RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-04

A PHASE II TRIAL OF PREOPERATIVE CHEMOTHERAPY AND CHEMORADIOThERAPY FOR POTENTIALLY RESECTABLE ADENOCARCINOMA OF THE STOMACH

Chairmen

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A PHASE II TRIAL OF PREOPERATIVE CHEMOTHERAPY AND CHEMORADIOThERAPY FOR POTENTIALLY RESECTABLE ADENOCARCINOMA OF THE STOMACH

SCHEMA

Treatment: (3/4/04, 4/30/04)

Preoperative Chemotherapy:  
All patients will first receive two courses of chemotherapy with the 5-FU/cisplatin/folinic acid (leucovorin) combination. 5-FU will be given at 200 mg/m²/d as continuous infusion by outpatient pump on days 1-21. Folinic acid will be given at 20mg/m² i.v. on days 1, 8, 15 and 22. Cisplatin will be given at 20 mg/m² as a one-hour bolus on days 1-5. Chemotherapy will be repeated beginning on Day 29. See Section 7.1.1.

Preoperative Chemoradiotherapy:  
At the end of the second 21 days of chemotherapy and one week of rest (day 57), a total of 45 Gy (1.8 Gy fx/d) of radiotherapy will be given with concurrent low-dose continuous infusion of 5-FU (300mg/m²/d Monday through Friday) by an outpatient portable pump and weekly Taxol 45mg/m² over 3 hours for 5 weeks.

Surgery:  
Four to five weeks after completion of chemoradiotherapy, all patients will be restaged and surgical resection of the primary tumor and lymph nodes (a D2 resection is encouraged) will be attempted. Peritoneal cytology will be obtained. The J-tube will be left in for at least 8 weeks after surgery to supplement patient’s nutrition.

Eligibility: (See Section 3.0 for details)
- Patients with potentially resectable adenocarcinoma of the stomach with histologic proof.
- EUS stage T2-3, any N, M0.
- Adequate bone marrow (defined as peripheral absolute granulocyte count of > 2,000/µL, and platelet count of >100,000/µL), liver (bilirubin ≤ 1.5 mg/dl), and renal functions (creatinine < 1.5 mg/dl).
- Absence of peritoneal disease by laparoscopic staging; no positive cytology of pleural, or pericardial effusion.
- No prior major surgery or radiotherapy to the stomach, or immunotherapy or chemotherapy for any reason.
- Patients must have a life expectancy of at least 16 weeks.
- Performance status of ≤ 2 (Zubrod scale).
- No biopsy proof of lymph node metastases outside the study field.
- No evidence of metastatic disease to distant organs.
- No presence of concurrent or previous malignancies ≤ 5 years, other than noninvasive skin cancer.
- No uncontrolled or severe cardiac disease, diabetes or hypertension.
- Signed study-specific consent form prior to study entry.

Required Sample Size: 49
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Does the patient have a potentially resectable adenocarcinoma of the stomach with histologic proof?</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>Is the tumor T2–3, M0?</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>Does the tumor involve the gastroesophageal junction?</td>
<td>Y/N</td>
</tr>
<tr>
<td></td>
<td>If yes, is the bulk of the tumor in the stomach?</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>Has the patient received prior RT or surgery to the stomach?</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>Does the patient have a life expectancy of at least 16 weeks and a performance status of ≤ 2 Zubrod scale?</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>Have the pretreatment evaluations been done within the time required in Section 4.0?</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>Does the patient have a jejunostomy?</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>Does the patient have adequate bone marrow, liver and renal function (granulocyte &gt;2,000 u/L, platelet &gt; 100,000/mL, bilirubin ≤ 1.5 mg/dl, creatinine &lt; 1.5 mg/dl)</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>Has the patient received prior immunotherapy or chemotherapy for any reason?</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>Does the patient have positive cytology of pleural or pericardial effusion?</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>Does the patient have peritoneal disease diagnosed by laparoscopy?</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>Does the patient have biopsy proof of lymph node metastasis outside the study field, such as supraclavicular, mediastinal, or para aortic nodes?</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>Does the patient have any evidence of metastatic disease to distant organs?</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>Does the patient suffer any intracurrent disease such as cardiac class III or IV, uncontrolled diabetes, hypertension, cerebrovascular disease, or infection that precludes him/her from entering the trial?</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>Does the patient have diabetic neuropathy?</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>Does the patient suffer abnormalities of mental status such that the patient can neither fully comprehend the therapeutic implications of the protocol or comply with the requirements?</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>Does the patient have a concurrent malignancy other than resected squamous or basal cell carcinoma of the skin?</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>Has the patient had a previous malignancy in the past 5 years (other than skin as per Question 17)?</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>Is the patient pregnant?</td>
<td>N/NA</td>
</tr>
</tbody>
</table>

(continued on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Medical Oncologist
17. Treatment Start Date

Completed by ___________________________    Date _______________________________
1.0 BACKGROUND

1.1 The Disease and Background

Carcinoma of the stomach continues to be a significant health problem around the world despite its continued decline since the Second World War. In the United States, it is estimated that nearly 21,900 new cases will be diagnosed in 1999 and approximately 13,500 patients will die as a result of gastric carcinoma.1 The incidence of proximal gastric carcinoma has risen in the past 15 years.2 It is estimated that only 50% of newly diagnosed patients with gastric carcinomas have only local-regional spread and the remainders have unresectable metastatic carcinoma.1 The cumulative 5-year survival rates of all patients with gastric carcinoma have changed only slightly over the past 4 decades but remain under 20%.3 The development of local-regional and distant metastases commonly results in death of patients.

The 'curative' surgical resection, which includes removal of all gross cancer, regional lymph node groups, and no cancer cells at the resection margins as determined by histopathologic examination, is the predominant method of potentially curing patients. However, curative resection is possible in < 40% of patients whose tumors are judged to be resectable by clinical staging.3 This indicates that newer strategies are necessary to improve the curative resection rate. The prognosis of patients who have undergone curative resection is dependent on the established prognostic factors including location of the primary, lymph node metastases, and depth of penetration.4,5 Curative resection has resulted in up to 30% 5-year survival rate and that for patients with proximal cancers is less than 10%.6-8 Unfortunately, these statistics have not improved with the use of adjuvant chemotherapy.9,12 Therefore, even under the best circumstances, only a minority of patients with local-regional gastric cancer can be cured with the most aggressive surgery.

1.2 Preoperative Chemotherapy (3/4/04)

The strategy of preoperative chemotherapy for patients with potentially resectable gastric carcinoma was first studied at MDACC in 1988.13 The rationale for preoperative treatment protocols is as follows: first, chemotherapy-induced reductions in tumor volume may increase the chances for curative resection; second, preoperative chemotherapy allows early targeting of systemic disease without the delays typically induced by surgery; third, preoperative chemotherapy allows a temporal window of assessment prior to surgery during which patients with disease progression while on therapy can be identified and spared a non-therapeutic laparotomy; and finally, preoperative chemotherapy represents an in vivo chemosensitivity test which may be utilized to determine the chances of benefit from continued treatment. Under such a strategy, non-responders avoid unnecessary toxicity.

Our first trial13 evaluated the use of preoperative etoposide, 5-FU, and cisplatin (EFP) in 25 consecutive patients. Eligibility criteria included biopsy-proven gastric adenocarcinoma, CT evidence of resectability, Zubrod performance status < 2, and normal hepatic and renal function. Patients were scheduled to receive two preoperative and 3 postoperative courses of EFP. Six patients (24%) had major clinical responses to EFP. Eighteen patients (72%) underwent potentially curative resection, and 3 resected specimens (12%) contained only microscopic foci of tumor. Minor responses were more common than major responses, and only one patient was observed to have progressive disease while receiving preoperative therapy. No complete pathologic responses were identified. Toxicities were acceptable, with no chemotherapy-related deaths and no surgical complications attributable to preoperative therapy. At a median follow-up of 25 months, median survival for the entire group of 25 patients was 15 months; median survival for resected patients has not yet been reached. Peritoneal carcinomatosis remained the dominant site of treatment failure.

In an attempt to identify a more effective preoperative regimen that might result in a 5-10% rate of complete pathologic response, a joint study (M.D. Anderson/Dana-Farber) was conducted.14 In the EAP regimen previously reported by Wilke, et al.15, forty-eight previously untreated patients with resectable gastric adenocarcinoma received three cycles of preoperative EAP, with responders receiving an additional two cycles postoperatively. Six patients (12%) were judged to have a complete clinical response to preoperative EAP, while nine (19%) had a partial response. Among 41 patients taken to surgery, 37 underwent a potentially curative resection. No complete pathologic responses were identified. Substantial toxicities were observed, with dose reductions required in 37 patients (77%), and hospitalization required in 19 patients (40%). At a median follow-up of 16 months, actuarial median survival was 15 months.

Other groups have reported the use of less toxic preoperative chemotherapy regimens in patients with locally advanced disease felt not likely to be rendered disease-free by surgery alone. Pfukker et al16 reported 20 patients with stage IIIB or IV disease treated with four cycles of high-dose methotrexate and 5-FU; among 17 patients completing all four cycles of preoperative chemotherapy, 14 were ultimately taken to surgery. Eight patients (40%) were reported to demonstrate a response to preoperative chemotherapy allowing for subsequent surgical resection. For the entire group, two patients (10%) remained alive at 54 and 41 months with no evidence of disease. Among patients failing after resection, five died with local-
The current study demonstrates that the degree of response to preoperative therapy strongly correlates with survival. Analysis of the outcomes of 83 patients treated preoperatively with either EFP, EAP, or CFI, shows that the majority of patients in each group awaits phase III trials, the response to preoperative chemotherapy does appear to predict for possible survival advantage in patients with gastric adenocarcinoma. Alexander and co-workers from the National Cancer Institute have also reported a protocol utilizing preoperative chemotherapy in patients with locally advanced disease. Their regimen involved three preoperative cycles of 5-FU, leucovorin (folinic acid), and interferon alpha-2a in patients with T3-4, N1-2, M0 gastric adenocarcinoma. In this phase II trial, an overall response rate of 46% and acceptable toxicity were reported; treatment-limiting toxicity was most frequently encountered when preoperative chemotherapy was extended to four cycles. Formal response, toxicity, and survival data from a phase II trial have not yet been reported.

Two centers have reported the use of preoperative chemotherapy combined with adjuvant intraperitoneal 5-FU and cisplatin. In a series from the Memorial Sloan-Kettering Cancer Center, 29 patients staged as T3-4, M0 by endoscopic ultrasound received three cycles of preoperative 5-FU, doxorubicin, and methotrexate (FAMTX) followed by surgery. Postoperatively, intraperitoneal 5-FU and CDDP were delivered in combination with continuous infusion systemic 5-FU. Using the pre-FAMTX endoscopic ultrasound to determine initial stage, 33% of patients ultimately undergoing resection showed evidence of pathologic downstaging in response to preoperative chemotherapy. Survival analysis awaits long-term follow-up.

Similarly, a series of 38 patients receiving preoperative systemic chemotherapy and postoperative intraperitoneal chemotherapy was reported from the University of Southern California. Patients were treated with preoperative continuous infusion 5-FU (200 mg/m²/day) for three weeks with weekly I.V. leucovorin (20 mg/m²) and cisplatin (100 mg/m² on days 1 and 29). Two cycles of chemotherapy were delivered prior to surgery. Among patients resected of all gross disease with negative margins, postoperative intraperitoneal chemotherapy with floxuridine and cisplatin was additionally delivered. Preoperative chemotherapy was associated with a 45% objective response rate as determined by CT scan; 60% of resected surgical specimens showed evidence of cellular damage attributed to preoperative chemotherapy. Three patients (8%) demonstrated a complete pathologic response, (no evidence of tumor in the resected specimen); all three patients had intestinal-type tumors of the body or distal stomach identified on pre-treatment biopsy. At the time of publication, the median survival for all patients had not been reached at a median follow-up of 17 months.

The recently completed preoperative protocol at M.D. Anderson Cancer Center, utilized several new strategies including: (a) staging laparoscopy, (b) staging endoscopic ultrasonography, (c) use of all chemotherapy prior to surgery and no planned postoperative therapy. Eligible patients received preoperative cisplatin, 5-FU, and interferon-alpha (CFI). Patients with gross peritoneal disease were not eligible for this study. Our strategy included enhanced staging (laparoscopy in all and endosonography when feasible), and up to five courses of CT (based on objective responses) with 5-FU (500 mg/m²/d as cont. inf. on d 1-5 and as bolus on d 12 and 19), Intron (3 milU s.c. 3 x/wk x 3 wks) & cisplatin (15 mg/m²/d as bolus on d 1-5). CFI was repeated every 28 d as in-patient or outpatient. Following CFI, patients were restaged and taken to surgery. Thirty patients were enrolled. Nineteen patients were enrolled. Seventeen patients were men and 11 were women; median age was 56 years (range, 33-75 years); all had a PS of 1; 63% had proximal tumors; 14 patients received all 5 courses of CFI, 10 received 3, and the total number of courses was 108. All patients were evaluated. Seven (23%) had clinical CR, five (17%) had PR, five had NC, and four had PD. Cancer became clinically unresectable in one patient and one is yet to have surgery. Thus 28 (97% of 29) had surgery; 23 (79%) had a curative resection. Two patients had a path CR and one had 99% necrosis. At a median follow-up of 16+ months (range, 5+ months to 32+ months), 22 (73%) patients are alive. Myelosuppression, myalgia, diarrhea, and mucositis were frequent but grade 3 or 4 non-hematologic toxicity was rare. No death occurred due to CFI or surgery. In conclusion, CFI is quite active in this stage of the disease.

Analysis of the outcomes of 83 patients treated preoperatively with either EFP, EAP, or CFI, demonstrates that the degree of response to preoperative therapy strongly correlates with survival. Sixty-one of the 83 (73%) patients had a curative resection. Twenty-four of 61 patients (29%) demonstrated major (complete or partial) responses to preoperative therapy. For these patients, actuarial five-year survival is 82%, vs. 32% for patients with lesser or no response. While demonstration of a survival benefit for the overall group awaits phase III trials, the response to preoperative chemotherapy does appear to predict for possible survival advantage in patients with gastric adenocarcinoma.

The current study (pilot # 4) at M. D. Anderson Cancer Center is examining the feasibility and value of preoperative chemoradiotherapy. All patients undergo laparoscopic staging in addition to routine staging and then receive continuous infusion 5-FU with XRT (45 Gy). Nineteen patients have been enrolled on this trial. Fifteen patients have had surgery; two patients had unresectable (metastatic) disease. Two patients had no malignant cells in the surgical specimen. One patient died post-operatively. These early data
suggest that preoperative chemo-radiotherapy in patients with local-regional gastric carcinoma is feasible and should be further explored in conjunction with systemic chemotherapy.

In the most recent study (a multi-institutional pilot: #5), we used chemotherapy first with 5-FU/cisplatin/folinic acid. This was followed by chemoradiotherapy (45 Gy and continuous infusion of 5-fluorouracil) and surgery. At this time, nearly 30 patients (targeted accrual is 34 patients) have been accrued. Among 16 patients taken to surgery, seven had a pathCR and 2 patients had >90% necrosis of the tumor. The tolerance has been acceptable with mild to moderate toxicity and one postoperative death (>60 days following surgery).

1.3 Role of Radiotherapy

Irradiation alone given postoperatively in patients with curatively resected tumors at high risk of relapse, has reduced local recurrences but has not had any impact on survival.22 Data from single institution phase II and small phase III studies suggest that combined modality adjuvant therapy may have a positive outcome in terms of local control and survival.

Relapses in the tumor bed, regional nodes, peritoneal cavity or distantly are common after a curative resection in clinical23,24, reoperative25, and autopsy studies.26-28 For lesions at the GE junction, lung, liver, and bone are the common sites of failure. The studies reporting patterns of failure suggest that the development of an effective therapy for local-regional disease as an adjuvant to surgery could potentially benefit at least 20% of patients. Effective systemic chemotherapy is also essential to improve the outcome for this group of patients. Innovative combined modality approaches will be required in order to improve survival with acceptable morbidity. Here we propose a strategy that incorporates preoperative chemotherapy and preoperative chemoradiotherapy.

Experience with chemoradiotherapy of the stomach is limited. This approach, however, has been reported in other gastrointestinal sites such as in the esophagus and pancreas. Algan et al.29 from Fox Chase Cancer Center have treated 24 patients with adenocarcinoma of the esophagus or GE junction with preoperative 60 Gy of radiotherapy concurrent with infusional 5-FU (1,000 mg/m²/d x 4) on weeks one and five, and mitomycin 10mg/m² on day two. One third of the resected patients had a complete pathologic response. Forty percent of patients had grade III or IV acute toxicity. Surgical complications were minor. Preoperative chemoradiotherapy has also been used in patients with local-regional carcinoma of the pancreas which involved many structures to be treated in this gastric study. Coia et al.30 and Evans et al.31 have reported programs using preoperative chemoradiotherapy in patients with carcinoma of the pancreas. There was only one perioperative death suggesting that operative mortality does not significantly change.

1.4 Rationale For This Protocol

Patients with localized gastric cancer often relapse either locally or systemically. A strategy to reduce relapses at common sites would be beneficial. Our prior trial has yielded intriguing results (particularly, the rate of pathCR). Thus, it would be important to improve the treatment with the addition of Taxol, which is an active agent in gastric carcinoma and has also been found effective as a radioenhancing agent. Weekly Taxol has been studied in patients with local-regional gastric carcinoma and continuous infusion of 5-FU and Taxol (and cisplatin) with radiotherapy has also been studied in patients with GE junction and esophageal carcinoma. It is our belief that increased morbidity is likely when cisplatin is combined with other agents during radiotherapy. We have demonstrated safety of low-dose continuous infusion 5-FU and concurrent radiotherapy. Thus, we believe, based on the data shown below, addition of lower doses of weekly Taxol to continuous infusion of 5-FU with concurrent radiotherapy should be much less toxic than the studies that combined cisplatin as well.

1.4.1 Weekly Taxol Chemoradiation in Localized Gastric or Esophageal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>Chemotherapy</th>
<th>Radiation</th>
<th>Toxicity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safran32</td>
<td>27% Squamous</td>
<td>Taxol 60 mg/m²</td>
<td>40 Gy/22 fx</td>
<td>Neutropenia 26%</td>
<td>CR: 26%</td>
</tr>
<tr>
<td></td>
<td>73% Adeno</td>
<td>(3 hr) D1,8,15,22</td>
<td></td>
<td>Infection 10%</td>
<td>PR: 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 25 mg/m²</td>
<td></td>
<td>Vomiting 16%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1, 8, 15, 22</td>
<td></td>
<td>Esophagitis 9%</td>
<td></td>
</tr>
<tr>
<td>Kelsen33</td>
<td>42% Squamous</td>
<td>Taxol over 96 hr weekly</td>
<td>50.4 Gy/30 fx</td>
<td>Skin 8%</td>
<td>CR: 33%</td>
</tr>
<tr>
<td></td>
<td>58% Adeno</td>
<td>10 mg/m², 20 mg/m²</td>
<td></td>
<td>Neutropenia 17%</td>
<td>PR: 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/m², 40 mg/m²</td>
<td></td>
<td>Fever 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 30 mg/m²/wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safran34</td>
<td>43% Squamous</td>
<td>Taxol 60 mg/m² (3 hr)</td>
<td>40 Gy</td>
<td>G3/4 toxicities 43%</td>
<td>CR: 9%</td>
</tr>
<tr>
<td></td>
<td>57% Adeno</td>
<td>D1,8,15,22</td>
<td></td>
<td>Neutropenia 29%</td>
<td>PR: 64%</td>
</tr>
</tbody>
</table>
Weiner\textsuperscript{35} 12% Squamous
88% Adeno  Taxol (1 hr) 25 mg/m\textsuperscript{2}, 40 mg/m\textsuperscript{2} OR Taxol 50 mg/m\textsuperscript{2} 5-FU 200 mg/m\textsuperscript{2} CI Cisplatin 25 mg/m\textsuperscript{2} 60 Gy/30 fx Mucositis 28% Neutropenia 4% Diarrhea 16% Bacteremia 12%

Safran\textsuperscript{36}  Taxol over 3 hr weekly 30 mg/m\textsuperscript{2}, 40 mg/m\textsuperscript{2} 50 Gy Abd pain 33% Nausea 50% PR: 70%

1.4.2  Non-Weekly Taxol Chemoradiation for Localized Esophageal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>Chemotherapy</th>
<th>Radiation</th>
<th>Toxicity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meluch\textsuperscript{37}</td>
<td>30% Squamous 70% Adeno</td>
<td>Taxol 200 mg/m\textsuperscript{2} D1, 22 Carboplatin AUC 6 D1, 22 5-FU 225 mg/m\textsuperscript{2}/d CI D1-42</td>
<td>45 Gy/25 fx</td>
<td>Esophagitis 28% Neutropenia 56% Febrile neut. 18%</td>
<td>CR: 50% PR: 31%</td>
</tr>
<tr>
<td>Nesbitt\textsuperscript{38}</td>
<td>16% Squamous 84% Adeno</td>
<td>Taxol 200 mg/m\textsuperscript{2} D1 and 29 Cisplatin 15 mg/m\textsuperscript{2} D1-5 and 29-34 5-FU 750 mg/m\textsuperscript{2}/d CI D1-5 and 29-34</td>
<td>45 Gy/25 fx with 5-FU 300 mg/m\textsuperscript{2} M-F Cisplatin 20mg/m\textsuperscript{2} D1-5</td>
<td>G4 toxicities 17%</td>
<td>CR: 50% PR: 20%</td>
</tr>
<tr>
<td>Hains\textsuperscript{39}</td>
<td>41% Squamous 59% Adeno</td>
<td>Taxol 200 mg/m\textsuperscript{2} D1,21 Carboplatin AUC 6 D1,21 5-FU 225 mg/m\textsuperscript{2}/d CI D1-42</td>
<td>45 Gy/25 fx</td>
<td>Neutropenia 66% Esophagitis 38%</td>
<td>CR: 69% PR: 15%</td>
</tr>
</tbody>
</table>

2.0  OBJECTIVES
2.1  To determine the feasibility of preoperative chemoradiotherapy for patients with potentially resectable adenocarcinoma of the stomach.
2.2  To determine the pathologic response rate, curative resection rate, survival, and tolerance of this strategy.

3.0  PATIENT ELIGIBILITY
3.1  Eligibility Criteria
3.1.1  Patients with potentially resectable adenocarcinoma of the stomach with histologic proof of adenocarcinoma, clinically staged T2-3, any N, M0. Gastric carcinoma may involve the gastroesophageal junction, however, the bulk of the tumor must be in the stomach (defined by radiographs, endoscopy, or endoscopic ultrasonography).
3.1.2  No prior surgery or radiation therapy to the stomach or immunotherapy or chemotherapy for any reason.
3.1.3  Patients must have a life expectancy of at least 16 weeks and a performance status of $\leq$ 2 Zubrod scale (Appendix II).
3.1.4 Patients must have adequate bone marrow function (defined as peripheral absolute granulocyte count of > 2,000/µL, and platelet count of > 100,000/µL), adequate liver function (bilirubin \( \leq \) 1.5 mg/dl), and adequate renal function (creatinine < 1.5 mg/dl).

3.1.5 Pretreatment evaluations must be done per the guidelines in Section 4.0.

3.1.6 A feeding jejunostomy must be inserted in all patients.

3.1.7 Patient must sign an informed consent prior to study entry.

3.2 Ineligibility Criteria

3.2.1 Patients with T1N0 carcinoma documented by endoscopic ultrasonography.

3.2.2 Positive cytology of pleural, or pericardial effusion or patients with any peritoneal disease diagnosed by laparoscopy.

3.2.3 Biopsy proof of lymph node metastases outside the study field such as supraclavicular, mediastinal, or para-aortic nodes.

3.2.4 Evidence of metastatic disease to distant organs (biopsy is suggested for questionable findings).

3.2.5 Patients with cardiac disease graded as New York Heart Association Class III or IV, severe uncontrolled diabetes, hypertension, cerebrovascular disease, or infection.

3.2.6 Patients with diabetic neuropathy.

3.2.7 Abnormalities of mental status such that either the patient cannot fully comprehend the therapeutic implications of the protocol or comply with the requirements.

3.2.8 Presence of concurrent or previous malignancies in the past 5 years (except for resected squamous or basal cell carcinoma of the skin).

3.2.9 Pregnant women are excluded from study entry due to the teratogenic effects of the study treatment.

4.0 PRETREATMENT EVALUATIONS

The following items are mandatory before patient can be treated on this study:

4.1 A complete history and physical, including documentation of signs and symptoms, weight loss, and performance status shall be necessary.

4.2 Laboratory studies shall include a CBC, platelet count, differential count, urinalysis, electrocardiogram, chemical profile with liver and renal functions, electrolytes, magnesium, and CEA. All laboratory studies must be performed within 14 days prior to registration.

4.3 Radiologic studies including barium study of the upper gastrointestinal tract, Chest X-ray, CT scan of the abdomen and pelvis (chest if warranted) will be performed on all patients. All radiographic studies must be performed within 28 days prior to registration.

4.4 Upper GI endoscopy and routine EUS (endoscopic ultrasonound), will be performed in all patients. Data on T stage (\( \geq T2 \)) and N stage will be collected and subsequently correlated with surgical pathology.

4.5 Laparoscopy and peritoneal staging will be performed. This should involve a port for the laparoscope and one or two ports for organ manipulation and evaluation. All visible peritoneal surfaces should be evaluated, along with inspection of the liver, lesser sac through the lesser omentum and the ligament of Treitz and porta hepatitis for evidence of N3 nodal disease. Any suspicious peritoneal nodules distinct from the primary tumor should be biopsied. A specimen may be stored for additional future studies. It is encouraged to have surgical clips placed around the tumor during laparoscopy for accurate field definition for radiotherapy.

4.6 Studies necessary to assess the surgical risk will be obtained.

4.7 Use the following general planning guidelines for therapy:

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Step No.</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed local-regional cancer</td>
<td>1</td>
<td>Clinical staging and endoscopic ultrasound</td>
</tr>
<tr>
<td>Nonmetastatic cancer</td>
<td>2</td>
<td>Laparoscopy and peritoneal staging. Place J-tube</td>
</tr>
<tr>
<td>No peritoneal cancer and eligibility criteria fulfilled</td>
<td>3</td>
<td>Get consent, register and start preoperative chemotherapy (x 2)</td>
</tr>
<tr>
<td>Completed preoperative chemotherapy</td>
<td>4</td>
<td>Preoperative chemoradiotherapy</td>
</tr>
<tr>
<td>Completed preoperative chemoradiotherapy</td>
<td>4</td>
<td>Rest 4-5 weeks then proceed with preoperative work-up</td>
</tr>
<tr>
<td>Non-metastatic cancer</td>
<td>5</td>
<td>Attempt surgery</td>
</tr>
<tr>
<td>Completed all therapy</td>
<td>6</td>
<td>Follow-up for 5 years or until death.</td>
</tr>
</tbody>
</table>
5.0  REGISTRATION PROCEDURES

5.1  Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered and a case number will be assigned and confirmed by mail. The following information must be provided:

-  Institution Name & Number
-  Patient's Name & ID Number
-  Verifying Physician's Name
-  Medical Oncologist's Name
-  Eligibility Criteria Information
-  Demographic Data
-  Treatment Start Date

6.0  EXTERNAL BEAM RADIOTHERAPY

6.1  General Irradiation Information

The intent of treatment is to deliver 45 Gy in 1.8 fractions, to the entire stomach and draining lymph nodes. The radiotherapy should begin 4 weeks post chemotherapy. Localization and portal verification films of initial fields will demonstrate the use of contrast media and blocking.

6.1.1  Equipment: Isocentric teletherapy units with minimum photon energies of 6 MV (preferably ≥ 10 MV) and a source-axis distance of 100 cm or greater are required.

6.1.2  Treatment Delay: External beam radiation therapy (EBRT) and concomitant chemotherapy infusion should begin 4 weeks after the last course of chemotherapy. However, prior to beginning EBRT, patient’s blood counts need to have recovered to ≥ 1,500 absolute granulocyte counts and platelets ≥ 100,000. Caloric intake should be ≥ 1,200 kilo-calories/d and general health should be sufficient to allow initiation of EBRT + chemotherapy. If patients fail to meet these criteria, EBRT + chemotherapy may be deferred for 2 weeks. If further delay is deemed necessary by the treating physicians, the study chairman should be called.

6.1.3  Technique: AP-PA - The gastric fundus, in a significant minority, extends too far posteriorly to routinely use lateral portals to spare spinal cord or kidney as in pancreatic or biliary lesions. Parallel opposed AP:PA portals are, therefore, the most practical field arrangement for most patients and are therefore recommended. Tightly contoured fields are used to spare as much bone marrow, small bowel, liver, and kidney as possible. Occasionally, patients may have pre-treatment CT or barium swallow definition of stomach (with a cross table lateral film) which demonstrates that the stomach is sufficiently anterior to allow treatment via laterals to the stomach and draining lymph nodes with 1.5-2.0 cm margin while sparing spinal cord. Patients with such pre-treatment demonstration of anterior target volume location may have more liberal use of laterals with multifeild techniques usually 4-field (AP:PA:opposed laterals). Patients without anteriorly located target volume should usually receive lateral field treatments only to the dose necessary to limit spinal cord dosage to 45 Gy.

6.1.4  Treatment Volume: The treatment volume will require some individualization. However, pre-treatment diagnostic studies (UGI, CT scan), clip placement (at laparoscopy; optional) should be used liberally to identify the stomach and pertinent nodal groups.

6.1.5  Tumor-Nodal Field: AP:PA - The tumor-nodal field described below receives 45 Gy; 1.8 Gy/d. The tumor-nodal field should include the entire stomach (plus perigastric extension) and major nodal chains. The tumor bed includes the entire stomach (in all patients) plus the perigastric local tumor extension in T3 primary tumors. The ports should be superimposed on the limiting organs of tolerance. Such idealized ports should be modified dependent on initial extent of disease. With accurate field definition, aided by clip placement in the splenic hilum and porta hepatitis, 1/2 to 2/3 of the left kidney can be spared in many patients, and inclusion of the porta hepatis and retroduodenal nodal areas may include only a minor portion of the right kidney. Target volume will include the tumor (stomach plus perigastric tumor extension) and draining lymph nodes in all cases. Nodal areas at risk include: the gastric and gastroepiploic, celiac, porta hepatitis, subpyloric, gastroduodenal, splenic-suprapancreatic, and retropancreaticoduodenal nodes. The splenic hilum, porta hepatitis, and usually celiac track can be identified on CT scan. The celiac axis will usually arise at approximately T12-L1 level. The porta hepatis nodes are ordinarily encompassed by a field 2cm to the right of the T11-L1 vertebral bodies, however, the lateral and cephalocaudal location can be quite variable and should be determined from CT scans. The remaining branches of the celiac axis are treated by a field including the stomach and the medial portion of the duodenal C loop. The C loop of the duodenum usually extends to the lower margin of L3. The following situations require special consideration.
6.1.6 **Extension Through Wall:** For proximal T3 lesions the medial 2/3-3/4 of the left hemidiaphragm should be included as target volume with 1.5 cm margins. If the lesion is confined to the gastric wall or is distal, left hemidiaphragm treatment is not necessary.

6.1.7 **Proximal Lesions Involving the Cardia or Gastroesophageal Junction:** The paraesophageal nodes are at risk and should be included in the target volume. A 5-cm margin of esophagus should be included in the cephalad field margin.

6.1.8 **Distal Lesion at or Near Gastroduodenal Junction:** A ≥ 5-cm margin of duodenum should be included if the gross lesion extends to the gastroduodenal junction as defined on endoscopy, UGI radiographs, or CT.

6.2 **Simulation**

6.2.1 Simulation is required for all patients and should be performed with the patient in the supine position. Simulation must be performed on a diagnostic quality radiation therapy simulator, which reproduces the geometry of the treatment machine. All patients are to be treated isocentrically. The maximum accepted field size is 400 cm² (i.e., 20 x 20 cm or the equivalent). Every attempt should be made to decrease actual volume to 225 cm² (15 x 15 cm or equivalent thereof).

6.2.2 **Initial Treatment Field Definition:** Prior to contrast and simulation, all pertinent radiographs, operative notes (if laparoscopy is done), and other diagnostic procedures should be reviewed. This will allow an informed determination of treatment volume and field borders prior to simulation. These field borders are then set after appropriate patient positioning during fluoroecopy.

6.2.3 **AP:PA Initial Field Borders:** In general:
- **Superior Border** - will be at the T8, T9, or T9, T10 interspace (to treat the celiac axis, gastroesophageal junction, gastric fundus, and dome of diaphragm).
- **Inferior Border** - the L3-L4 interspace (to cover the gastroduodenal nodes and gastric antrum).
- **Right Margin** - will be 3-4 cm lateral to the vertebral body (to encompass the porta hepatis, gastric antrum, mediad duodenal wall, and gastroduodenal nodes). If the distal stomach is involved the entire circumference of duodenum should be included in the field for > 5 cm beyond gross disease.
- **Left Margin** - sufficiently lateral to include 2/3 - 3/4 of the left hemidiaphragm (to include the gastric fundus, splenic and suprapancreatic nodes, and left hemidiaphragm in proximal T3 lesions). These borders may be modified based on pre-treatment imaging, laparoscopy descriptions, clip placement and post-laparoscopic imaging information of the tumor and nodal site location.

6.2.4 **Lateral Field Borders:** The borders of the lateral fields are usually as follows:
- **Superior and Inferior Margin:** Identical to the AP:PA field;
- **Posterior Margin:** Posterior enough to treat at least 1/2 -2/3 of the vertebral bodies along the entire length of the field while sparing spinal cord. Almost always, the superior portion of the field will require the most posterior coverage; in view of the posterior location of suprapancreatic and splenic hilar nodes and gastric fundus, the lateral fields may need to be obliqued slightly to spare the spinal cord.
- **Anterior margin:** The stomach extends anteriorly to the anterior abdominal wall in most patients. Therefore, the anterior abdominal wall is the appropriate anterior border for the majority. These borders will require individualization according to Section 6.1.3.

6.2.5 Radiographs are then obtained for AP:PA and lateral fields prior to Step 2. Appropriate skin localization marks are made on the patient to ensure that patient positioning will be identical in Steps 2 and 3 as during Step 1.

6.2.6 **Kidney Volume Definition - Intravenous Pyelogram (IVP):** After Step 1, radiographs are obtained and localizing skin marks placed, definition of kidney volumes is determined. 50-60 ml of intravenous contrast is injected. The patient is then repositioned identically to Step 1 utilizing the skin localization points already placed. Field borders are set up so that the identical treatment volume produced in Step 1 is achieved. When satisfactory volume of contrast accumulates in the nephrogram phase. AP:PA and lateral field radiographs are filmed. Patients with contrast allergies will require kidney volume definition based on interpolation of CT scans.

6.2.7 Definition of stomach and duodenum: Oral contrast. After Steps 1 and 2, the patient drinks oral contrast (barium or gastrograffin +/- esophagast) in order to document the position of the stomach, distal esophagus, and duodenum. Radiographs are again obtained for the AP:PA and lateral fields as in Steps 1 and 2.

6.3 **Blocking:** Custom blocking is necessary to reduce unnecessary dose to normal structures including liver, lung, small bowel, kidneys, and heart. Special attention should be given to renal and cardiac shielding (vide infra).

6.3.1 **Renal Shielding:** In most patients, a portion of both kidneys is within the treatment field and one should, therefore, shield at least 2/3 of one kidney. For proximal gastric lesions, at least 1/2 of left kidney is usually within the EBRT portal and the right kidney must be appropriately spared. For distal lesions with
duodenal inclusion, a similar amount of right kidney is often included and then every effort should be made to spare enough left kidney.

6.3.2 **Cardiac Shielding:** With proximal gastric lesions or lesions at the esophagogastric junction, inclusion of a 3-5 cm margin of distal esophagus is indicated as well as inclusion of a major portion of the left hemidiaphragm when a lesion extends through the entire alimentary wall. In these circumstances, blocks should be used to decrease the amount of heart within the field. When lesions involve distal esophagus and AP: PA fields include excess heart; lateral fields can be very useful in decreasing cardiac volume.

6.4 **Dose - Time Factors**

6.4.1 The specification of the target dose is in terms of a dose to a point at or near the center of the target volume. The following portal arrangements are specified for photon beams:

6.4.2 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.4.3 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
6.4.4 For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
6.4.5 Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).

6.4.6 At least two fields per day will be treated.
6.4.7 Central axis isodose distributions are mandatory.
6.4.8 Isodose distributions should have no more than +/- 10% dose variation within the target volume.

6.5 **Dose Limiting Structures**

6.5.1 The spinal cord dose must not exceed 45 Gy.
6.5.2 The cardiac silhouette must not have greater than 30% of its area exposed to a dose of 40Gy.
6.5.3 At least 2/3 of one functioning kidney should receive a dose < 20 Gy.
6.5.4 The liver must not have more than 60% of its volume exposed to more than 30 Gy.

6.6 **Radiation Checklist (3/4/04)**

6.6.1 During irradiation, patients are seen for status check at least once a week with notation of tolerance, weight, and blood counts. Blood counts are obtained weekly to minimize the chance of continuing irradiation during unacceptable nadir counts. If the absolute granulocyte falls below 1,000 or the platelet count falls below 50,000 during the course of radiation therapy, treatment should be delayed until the counts rise above these levels.

6.6.2 Port films will be taken of each field at the initiation of treatment and at least every other week during treatment.

6.6.3 **Supportive Therapy:** If estimated caloric intake is less than 1200 kilo-calories or if weight loss is ≥ 5% of pretreatment weight, oral, enteral and/or intravenous hyperalimentation should be considered. Refer to Section 9 for Nutritional Therapy.

6.6.4 **Ancillary Treatment:** The physician in charge of the patient may prescribe any non-chemotherapeutic agent as necessary or advisable. Prophylactic medication to inhibit peptic ulceration, antiemetics, and anti-diarrheal agents are allowed.

6.6.5 **Treatment Interruptions or Modifications:**

Treatment Interruptions: Therapy interruptions will usually not be necessary. Interruptions may be kept to a minimum by the use of ancillary therapy and vigorous nutritional support. Interruptions are permitted only on the basis of toxicity. Therapy may be interrupted for absolute granulocyte counts ≤ 1,000; platelet count ≤ 50,000; vomiting ≥ 3/d unresponsive to antiemetics; diarrhea ≥ 5 watery stools/day unresponsive to antidiarrheals; or weight loss ≥ 10% of pretreatment weight. Rarely, nontreatment related or unexpected toxicities may require interruption of therapy at the discretion of the treating oncologist. Interruption of therapy may continue until the toxicity has resolved sufficiently to allow resumption of therapy. Every effort should be made to limit treatment interruptions to 1-2 weeks.

6.7 **Dose Modifications**

Every effort must be made to deliver the full 45 Gy to all patients. Toxicity may be encountered that is sufficiently severe to require treatment interruption. Once the toxicity has resolved, the patient’s therapy should resume and full protocol dose delivered. The toxicity, which forced any dose reduction, must be documented.

7.0 **CHEMOTHERAPY**

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 **Preoperative Chemotherapy (3/4/04)**

7.1.1 **Schedule:** Venous access (long line, subclavian catheter, or implantable device) will be established in all patients. Patients will receive up to two courses of chemotherapy prior to chemoradiotherapy depending on response. Outpatient administration of chemotherapy is encouraged. Chemotherapy schedule will be as follows:
Drugs  | Daily Dose  | Schedule  | On days  
--- | --- | --- | ---  
5-FU  | 200 mg/m²  | 24-hour continuous infusion by a portable pump  | 1-21  
Cisplatin  | 20 mg/m²  | 1-hour bolus  | 1-5  
Folinic acid (leucovorin)  | 20 mg/m²  | i.v. in 15 min or less  | 1,8,15, and 22  

Subsequent doses of 5-FU and cisplatin may be decreased by 20% based on toxicity experienced during the preceding course; however, none of the drug doses may be increased once a dose reduction has been made.

Adequate hydration, electrolyte supplementation, and antiemetic support will be provided when administering cisplatin. Patients will receive at least 1.5 liters i.v. of 1/2 NS with magnesium and potassium supplements, as indicated, on all cisplatin days. All patients will be encouraged to drink at least 2L of fluid daily.

The second course will be repeated on day 29 provided the patient has recovered from all toxicities and peripheral counts (absolute granulocyte count \( \geq 1,500/\mu L \) and platelet counts \( \geq 100,000/\mu L \)) are adequate.

The following decision guidelines will be used for recommending the next step after patients start chemotherapy (see Section 11.0 regarding studies to obtain during treatment):

<table>
<thead>
<tr>
<th>Event</th>
<th>Action To Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local progression, when about to start the second course of chemotherapy (Upper GI barium study or upper GI endoscopy)</td>
<td>Proceed to chemoradiotherapy</td>
</tr>
<tr>
<td>Stable or response to the first course of chemotherapy</td>
<td>Administer the second course</td>
</tr>
<tr>
<td>Completed two courses of chemotherapy</td>
<td>Restage patients to determine the response to chemotherapy then proceed to chemoradiotherapy</td>
</tr>
</tbody>
</table>

If there is any evidence of metastatic disease prior to surgery, patients will be taken off study and followed for survival.

7.1.2 Dose Modifications

7.1.2.1 Dose modification for 5-FU and cisplatin will be based on hematologic toxicities.

7.1.2.2 Reduction of subsequent chemotherapy dose will be based on the degree of hematologic and nonhematologic toxicities (see below for 5-fluorouracil dose reduction during therapy). The goal is to administer the doses of chemotherapy that do not result in grade 3 nonhematologic toxicity or grade 4 hematologic toxicity.

<table>
<thead>
<tr>
<th>Granulocyte Nadir*</th>
<th>Platelet Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1,000 AND &gt;75,000</td>
<td></td>
<td>No Change</td>
</tr>
<tr>
<td>( \geq 500 ) but &lt;1,000 AND/OR ( \geq 50,000 ) but &lt;75,000</td>
<td></td>
<td>No Change.</td>
</tr>
<tr>
<td>&lt;500 AND/OR &lt;50,000</td>
<td></td>
<td>Use colony stimulating factor (for granulocyte toxicity) with the subsequent course or decrease 20% (applies to both)</td>
</tr>
</tbody>
</table>

Infection or bleeding related to myelosuppression | Use colony stimulating factor with the subsequent course or decrease 20% |

* Lowest count during therapy, usually around Day 15.

7.1.2.3 The following dose modifications for 5-FU and cisplatin based on non-hematologic toxicities will be applicable to all courses.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>No Change</td>
</tr>
<tr>
<td>3 or 4</td>
<td>Decrease 20%</td>
</tr>
</tbody>
</table>
7.1.4 Dose modification for cisplatin based upon renal insufficiency will be as follows:

<table>
<thead>
<tr>
<th>Serum Creatinine * (mg/dL)</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.4</td>
<td>No change</td>
</tr>
<tr>
<td>&gt; 1.4 but &lt; 2.0</td>
<td>Decrease 50%</td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

* In a well-hydrated state (two readings necessary when abnormal).

7.2 Preoperative Chemoradiotherapy (3/4/04)

Chemoradiotherapy should begin at the end of the second 21 days of chemotherapy and one week of rest (day 57).

7.2.1 Chemotherapy During Radiotherapy

5-FU at 300 mg/m²/d as continuous infusion by a portable pump 5 days per week will be administered during radiotherapy. Typically, 5-FU infusion can be initiated Monday morning and would be terminated Friday evening. Patients would not receive 5-FU on Saturday or Sunday. Taxol will be given on days 1, 8, 15, 22, and 29 of radiotherapy at a dose of 45mg/m² i.v. over 3 hours. It is preferred that radiotherapy be initiated on a Monday or Tuesday. Premedication for Taxol will include dexamethasone 20mg, cimetidine 300mg, and diphenhydramine HCl 25mg, all i.v., 30 minutes before Taxol administration.

7.2.2 Dose Modification

Potential toxicities of chemoradiotherapy include nausea, loss of appetite, vomiting, malaise, mucositis, hand-foot syndrome, and rarely myelosuppression and neuropathy. Major toxicities include mucositis and hand-foot syndrome. Patients will be observed weekly. 5-FU doses will be modified as follows based on the level of toxic effects observed during chemoradiotherapy:

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>No change</td>
</tr>
<tr>
<td>3 or 4</td>
<td>Hold 5-FU for 5 days (one treatment week) and resume (at 250 mg/m²/d dose 5x/week for the remaining duration of therapy) provided the toxicity has resolved to grade ≤ 1.</td>
</tr>
</tbody>
</table>

7.2.3 Taxol Doses During Radiotherapy will be Modified Based on Myelosuppression

<table>
<thead>
<tr>
<th>Granulocyte Nadir</th>
<th>Platelet Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1,000</td>
<td>AND &gt;75,000</td>
<td>No Change</td>
</tr>
<tr>
<td>≥ 500 but &lt;1,000</td>
<td>AND/OR ≥50,000 but &lt;75,000</td>
<td>No Change</td>
</tr>
<tr>
<td>&lt;500</td>
<td>AND/OR &lt;50,000</td>
<td>Skip dose until AGN &gt;1,000 and/or plt &gt;100K then resume with 20% dose reduction.</td>
</tr>
</tbody>
</table>

* One weekly dose of Taxol may be held for grade 3-4 abdominal pain. Weekly Taxol may be resumed when the abdominal pain is grade ≤ 1.

7.3 Drug Information (3/4/04)

7.3.1 Cisplatin is an alkylating antineoplastic agent. Doses range from 40 to 120 mg/m² on day 1 every 3 weeks or 15 to 20 mg/m² on days 1 through 5 every 3 to 4 weeks. Cisplatin is highly protein bound with distribution to kidneys, liver, and intestines. The drug undergoes non-enzymatic metabolism to 1 or more metabolites. Only 25% to 45% of the administered dose are excreted in the urine. The estimated elimination half-life is 16 to 73 hours. Neurotoxicity, nephrotoxicity, ototoxicity, and severe nausea and vomiting are the most common adverse effects. Nephrotoxicity may be lessened with proper hydration. Cisplatin is commercially available.

7.3.2 Paclitaxel is a diterpene antineoplastic agent. A dose of 135 mg/m² over 24 hours repeated every 3 weeks has demonstrated effectiveness in the treatment of refractory ovarian cancer. Peak serum levels
are generally proportional to the dose administered; paclitaxel is highly protein bound. Only minimal amounts of the drug are excreted in urine. Systemic clearance appears to be accounted for by metabolism, biliary excretion, and/or extensive tissue binding. The elimination half-life ranges from 1 to 9 hours. The major dose-limiting toxicity is neutropenia. Other adverse effects include hypersensitivity reactions, mucositis, alopecia, neuropathies, myalgias, arthralgias, gastrointestinal disturbances, and arrhythmias.

Paclitaxel should be administered through an in-line filter not greater than 0.22 micron as a 24-hour infusion to lessen the probability of hypersensitivity reactions; premedication with dexamethasone plus diphenhydramine plus either an H2-antagonist or ephedrine is also recommended. Paclitaxel is commercially available.

7.3.3 Fluorouracil is a fluorinated pyrimidine antimetabolite, which functions as an antineoplastic agent. The recommended dose of fluorouracil is 12mg/kg/day i.v. for 4 days. If no toxicity occurs, 6mg/kg i.v. is given on days 6, 8, 10, and 12. The drug should be administered in 50 ml of D5W over 15 minutes. Doses of 20mg/kg/day for 5 days repeated every 5 weeks have been used for colorectal cancer. The total daily dose should not exceed 800 mg. Dosage reduction is necessary in hepatic failure. Fluorouracil is incompletely absorbed following oral administration with a bioavailability of 0% to 80%. The drug is localized in tissues, especially neoplastic tissue; the volume of distribution is 0.12 L/kg. Inactive and nontoxic metabolites are formed following hepatic metabolism; however, most of an administered dose is expired as carbon dioxide in the lung. The plasma half-life ranges from 8 to 22 minutes. Blood dyscrasias, especially leukopenia, are the most common adverse effects of fluorouracil therapy. Cardiac toxicities including chest pain, tightness of the chest, dyspnea, and cardiogenic shock have also occurred. Other frequent reactions include nausea, vomiting, anorexia, diarrhea, and pruritic maculopapular rash. 5-FU is commercially available.

7.3.4 Leucovorin (Folinic acid), a reduced folate, is a biochemical modulating agent of fluoropyrimidines and a chemoprotective agent consisting of equal amounts of l- and d-isomers. It is used in combination with 5-FU for both adjuvant therapy and treatment of advanced colorectal, head and neck, and esophageal cancers, and other GI malignancies. When given before-with 5-FU, leucovorin provides the folate cofactors that stabilize the binding of 5-dUMP (active metabolite of 5-FU) and thymidylate synthase (TS). When used as a biochemical modulating agent (as in this protocol) on a weekly schedule, the dose is 20 mg/m² administered via IV in combination with 5-FU. The l-isomer is preferentially absorbed and converted to 5,10-methylenetetrahydrofolate, which forms a ternary complex with the 5-FU metabolite, FdUMP, and TS. It is associated with enhanced inhibition of TS, resulting in inhibition of DNA synthesis and function. Leucovorin is rapidly absorbed after oral administration. Oral bioavailability is saturable at doses of 25 mg, and oral bioavailability is 97% for 25 mg. Time to peak concentration of total reduced folates after oral administration is about 2 hours vs. 10 minutes after IV administration. It does not cross the blood-brain barrier. Leucovorin is metabolized intracellularly by the enzyme folylpolyglutamate synthase (FPGS) to higher polyglutamate forms that are retained selectively within the cell. About 50% of a dose of drug is excreted in urine and stool within 6 hours. Toxicity includes allergic reactions with rash, urticaria, facial flushing, and rarely anaphylaxis. Nausea and vomiting are rare. Leucovorin should NOT be mixed in the same solution as 5-FU as a precipitate will form. Leucovorin is commercially available.

7.4 Toxicity Reporting

7.4.1 The revised NCI Common Toxicity Criteria (CTC) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities. A copy of the CTC version can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol, which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.4.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.4.1.3 Any death on study if clearly related to the commercial agent(s).
7.4.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
7.4.2 The ADR report should be documented on Form FDA 3500 and mailed to:

**Investigational Drug Branch**  
P.O. Box 30012  
Bethesda, Maryland 20824  
Telephone (301) 230-2330  
available 24 hours  
fax (301) 230-0159

7.4.3 Protocol treatment toxicities requiring hospitalization should be reported to RTOG HQ within 5 days of the hospitalization.

7.4.4 This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

8.0 SURGERY AND SURGICAL PATHOLOGY

8.1 Approximately 4 to 5 weeks after chemoradiotherapy, the patient will be evaluated for metastatic disease by physical examination and repeat CT scan. If there is no evidence of metastatic disease, the patient will be taken to the operating room to attempt a curative resection of the primary. The patient may have repeat laparoscopy at this time but this is optional. Peritoneal washings will be obtained at the beginning of the procedure for cytology.

8.2 The type of surgery will depend upon the location and extent of the primary tumor. A luminal gastric margin of at least 5 cm will be obtained when feasible. For distal lesions, a 2 cm duodenal margin will be obtained when feasible and frozen section confirmation of a negative margin will be sought. For proximal lesions, a 3 cm esophageal margin will be obtained and frozen section confirmation of a negative margin sought. For distal lesions, a subtotal gastrectomy will be considered adequate with total gastrectomy at the discretion of the surgeon. For proximal lesions, either a total gastrectomy or esophagogastrectomy will be permitted.

8.3 En bloc resection of adjacent organ(s) will be required when there is question of involvement of that organ. The spleen will be preserved when feasible. An attempt will be made to perform a d2 type nodal dissection though omental bursectomy is not required. All patients should have the left gastric artery divided at its origin and the hepatic, celiac and proximal splenic nodes removed. Clips should be placed to mark areas of tumor adhesions for purpose of follow-up CT studies.

8.4 The pathologist will evaluate the tumor for histologic grade, depth of invasion, evidence of vascular or lymphatic invasion, resection margins, lymph node metastases (including number and location), and the degree of tumor necrosis. If a pathologic complete response is suspected, then serial section will be requested.

9.0 NUTRITIONAL THERAPY

9.1 General  
Nutritional support will be an important aspect during this study. All patients will be carefully evaluated and vigorously supported to meet their optimum nutritional needs. Jejunostomy will be used for night feeding to meet the optimum nutritional needs.

9.2 Nutrition Therapy Guidelines

9.2.1 Initial assessment of nutritional status of a patient should be based on the following parameters:
- Percent weight loss per unit time
- Current calorie intake
- Serum albumin level

9.2.2 Basal Energy Expenditure (BEE) will be calculated by using Harris-Benedict equation

\[
\text{BEE (Men)} = 66 + (13.7 \times \text{Weight [kg]}) + (5 \times \text{Height [cm]}) - (6.8 \times \text{Age [yrs]}) \\
\text{BEE (Women)} = 65 + (9.6 \times \text{Weight [kg]}) = (1.7 \times \text{Height [cm]}) - (4.7 - \text{Age [yrs]})
\]

9.2.3 Anabolic need of a patient will be calculated based on the recommendations made by Blackburn et al. as follows:

- Anabolic need in Kcals = BEE x 1.2 - 1.5
- Protein requirement in grams = Actual weight (kg) x 1.5
The following criteria can be used for recommending various nutritional modalities:
- J-tube should be used to achieve a total of 2,000 Kilocalories. Night feeding is preferred using either gravity method or a pump.
- Oral alimentation: If the daily intake of patients is 500 calories less than their daily anabolic needs, oral alimentation should be started. Oral alimentation is contraindicated in the presence of fistula formation or complete obstruction.
- Intravenous hyperalimentation (IVH): Failure to support adequate nutrition by any one of the above methods should lead to use of IVH. Standard techniques of IVH will be utilized. Home IVH, when possible, is preferred.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

10.1.1 Patients entered on this study should submit pre-treatment and post-treatment (for patients with residual cancer in the surgical specimen) materials to the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One H&E stained slide.

10.1.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained cryostat slides (ten 5-micron thick and five 15-micron thick sections). Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.3 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.1.3 RTOG will reimburse pathologists from submitting institutions $100. per case if proper materials are submitted (reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement).

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).

10.1.5 Materials will be sent to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT  84143
(801) 321-1929
FAX (801) 321-5020
## 11.0 PATIENT ASSESSMENTS
### 11.1 Study Parameters (3/4/04)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Prior to registration</th>
<th>Prior to Every Induction Chemo</th>
<th>Weekly During Chemoradiotherapy</th>
<th>Prior to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;P + Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC, Diff, platelets</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Liver and kidney functions, lytes, Mg.</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CEA</td>
<td>X</td>
<td>X (^{a})</td>
<td>X (^{a})</td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Abdomen (chest and pelvis as necessary)</td>
<td>X</td>
<td>Only if clinically warranted</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>UGI radiographs</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGI endoscopy and ultrasonography</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal Staging</td>
<td>X</td>
<td></td>
<td>Only if clinically warranted</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>As necessary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J-Tube Placement</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

### Follow-up Evaluation

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>3 months from surgery</th>
<th>6 months from surgery</th>
<th>9 months from surgery</th>
<th>12 months from surgery</th>
<th>then every 6 months until year 5, See Section 12.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC, Chemistry(^b)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CEA(^a)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CXR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Upper GI Radiographs</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X (alternating with UGI endoscopy)</td>
</tr>
<tr>
<td>Upper GI Endoscopy</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X (alternating with UGI radiographs)</td>
<td></td>
</tr>
<tr>
<td>CT abdomen</td>
<td>X</td>
<td></td>
<td>X</td>
<td>PRN</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) If the baseline CEA is elevated.

\(^b\) Chemistry profile to include electrolytes, liver, and renal functions.

### 11.2 Evaluation During Study

#### 11.2.1 Patients will have CBC, platelet count, and differential count performed weekly during chemotherapy and chemoradiotherapy. Patients who develop grade 4 hematologic toxicity will have these counts performed more frequently (for example, daily if necessary) until it becomes grade 3 or lower.

#### 11.2.2 Chemical profile (to include liver and renal functions), electrolytes, urinalysis, and magnesium levels shall be performed before each course of chemotherapy and at the beginning of chemoradiotherapy and prior to surgery. Where appropriate, these tests should be performed more frequently.

#### 11.2.3 If a patient has prolonged myelosuppression (beyond day 35), a bone marrow examination is advised to rule out tumor invasion as the cause of pancytopenia.

#### 11.2.4 Double contrast upper gastrointestinal series will be performed after the first and second courses of chemotherapy and prior to surgery. Upper GI endoscopy may be repeated after the first two courses.

#### 11.2.5 CT scan of the abdomen (and chest and pelvis if necessary) will be repeated prior to surgery (and if clinically indicated, prior to chemoradiotherapy).

#### 11.2.6 All relevant information regarding drug dosages, measurable lesions, tumor response, laboratory examinations, concurrent medications and treatment-related toxicities will be recorded.
11.2.7 Procedures prior to surgery: Endoscopic ultrasonography, endoscopy, and laparoscopic peritoneal staging.

11.3 Criteria For Response
Primary gastric carcinoma is not measurable by conventional criteria. Therefore, the usual criteria for response cannot be applied. The following criteria for response assessment will be applied:

11.3.1 Complete Pathologic Response: Absence of tumor cells in the surgical specimen.
11.3.2 Complete Clinical Response: Absence of tumor on endoscopy, biopsy, cytology, or both.
11.3.3 Partial Response (Major Response): Marked objective reduction in the evaluable tumor by radiographs or endoscopy (including endoscopic ultrasound-50% volumetric reduction in quantifiable disease) as judged by at least two observers.
11.3.4 Minor Response: Objective reduction in the evaluable lesion but less than that required for a partial response.
11.3.5 No Change: No change in the tumor dimensions.
11.3.6 Progressive Disease: Any objective increase in the tumor by upper GI radiographs, CT scan, or endoscopy, or appearance of new lesions.
11.3.7 Curative Resection: Curative resection will be defined when in surgeon’s opinion all gross tumor is removed and histopathological examination of proximal, distal, and circumferential margins reveals absence of malignant cells > 2 mm from the edge.
11.3.8 Operative Mortality: Operative mortality will be defined as death occurring within 30 days from surgery or during the same hospitalization as the surgical resection.

11.3.9 Surgical complications will be recorded and analyzed separately.
11.3.10 The survival of patients will be calculated from the initiation of the preoperative chemotherapy.

11.4 Criteria for Removal from the Study
11.4.1 Increasing disease (as defined above).
11.4.2 The development of unacceptable toxicity (If a patient develops Grade 4 non-hematologic toxicity requiring hospitalization then the treating physician(s) may remove the patient from the study).
11.4.3 Patient refusal or non-compliance.
11.4.4 Patients will be continued to be followed if removed from study.

12.0 DATA COLLECTION
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission (3/4/04)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Induction Chemo Summary Form (TF)</td>
<td>Within 1 week of the end of chemo course 1</td>
</tr>
<tr>
<td>Induction Chemo Summary Form (TF)</td>
<td>Within 1 week of start of RT (for chemo course 2 beginning on day 29)</td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td></td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Treatment Summary Chemoradiotherapy (FO)</td>
<td>Within 4 weeks completion of chemoradiation and prior to surgery</td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td>Within 4 weeks of surgery</td>
</tr>
</tbody>
</table>
Surgery Note (S2)  
Surgical Path Report (S5)  
Pathology Slides/Blocks (P2)  
For patients with residual cancer in the surgical specimen  
Follow-up Form (F1)  
At 6 and 12 months from start of treatment; then q 6 months x 4 years, then annually. Also at progression/relapse and at death.  
Long Term Follow-up Form (FF)  
Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.  
Autopsy Report (D3)  
As applicable

13.0 STATISTICAL CONSIDERATIONS  
13.1 Study Endpoints
13.1.1 Complete pathologic response  
13.1.2 Feasibility of the treatment  
13.1.3 Curative resections  
13.1.4 Toxicity  
13.1.5 Pattern of failure  
13.2 Sample Size and Patient Accrual  
13.2.1 Sample Size
  
13.2.1.1 Apart from assessing feasibility, one of the major objectives is to determine the complete pathologic response (path CR) rate after the treatment. The path CR is defined as absence of tumor cells in the surgical specimen. All registered patients will be included in the denominator where path CR rate is calculated. A path CR rate of less than 5% will not be clinically desirable. If a path CR rate of 20% or greater is achieved, the treatment will be considered for further study of survival outcomes. The calculation of the sample size is based on the path CR rate and Simon’s Optimal Two-stage Design. If the path CR rate of 5% is set as the lowest desirable rate and 20% is the rate we are targeting. We chose type I error of 0.05 and type II error of 0.10. That is, if the true response rate is less than 5%, the probability of wrongly accepting the treatment for further study is 5%, and if the true response rate exceeds 20%, the probability of wrongly rejecting it for further study is 10%. According to the algorithm, a maximum of 41 pathologically evaluable patients will be needed. In the first stage, 21 patients will be evaluated. If less than or equal to one (1) path CR are observed, the study will be terminated. However, if more than one (1) path CR is observed, then an additional 20 patients (second stage) will enter the study. Finally, if more than four path CR are observed among 41 patients, then this strategy and regimen may be considered as the experimental arm of an intergroup phase III trial comparing it with surgery (+/-) postoperative chemoradiotherapy in patients with potentially resectable carcinoma of the stomach. Accrual will not be suspended between the two stages. While evaluating the first 21 patients’ pathology outcomes, subsequent eligible patients will continue to accrue to study. Assuming at least 85% of patients’ treatment responses can be pathologically assessed, this study calls for a total sample size of 49.

13.2.1.2 As our secondary objective, we will also estimate the proportion of patients completing protocol therapy (feasibility). The feasibility will be defined as the proportion of patients who receive preoperative therapy and undergo surgery over total registered. Table 1 gives various feasibility rates and their 95% confidence intervals based on sample size of 49.

Table 1  
Feasibility and its confidence interval with a sample size of 49:

<table>
<thead>
<tr>
<th>Rate of Feasibility (%)</th>
<th>75</th>
<th>80</th>
<th>85</th>
<th>90</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% C.I.*</td>
<td>63 - 87</td>
<td>68 - 90</td>
<td>75 - 94</td>
<td>80 - 97</td>
<td>89 - 100</td>
</tr>
</tbody>
</table>

*Exact method is used for calculating confidence interval.
The curative resection rate will similarly be estimated in the population of patients who undergo surgery. Assuming 41 patients (84% of registered patients) will undergo surgery and have evaluable surgical specimens, Table 2 gives various curative resection rates and their 95% confidence intervals.

Table 2
Curative resection rate and its confidence interval based on a sample size of 41.

<table>
<thead>
<tr>
<th>Rate of Curative Resection (%)</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
</tr>
</thead>
</table>

*Exact method is used for calculating confidence interval.

13.2.3 **Patient Accrual**
Based on the SWOG intergroup gastric study, INT 0116/RTOG 90-18, which completed accrual in July 1998, RTOG entered two to three cases per month to the study (about 80% of cases met the eligibility criteria for this study). Assuming two eligible patients will be accrued per month, this new study will take 2.5 years to reach the required total accrual of 49 cases allowing six months to allow for institutional IRB approvals. If the average accrual rate is less than one case per month, then the study will be re-evaluated with respect to feasibility.

13.3 **Inclusion of Women and Minorities**
In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regarding to inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. In the SWOG intergroup gastric study INT 0116/RTOG 90-18, 70% are male and 30% are female, and 70% are Whites, 17% are Blacks, 5% are Hispanics, 5% are Asians, and 3% are other. No study so far has indicated any significant racial or gender differences in treatment effects for gastric cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. The estimated path CR rates and other interested end points will be given by gender and race at the end of this study. But a definitive statistical analysis to examine the possible differences in path CR rates between genders and among races is unlikely with this rather small sample size of 49 patients.

13.4 **Analysis Methods and Plans**

13.4.1 **Interim Analysis**
Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a) The patient accrual rate with a projected completion date for the accrual phase;
b) The compliance rate of treatment delivery with respect to protocol prescription;
c) The quality of submitted data with respect to timeliness and completeness, and accuracy;
d) The frequency and severity of toxicities;

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG GI committee responsible for the study and, if necessary, to the RTOG Research Strategy Committee, so that corrective action can be taken.

13.4.2 **Analysis for Reporting the Initial Treatment Results**
This analysis will be undertaken when each specimen from patient undergoing surgery has been assessed. The usual components of this analysis are:

a) Tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
b) Reporting of institutional accrual;
c) Distribution of important prognostic baseline variables;
d) Observed results with respect to the endpoints described above.
REFERENCES


APPENDIX I

RTOG 99-04

A PHASE II TRIAL OF PREOPERATIVE CHEMOTHERAPY AND CHEMORADIOOTHERAPY FOR POTENTIALLY RESECTABLE ADENOCARCINOMA OF THE STOMACH

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits, and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY

The goal of this clinical research study is to find out how well the chemotherapy drugs cisplatin, folinic acid, Taxol, and 5 fluorouracil (5-FU) and radiotherapy when given before surgery work against stomach cancer. The safety of this treatment will also be studied.

DESCRIPTION OF PROCEDURES (3/4/04)

Before the study begins, you will have a complete examination. Blood samples will be taken. A chest x-ray and EKG will be done. A CT scan of the abdomen and pelvis will be done. A CT scan of the chest may be done. X-ray of the stomach region will be done. Your stomach and intestines will be examined by an endoscope. An ultrasound scan of the stomach will be done. Since you will have a hard time eating enough calories to keep up your strength, you will need a temporary feeding tube.

A tube (catheter) will be inserted into a vein under your collarbone or in one of your arms. 5-FU will be given through this tube nonstop for 21 days. Cisplatin will be given by vein for 5 days in a row. Cisplatin and 5-FU will begin on the same day. Folinic acid will be given once a week four times. This 21-day treatment (course) will be repeated after one week of rest. This chemotherapy can be given on an outpatient basis. At the end of the second 21 days of chemotherapy and one week of rest (day 57), radiotherapy will be given Monday through Friday for 5 weeks. Five days of 5-FU will be given during each week of radiotherapy. Taxol will be given for 3 hours once a week during the 5 weeks of radiotherapy. Four to five weeks after chemoradiotherapy is stopped, you will have surgery to remove your stomach tumor.

You will have complete examinations before the second chemotherapy course, before chemoradiotherapy, and before surgery. X-rays of the chest and abdomen will be done. These will also be done before surgery. Your stomach and upper intestines may be examined using a flexible tube (endoscope) before surgery. An ultrasound scan of the stomach will also be done with the endoscope. You will visit the clinic for examinations and tests 3 and 6 months after surgery, then every 6 months for 5 years, then once a year.

RISKS AND DISCOMFORTS (3/4/04)

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (side effects). The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.
**Chemotherapy**

5-Fluorouracil (5-FU) can cause diarrhea, a metal taste in the mouth, dry skin, dry nose, and watery eyes. The drug can cause soreness or painful ulcers of the mouth and throat. Loss of hair may result. The drug may cause thinning of the skin, nail changes, redness or darkening of the skin, rash, and increased sensitivity to the sun. 5-FU may cause headaches, which continue after treatment is stopped. Rarely, the drug can cause reversible unsteadiness upon walking, dizziness, and slurred speech. It has also rarely been associated with heart attack.

Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss, ringing of the ears, and numbness of the fingers and toes. It can also cause damage to the kidneys; You will be given extra amounts of fluids and other medications to lessen the risk of kidney injury. It can lower the blood counts and the levels of calcium and magnesium in your blood. It is possible that you may become anemic and require transfusion. Other less common side effects include allergic reactions such as sweating, difficulty breathing, and rapid heart beat. Rarely the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps, or acute leukemia.

Paclitaxel (Taxol) commonly causes a lowering of blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from your vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If you are treated with a high dosage or for a prolonged period, you may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that you would notice. In addition, paclitaxel may increase the risks of radiation as listed below.

Leucovorin (Folinic acid) may cause allergic reactions with rash, hives, facial flushing, and rarely severe allergic reaction. Nausea and vomiting are rare.

These chemotherapy agents are available commercially.

**Radiation Therapy** may cause reddening or tanning of the skin, hair loss in the treatment area, nausea, vomiting, loss of appetite, weight loss, and weakness. Kidney damage may occur if the kidney is in the same field of radiation.

**Intravenous Catheter** may cause pain, redness, swelling, bruising, and/or clotting at the entrance spot.

**Surgery** may cause infection, bleeding, blood clots, and death.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

This study is harmful to an unborn child. The study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. You must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on this study, you must tell your doctor immediately.

**COSTS**

Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.
CONTACT PERSONS
(This section must be completed)

For information about your disease and research-related injury, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about your rights as a research subject, you may contact:
(ORPP suggests that this person not be the investigator or anyone else directly involved with the research)

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

ALTERNATIVES

Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread.

These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than the standard treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.
CONFIDENTIALITY

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or legal Representative) ____________________________ Date ____________________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100  Normal; no complaints; no evidence of disease
90   Able to carry on normal activity; minor signs or symptoms of disease
80   Normal activity with effort; some sign or symptoms of disease
70   Cares for self; unable to carry on normal activity or do active work
60   Requires occasional assistance, but is able to care for most personal needs
50   Requires considerable assistance and frequent medical care
40   Disabled; requires special care and assistance
30   Severely disabled; hospitalization is indicated, although death not imminent
20   Very sick; hospitalization necessary; active support treatment is necessary
10   Moribund; fatal processes progressing rapidly
  0   Dead

ZUBROD PERFORMANCE SCALE

  0  Fully active, able to carry on all predisease activities without restriction
     (Karnofsky 90-100).

  1  Restricted in physically strenuous activity but ambulatory and able to carry out
     work of a light or sedentary nature. For example, light housework, office work
     (Karnofsky 70-80).

  2  Ambulatory and capable of all self-care but unable to carry out any work
     activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

  3  Capable of only limited self-care, confined to bed or chair 50% or more of waking
     hours (Karnofsky 30-40).

  4  Completely disabled. Cannot carry on any self-care. Totally confined to bed or
     chair (Karnofsky 10-20).
APPENDIX III
AJCC STAGING SYSTEM,
STOMACH, 5TH EDITION

DEFINITION OF TNM

Primary Tumor (T)

TX  Primary Tumor cannot be assessed
T0  No evidence of primary tumor
Tis  Carcinoma in situ: intra-epithelial tumor without invasion of the lamina propria
T1  Tumor invades lamina propria or submucosa
T2  Tumor invades muscularis propria or subserosa*
T3  Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures**,***
T4  Tumor invades adjacent structures**,***

*Note: A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T3.

**Note: The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Note: Intramural extension to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including stomach.

Regional Lymph Nodes (N)

NX  Regional lymph nodes(s) cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in 1 to 6 regional lymph nodes
N2  Metastasis in 7 to 15 regional lymph nodes
N3  Metastasis in more than 15 regional lymph nodes

Distant Metastasis (M)

MX  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
### STAGE GROUPING

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### HISTOLOGIC GRADE (G)

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APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.
C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (≥ grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (≥ grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330      FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters. ** A written report to follow within 10 working days.

- All deaths within 30 days As above
of termination of the agent.

- All life threatening (grade 4) events which may be due to agent. As above

- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. **Phase II, III Studies Utilizing Investigational Agents**

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.

**See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**