
2006	Tsuboshima, K	1	adenocarcinoma	Sternal resection/Wedge resection	NED at 8 months
2006	Takahiro, S	2	adenocarcinoma	Lobectomy/Wedge resection	
2007	Sakaguchi, K	7	adenocarcinoma	Lobectomy/Wedge resection	5 year OS: 42.9%
2007	Mikami K	2	adenocarcinoma		
2008	Nakayama H	1	adenocarcinoma	Lobectomy, Lobectomy	Died 65 months after first lung resection from CVA
	Total	**45**			

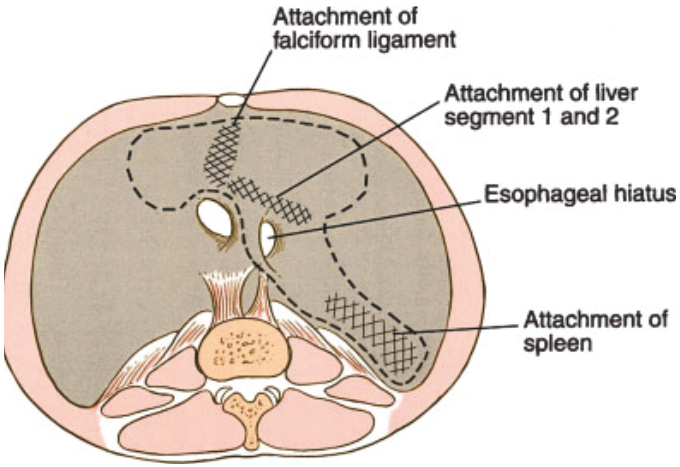
Figure 1: Tumor Cell Entrapment Hypothesis [37]

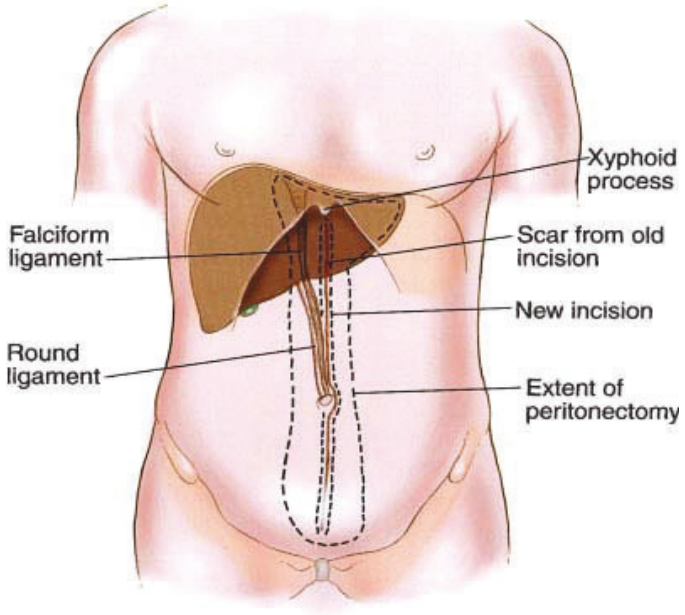


APPENDIX I

Partial peritonectomy for gastric cancer







Appendix 2

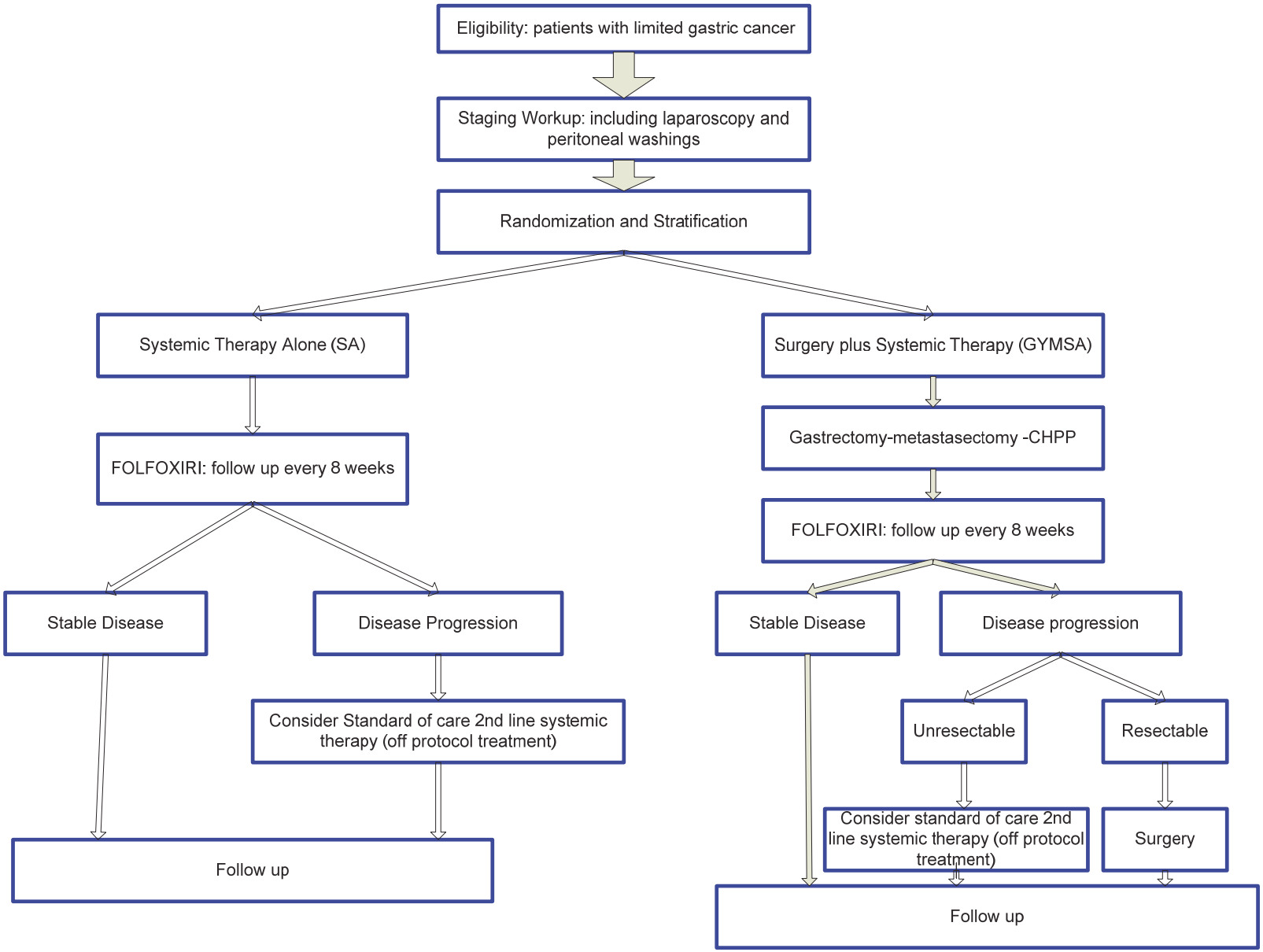
First-Line Regimens for *Helicobacter pylori* Eradication

Am J Gastroenterol. 2007;102(8):1808-1825.

Regimen	Duration	Eradication Rates	Comments
Standard dose PPI b.i.d. (esomeprazole is q.d.), clarithromycin 500 mg b.i.d., amoxicillin 1,000 mg b.i.d.	10–14	70–85%	Consider in nonpenicillin allergic patients who have not previously received a macrolide
Standard dose PPI b.i.d., clarithromycin 500 mg b.i.d. metronidazole 500 mg b.i.d.	10–14	70–85%	Consider in penicillin allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy
Bismuth subsalicylate 525 mg p.o. q.i.d. metronidazole 250 mg p.o. q.i.d., tetracycline 500 mg p.o. q.i.d., ranitidine 150 mg p.o. b.i.d. or standard dose PPI q.d. to b.i.d.	10–14	75–90%	Consider in penicillin allergic patients
PPI + amoxicillin 1 g b.i.d. followed by: PPI, clarithromycin 500 mg, tinidazole 500 mg b.i.d.	5 5	>90%	Requires validation in North America

PPI = proton pump inhibitor; pcn = penicillin; p.o. = orally; q.d. = daily; b.i.d. = twice daily; t.i.d. = three times daily; q.i.d. = four times daily.
*Standard dosages for PPIs are as follows:
lansoprazole 30 mg p.o., omeprazole 20 mg p.o., pantoprazole 40 mg p.o., rabeprazole 20 mg p.o., esomeprazole 40 mg p.o.
Note: the above recommended treatments are not all FDA approved. The FDA approved regimens are as follows:
1. Bismuth 525 mg q.i.d. + metronidazole 250 mg q.i.d. + tetracycline 500 mg q.i.d. × 2 wk + H_2RA as directed × 4 wk.
2. Lansoprazole 30 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
3. Omeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
4. esomeprazole 40 mg q.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 10 days.
5. Rabeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d. × 7 days.

Appendix 3
Trial Schema



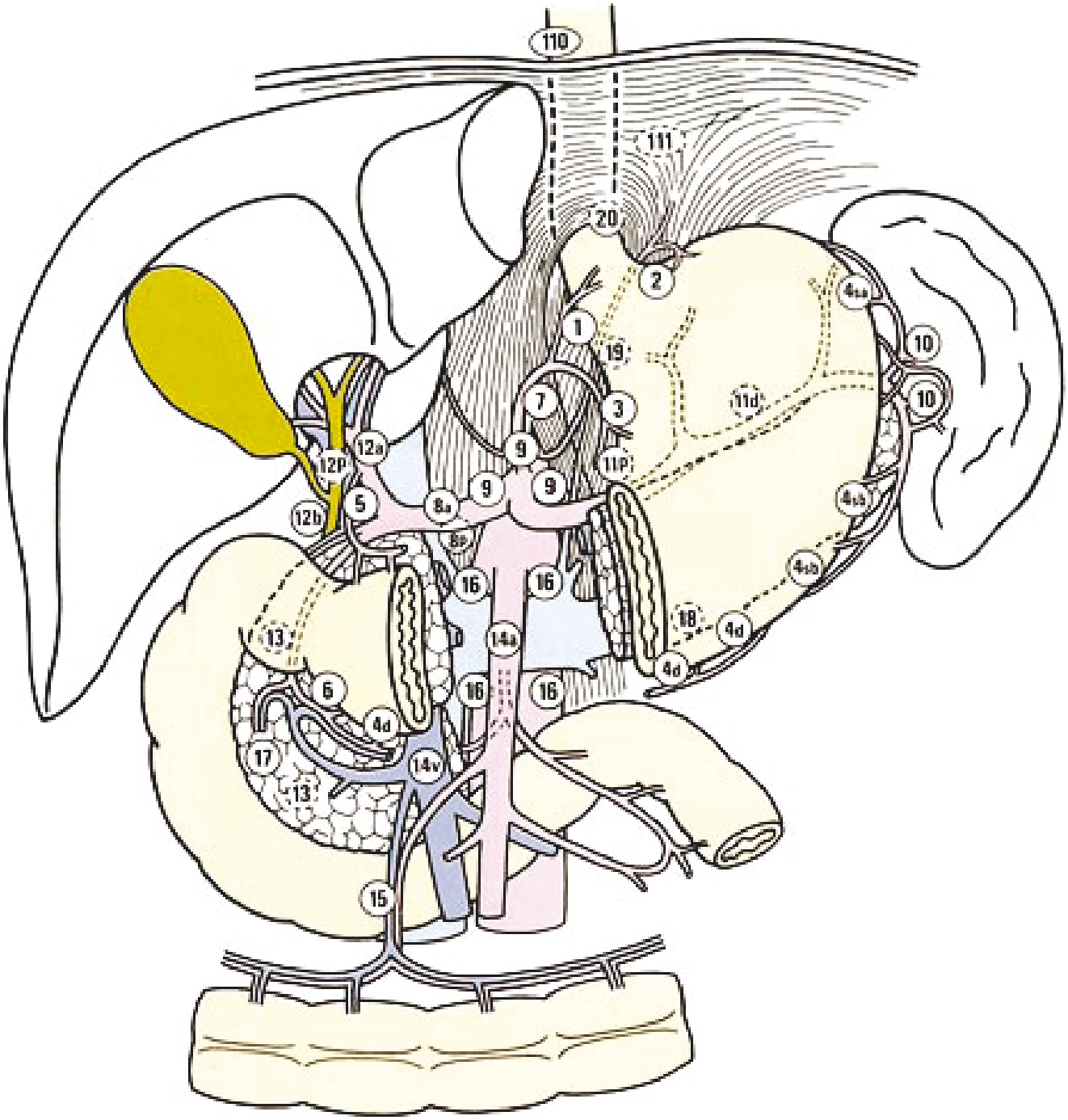
Appendix 4 Dose Modification FOLFOXIRI

event-grade	irinotecan	oxaliplatin	5FU
neutropenia**			
grade 1	maintain dose level	maintain dose level	maintain dose level
grade 2	maintain dose level	maintain dose level	maintain dose level
grade 3	maintain dose level	maintain dose level	maintain dose level
grade 4> 5 days	↓ 1 dose level	↓ 1 dose level	maintain dose level
febrile neutropenia grade 4	↓ 1 dose level	↓ 1 dose level	maintain dose level
thrombocytopenia**			
grade 1	maintain dose level	maintain dose level	maintain dose level
grade 2	maintain dose level	maintain dose level	maintain dose level
grade 3	↓ 1 dose level	↓ 1 dose level	maintain dose level
grade 4	↓ 1 dose level	↓ 1 dose level	maintain dose level
anemia			
grade 1	maintain dose level	maintain dose level	maintain dose level
grade 2	maintain dose level	maintain dose level	maintain dose level
grade 3	maintain dose level	maintain dose level	maintain dose level
grade 4	maintain dose level	maintain dose level	maintain dose level
diarrhea**			
2-3 stools/day > baseline	maintain dose level	maintain dose level	maintain dose level
4-6 stools/day > baseline	maintain dose level	maintain dose level	maintain dose level
7-9 stools/day > baseline	↓ 1 dose level	maintain dose level	↓ 1 dose level
≥ 10 stools/day > baseline	↓ 2 dose levels	maintain dose level	↓ 2 dose levels
mucositis/stomatitis**			
grade 1	maintain dose level	maintain dose level	maintain dose level
grade 2	maintain dose level	maintain dose level	maintain dose level
grade 3	maintain dose level	maintain dose level	↓ 1 dose level
grade 4	maintain dose level	maintain dose level	↓ 2 dose levels
hand foot syndrome			
grade 3-4	maintain dose level	maintain dose level	discontinue
other non-heme toxicities*&**			
grade 1	maintain dose level	maintain dose level	maintain dose level
grade 2	maintain dose level	maintain dose level	maintain dose level
grade 3	↓ 1 dose level	↓ 1 dose level	↓ 1 dose level
grade 4	↓ 2 dose levels	↓ 2 dose levels	↓ 2 dose levels
neuropathy			
grade 1: resolves - does not interfere with functioning	maintain dose level	maintain dose level	maintain dose level
grade 2: interferes with functioning but not daily activities and does **not** resolve	maintain dose level	maintain dose level	maintain dose level
grade 3: pain or functional impairment that interferes with daily activities	maintain dose level	discontinue	maintain dose level
grade 4: persistent impairment that is disabling or life-threatening.	maintain dose level	discontinue	maintain dose level

*excludes alopecia, anorexia, asthenia, lab toxicities

**The next dose should be delayed until: WBC >3000, neutrophils >1000 - platelets > 100,000

Appendix 5
Lymph Node Stations [78]



Regional lymph nodes

No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN

Appendix 6
Health Related Quality of Life forms - English
Appendix 6a
Health Related Quality of life forms - Spanish

Appendix 7
Sample Fax Cover Sheet and Patient Diary