RADIATION THERAPY ONCOLOGY GROUP

RTOG G-0114

A RANDOMIZED PHASE II COMPARISON OF TWO CISPLATIN-PACLITAXEL CONTAINING CHEMORADIATION REGIMENS IN RESECTED GASTRIC CANCERS

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SCHEMA (11/01/02)

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*Treatment must begin within 8 weeks after surgery

** Cycle 1: Days 1-5 5-FU and CDDP; Day 1 paclitaxel; Cycle 2: Days 29-33 5-FU and CDDP; Day 29 paclitaxel

*** Cycle 1: Day 1 CDDP and paclitaxel; Cycle 2: Day 29 CDDP and paclitaxel

Eligibility: (See Section 3.0 for details) (2/18/02) (11/01/02)

- Histologic proof of adenocarcinoma of the stomach or GE-junction;
- Patients with tumor stages IB through IIIB who have undergone a potentially curative resection of primary gastric or GE-junction tumor; treatment must begin within 8 weeks of surgery;
- Zubrod Performance Status 0-1;
- No prior chemotherapy or radiation therapy to the treatment field;
- WBC ≥ 4,000/mm³, platelets ≥ 150,000 /mm³, BUN < 30 mg/dl, creatinine ≤ 1.4 mg/dl, serum bilirubin ≤ 1.5 mg/dl, AST and ALT ≤ 2.5 x ULN, creatinine clearance of > 50 ml/min actual or calculated;
- No prior history of cancer within last three years except non-melanoma skin cancers or carcinoma in situ of the cervix;
- Signed study-specific consent prior to study entry.
- Required Sample Size: 94
1. Is there microscopically confirmed adenocarcinoma of the stomach or GE-junction?
2. Is the tumor stage IB through IIIB?
3. Did the patient have a potentially curative resection of a primary gastric or GE-junction tumor?
4. Will treatment begin within eight weeks of surgery?
5. Is the Zubrod Performance Status 0 or 1?
6. Has the patient had prior chemotherapy?
7. Has the patient had prior radiation therapy to the treatment field?
8. Was the pretreatment evaluation completed as per Section 4.0 in the protocol?
9. Is the WBC count $\geq 4,000$ mm$^3$?
10. Is the platelet count $\geq 150,000$ mm$^3$?
11. Is the BUN $< 30$ mg/dl?
12. Is creatinine $\leq 1.4$ mg/dl and creatinine clearance $> 50$ ml/min (based on actual measurement or calculated)?
13. Is serum bilirubin $\leq 1.5$ mg/dl?
14. Are the ALT and AST values $\leq 2.5$ times upper limit of normal?
15. Is there metastatic disease?
16. Is there NYHA Class III or IV heart disease?
17. Is the patient pregnant, lactating, or not using effective contraception?
18. Are there any major medical or psychiatric illnesses which would prevent completion of treatment, interfere with follow-up or which would be jeopardized by complications of this therapy?
19. Is there a history of previous or concurrent malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix within the past three years?
20. Is there clinically significant hearing loss?

(cont’d 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. Treatment Start Date
17. Medical Oncologist
18. Specify T-stage as T1-2, T3, or T4.
19. Specify lymph node status as none, 1-3 positive nodes, or 4 or more positive nodes.
20. Treatment Assignment

Completed by ________________________________ Date __________________________
1.0 INTRODUCTION

1.1 History

Gastric cancer is a highly virulent disease with an extremely poor prognosis. While the overall incidence in the United States has declined, it has remained constant over the last decade in other parts of the world including China, Korea, Southeast Asia, the Soviet Union, Africa, much of South America and parts of Europe. Moreover, while the incidence of distal gastric cancers is stable in the United States, the incidence of proximal gastric cancers (which are more virulent) is rising rapidly, particularly among white males (ages 35-70). On a global basis, cancer of the stomach is one of the most prevalent malignancies known to man. While surgery remains the mainstay of potentially curative treatment, preoperative staging techniques are unsatisfactory, recurrence is frequent despite potentially curative resections, and thus survival rates are poor. The relapse pattern for gastric cancer patients includes both intra-abdominal and systemic sites. There have been many studies using adjuvant systemic chemotherapy as monotherapy, but there are no confirmed positive trials. There is a paucity of information regarding the biology of this important disease.

1.2 Results of Surgery

The survival rate of patients after resection of gastric carcinoma performed with curative intent depends most heavily on the stage of the tumor, most importantly on the T and N stage. In Japan, a substantial proportion of screened patients have T1N0 tumors; 90% or more of such patients are cured by resection. In the United States, such early lesions are much less common. In both U.S. and Japanese studies, the prognosis for T3N0M0 patients is poor (30-50% 5 year survival); T3-4 N1-2 patients have an even poorer outcome. Overall, less than 20% of all U.S. explored patients are cured. The major difference in survival between Japan and the U.S. is seen in patients with resected N1 or N2 disease; unfortunately, most U.S. patients have lymph node metastases. Poorer survival for U.S. N1-2 patients may be due to differences in the scope of surgical resection, different techniques of pathologic examination and hence staging, or differences in the biology of the disease.

1.3 Definition of Local Regional Disease

The 1997 edition of the Manual for Staging of Cancer, by the American Joint Committee on Cancer, revised the staging of gastric tumors. Using the TNM system, it defined local regional disease as including the primary site and regional lymph nodes. The T stage was defined by the depth of invasion of the primary. Regional lymph nodes include the inferior (right) gastric area, splenic area, superior (left) gastric area, perigastric area, celiac lymph nodes and hepatic lymph nodes. In the new schema, all other lymph node sites are considered to be distant metastatic disease (M1). Thus, cancer in lymph nodes in the retropancreatic, hepatoduodenal, aortic, portal, retroperitoneal, and mesenteric areas represents metastatic disease. Distant spread to sites other than listed above is also considered to be metastatic disease. For the purpose of these studies, we will consider local regional disease to include tumors of TNM stages IB-IIIB (T1-3, N0, M0). High risk patients are defined as T2N1-2M0 or T3NanyM0 (stages II, IIIA, IIIB).

1.4 The Failure Pattern of Recurrent Gastric Cancer

Results of autopsy and second-look laparotomy indicate that intra-abdominal recurrence is the major site of failure for patients with resected gastric cancer. Recurrent tumor in regional lymph nodes, the gastric bed, the peritoneum, and the liver are probably the most common sites of disease. However, 30-50% of patients will also have extra-abdominal metastases. These data suggest that, short of earlier diagnosis, an improvement in survival will only come with the development of effective multimodality treatment plans.

1.5 Results of Systemic Adjuvant Therapy

Postop adjuvant chemotherapy for gastric cancer has been thoroughly explored over the past 10-15 years. These studies have not yielded confirmed positive results. Several recent meta-analyses indicated that even with pooled data, postoperative adjuvant systemic therapy caused only a modest improvement in survival. These analyses, one of which has been reported in complete text and one in abstract form, indicate an approximately 5% benefit to systemic chemotherapy, primarily using a fluorouracil based regimen compared to surgery alone.
1.6 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. These trials were relatively small in size and frequently included patients who had less than an R0 resection (R1 or R2). With this understanding, the data to date do not show a clinically or statistically significant impact on outcome when measured as survival for patients receiving radiation as a single modality following resection.

1.7 Chemotherapy Plus Radiation Therapy: Theoretical Rationale

An extensive database has been established for the combination of chemotherapy and concurrent radiation in the treatment of malignancies, particularly solid tumors. Vokes reviewed the theoretical rationale behind the combination of chemotherapy and concurrent radiation. Radiation and chemotherapy may have independent activity against different tumor cell sub-populations. Furthermore, cells that are intrinsically resistant to one modality may be sensitive to the other. The use of combined modality therapy thus might allow destruction of resistant cell sub-populations at initial therapy, preventing their later cellular expansion. Secondly, chemotherapy might delay the regrowth of tumor cell sub-populations that are sensitive to radiation. This delay in regrowth may increase total cell kill when the next radiation treatment is given. Furthermore, chemotherapy may, by causing cell cycle synchronization, increase the fraction of tumors in a radiation therapy responsive phase of the cycle, or, by destroying cells in cycle, recruit additional tumor population from the G0 phase which is resistant to either radiation or chemotherapy. Chemotherapy-radiation interactions may improve as tumor masses decrease in size. Better oxygenation of the central portions of a smaller mass may improve radiation cell kill. Steel and Peckim proposed three additional mechanisms that enhance the activity of chemotherapy and radiation when delivered together. Spatial cooperation involves the fact that radiation will have a high degree of local regional activity while chemotherapy can be active both locally and systemically. Spatial cooperation does not necessarily require the two modalities be given together. Independent toxicity may allow full doses of both modalities to be given as is the case in esophageal carcinoma. Normal tissue protection is a theoretical goal that might be achieved by either technical improvements in radiation (3-D treatment planning) or by the development of pharmacologic agents that protect normal tissue while leaving tumor vulnerable.

1.8 Chemoradiation Therapy in Gastric Cancer

While radiation therapy given as a single modality has had minimal effect on outcome (see below), chemoradiation therapy has recently been demonstrated to cause a significant improvement in overall and disease-free survival. A USA national Intergroup trial (Intergroup 116 – RTOG 90-18) has now been reported in abstract form. In this study involving a total of 556 evaluable patients, fluorouracil-leucovorin chemotherapy plus concurrent radiation therapy was compared to expectant observation in patients undergoing an R0 resection. 85% of patients had lymph node positive tumors, but all were clinically free of disease at the end of the operative procedure. The treatment regimen involved one cycle of fluorouracil and leucovorin given at a dose of fluorouracil 425 mg/m² and leucovorin 20 mg/m² daily for 5 days in a row. One month later, chemoradiation therapy giving a total of 45 Gy was initiated. Chemotherapy also involved fluorouracil-leucovorin and was given at 400 mg/m² of fluorouracil plus 20 mg/m² of leucovorin for the first four days of radiation and for three days during the fourth week of radiation therapy. One month from completion of radiation, two additional cycles of fluorouracil-leucovorin chemotherapy using the identical doses as given during the first week of chemotherapy alone were initiated. At the time of the analysis for abstract presentation, a highly statistically significant improvement in three year disease-free and overall survival was noted; median disease free survival 30 months vs. 19 months, p=0.0002; median overall survival 40 months vs. 26 months. The results of this study indicate that chemoradiation therapy has a positive influence on increasing the overall survival for patients at high risk for recurrence after undergoing surgery alone.

However, despite the improvement in outcome, over 50% of patients will still die within three years of a potentially curative operation, emphasizing the need for the development of newer treatment modalities. Failure pattern data from Intergroup 116 suggests a minimal effect of FU-leucovorin on regional and distant failure. The high recurrence rate, even in the superior chemoradiation arm, clearly indicates the need for improved systemic therapies. New systemic treatments have been developed in gastric cancer over the last five years. These studies are detailed below and lead to the current proposal. Paclitaxel has been studied in phase II trials in patients with advanced gastric cancer using a variety of regimens. These single agent trials demonstrate activity determined as complete and partial responses in approximately 20% of previously untreated patients. Toxicity has been typical of that seen using paclitaxel as a single agent in other diseases and primarily involves myelosuppression, alopecia and peripheral neuropathy. With proper premedication, allergic reactions have been well controlled. The median duration of response is 6-9 months. This response rate is competitive for other active single agents including cisplatin and cisplatin-
based combinations. Many patients with esophageal cancer have adenocarcinomas of the GE-junction or the lower esophagus. These patients have been included in single agent paclitaxel studies (where paclitaxel is also an active agent) and pertinent to this proposal, chemoradiation regimens have been used in esophageal cancer including large numbers of patients with GE-junction tumors. The basic chemoradiation therapy preliminary studies to be presented involve patients with esophageal tumors including GE-junction tumors.

1.9 Paclitaxel Combination Chemotherapy

Paclitaxel has been combined with cisplatin in a number of solid tumors including esophageal, breast, ovarian and lung cancers. The rationale for combination is that the common toxicities of each agent are non-overlapping (paclitaxel – alopecia, myelosuppression and cardiotoxicity; cisplatin – nausea, vomiting, renal toxicity). Both, however, can cause a peripheral neuropathy. Klastersky and Sculier performed a phase I trial of paclitaxel plus cisplatin in patients with non-small cell lung cancer.10 Cisplatin 100 mg/m² was given with escalating doses of paclitaxel which was delivered as a three-hour infusion prior to cisplatin. Therapy was given on an every three week schedule. At the time of their preliminary report, doses of 100 mg/m² of cisplatin and 200 mg/m² of paclitaxel respectively were being administered. Dose escalation was continuing. Responses were seen in four of the first ten patients treated. Extensive data in esophageal cancer has been reviewed.

1.10 Paclitaxel as a Radiation Sensitizer

A number of in vitro studies have demonstrated that paclitaxel is a radiation-sensitizing anti-neoplastic agent. Using hamster cell cultures, Sinclair and Morton demonstrated that the most sensitive cells were those in M and that cells in G1 and late S were most resistant to ionizing radiation.11 Other studies have clearly demonstrated that the most sensitive period for radiation is at the G2-M interface. Studies with paclitaxel have clearly demonstrated that even at low concentrations and after only a few hours, cells are blocked at the G2-M interface. Recently, Liebmann et al. demonstrated in breast cancer and lung cancer adenocarcinomas the radiation-sensitizing effects of paclitaxel.12 Cells were exposed to paclitaxel from 6-72 hours. Even at concentrations as low as 100 nM > 90% of cells were blocked at G2-M; the overwhelming majority of these cells remained at G2-M for at least 72 hours after paclitaxel exposure. Importantly, in one experiment, cells exposed to drug for 48 or 72 hours demonstrated the highest degree of radiation sensitization, with SERs of 1.9 and 2.0 respectively. A cautionary note was shown when one cell line, an adenocarcinoma lung cancer line, was not sensitized to radiation by paclitaxel even though a G2-M block was established.

1.11 Paclitaxel as a Continuous Intravenous Infusion During Concurrent Radiation

In vitro data noted above indicates that paclitaxel blocks cell progression at the G2-M interface, the most sensitive point for radiation therapy. When given on a once a week basis, the G2-M block appears to last for between 24 and 72 hours. It would appear rational to attempt to prolong cells in the G2-M phase of cycle by giving paclitaxel as a continuous intravenous infusion. Emerging data suggests that the longer the duration of infusion of paclitaxel the more likely one is to see a response. For example, paclitaxel given as a 96-hour infusion can cause remission in patients who have failed to respond or who have relapsed after receiving paclitaxel for shorter periods of time. We therefore propose in the current trial to give paclitaxel as a continuous 96-hour infusion throughout the radiation therapy period.

1.12 Paclitaxel Combinations with Radiotherapy in the Adjuvant or Neoadjuvant Treatment of Gastro-esophageal Cancers

The use of paclitaxel has been evaluated in two pilot adjuvant and neoadjuvant trials in the treatment of gastro-esophageal cancers. The first is the Memorial Sloan-Kettering pilot, which was presented at the American Society of Clinical Oncology meeting in 1999 by Kelsen et al.17 In this trial, patients were treated with fixed doses of weekly cisplatin at 30 mg/m² and radiotherapy with 5040 cGy in 180 cGy fractions 5 days per week for 6 weeks. Paclitaxel was given as a 96-hour continuous infusion each week throughout the radiotherapy in escalating doses. No prior chemotherapy or RT was allowed. Dose levels of 10 to 80 mg/m² of paclitaxel were completed. Because of dose-limiting hematologic toxicity at 80 mg/m², 60 mg/m² was selected as the recommended phase II dose in this combination. There was no evidence of grade 3 or greater esophagitis. In the first 19 patients evaluable for response, there were 6 complete responses and 3 partial responses. The complete responses were observed at paclitaxel doses of 40 and 60 mg/m² respectively, suggesting a dose response to paclitaxel as a radiotherapy sensitizing agent. No long-term toxicities including pulmonary toxicity, esophageal stricture, cardiomyopathy, or myelopathy, were reported. This regimen was very well tolerated and appeared highly active in this phase I trial. The second trial is the MD Anderson pilot conducted by Ajani et al. In this trial, patients received neoadjuvant chemotherapy and radiation with infusional 5-Fluorouracil at 300 mg/m², 5 days/week x 5 weeks and paclitaxel at 45 mg/m² days 1, 8, 15, 22, and 29 during the 5 week course of fractionated RT.
With this approach there was significant downstaging of the tumors. In 28 evaluable patients, who underwent preoperative endoscopic ultrasound (EUS), over half had significant downstaging of their tumor at the time of surgical resection. Four patients who had T$_{2,3}$N$_{0,1}$ disease at the time of EUS had over 90% tumor necrosis at the time of surgical resection. Seven patients who presented with T$_{3}$N$_{0,X}$ at EUS were downstaged to T$_{0}$N$_{0}$M$_{0}$ at the time of surgical resection. Four patients were found to have unsuspected peritoneal metastases at the time of surgery.

2.0 OBJECTIVES

2.1 To evaluate, using a random assignment phase II design, two new chemoradiation regimens in patients having undergone potentially curative resections for locally advanced gastric cancer. Both arms will include cisplatin and paclitaxel and one arm will contain 5-FU. This trial is designed to determine if either of the two treatment arms under consideration is promising enough to be pursued in a subsequent phase III study against the recently completed intergroup protocol 0116 (RTOG 90-18)\textsuperscript{16} adjuvant arm. This decision will be based on the evaluation of several objectives:

2.2 The first objective will be to determine whether there is improvement in two year disease-free survival relative to the adjuvant arm of the intergroup adjuvant trial.

2.3 The secondary objective will be to determine whether the treatment arms can be delivered as safely and successfully as the intergroup adjuvant trial.

2.4 The third objective will be to determine whether treatment toxicities of the two arms under study are at least no worse than the adjuvant arm of the intergroup study.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 All patients must have microscopically confirmed adenocarcinoma of the stomach or GE-junction.

3.1.2 All patients must have undergone a potentially curative resection of a primary gastric or GE-junction tumor (R0 resection). Patients with tumor stages IB through IIIB are eligible for this study. Patients with stage IA cancers (T1N0M0) are ineligible for this trial because of their good prognosis with surgery alone. Treatment must begin within 8 weeks of surgery. (11/01/02)

3.1.3 Zubrod performance status 0-1.

3.1.4 Patients may not have received prior chemotherapy.

3.1.5 Patients may not have received prior radiation therapy to the treatment field. (2/18/02)

3.1.6 Patients must have WBC $\geq$ 4000 cells/mm$^3$, platelets $\geq$ 150,000/mm$^3$, BUN < 30 mg/dl, total serum bilirubin $\leq$ 1.5 mg/dl, AST and ALT $\leq$ 2.5 x ULN, creatinine $\leq$ 1.4 mg/dl and creatinine clearance of $> 50$ ml/min based on actual measurement (24-hr. urine) or calculated.

3.1.7 Patients must have study-specific signed informed consent.

3.1.8 Patient must have completed all pretreatment evaluations in Section 4.0.

3.2 Exclusion Criteria

3.2.1 Any metastatic disease (M1).

3.2.2 NYHA Class III or IV heart disease (see Appendix II). History of active angina or myocardial infarction within six months. History of significant ventricular arrhythmia requiring medication with antiarrhythmics or a history of a clinically significant conduction system abnormality. (11/01/02)

3.2.3 Pregnant or lactating women are ineligible because of potential teratogenic effects of the chemotherapy and radiation. Fertile men and women must use effective contraception. A pregnancy test will be performed on each premenopausal female prior to entry into the study. Treatment may not begin until the results of the pregnancy test are ascertained.

3.2.4 Serious intercurrent infections, or nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this therapy.

3.2.5 Psychiatric disorders rendering patients incapable of complying with the requirements of the protocol.

3.2.6 Any concurrent active malignancy other than non-melanoma skin cancers or carcinoma-in-situ of the cervix. Patients with previous malignancies but without evidence of disease for $\geq$ 3 years will be allowed to enter the trial.

3.2.7 Clinically significant hearing loss.

4.0 PRETREATMENT EVALUATION (11/01/02)

4.1 The following laboratory tests will be required within two weeks prior to study entry.

- CBC including WBC differential and platelet count
- Biochemical serum screening profile including alkaline phosphatase, BUN, ALT, AST, LDH, bilirubin, albumin, total protein, creatinine, electrolytes
Creatinine clearance
- Pregnancy test if applicable

4.2 The following tests will be required within four weeks prior to study entry:
- History and physical examination
- A chest radiograph
- CT scan of the abdomen and pelvis
- Audiogram if clinically indicated
- Additional radiographic and radionuclide studies will be performed when clinically indicated

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 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY (8/25/03)

6.1 External Beam Radiotherapy (Both Arms 1 and 2) (Arm 1 Closed May 21, 2003)

6.1.1 General Irradiation Information
The intent of treatment is to deliver 45 Gy in 1.8 Gy/fraction, 5 days a week for 5 weeks, to the entire gastric bed (including anastomosis) and draining lymph nodes. The radiotherapy plus concurrent chemo should begin within 6 weeks after postop chemotherapy. CT planning will be used. Localization (simulation) films of initial fields will demonstrate the use of contrast media and blocking. Portal films will demonstrate the use of blocking. Films must be sent to RTOG Headquarters for rapid review. (11/01/02)

6.1.2 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.

6.1.3 Treatment Delay
External beam radiation therapy (EBRT) and concomitant chemotherapy infusion should begin within 6 weeks after the last cycle of postop chemotherapy. However, prior to beginning EBRT, patient’s blood counts need to have recovered to ≥ 1,500 absolute neutrophil count and platelets ≥ 100,000. Caloric intake should be ≥ 1,500 kilocalories/day 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. (11/01/02)

6.1.4 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 pretreatment 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 multifield 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.

6.1.5 Treatment Volume
The treatment volume will require some individualization. However, pre-treatment diagnostic studies (UGI, CT scan) and clip placement should be used liberally to identify the tumor/gastric bed and pertinent nodal groups.

6.1.6 Definition of Target Volume
6.1.6.1 Clinical target volume (CTV) is equal to the gastric remnant and the adjacent remaining perigastric nodal tissue, anastomosis(es), lymph node regions of the celiac axis (celiac, splenic, pancreatoduodenal, suprapancreatic nodal beds), porta hepatis lymph node bed, and upper para-
aortics (to the level of approximately L3). For patients who had proximal gastric lesions, CTV should also include the lower paraesophageal nodal regions (to the level of approximately T9). Planning target volume (PTV) is equal to the CTV and an appropriate margin for organ and setup variation as per the discretion of the physician, but a minimum of 0.5 cm. In some cases, this may have to be considerably more, such as when respiratory variation causes significant superior-inferior movement of the gastric remnant.

6.1.6.2 Extension Through Wall: For proximal T3 and T4 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.

6.1.6.3 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.

6.1.6.4 Distal lesion at or near gastroduodenal junction: A ≥ 5 cm margin of duodenal stump should be included if the gross lesion extended to the gastroduodenal junction as defined pathologically.

6.1.7 Simulation
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).

6.1.8 Initial Treatment Field Definition
Prior to simulation, pertinent radiographs, operative notes and the surgical pathology report must 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 patients’ positioning using fluoroscopy.

6.1.9 AP:PA Initial Field Borders: In general:
• Superior Border – will be at the T8, T9 or T10 interspace (to treat the celiac axis, gastroesophageal junction), gastric fundus, and dome of diaphragm).
• Inferior Border – the L3-L4 lateral to the vertebral body (to encompass the porta hepatis, gastric antrum, medial duodenal wall, and gastroduodenal nodes). If the distal stomach was involved, the entire circumference of duodenum should be included in the field for ≥ 5 cm beyond gross disease.
• Left Margin: Sufficiency lateral to include the tumor bed and if appropriate, 2/3 – 3/4 of the left hemidiaphragm (to include the gastric fundus, splenic and suprapancreatic nodes, and left hemidiaphragm in proximal T3, T4 lesions). These borders may be modified based on pre-treatment imaging, laparoscopy descriptions, clip placement and postoperative imaging (including planning CT) information of the tumor and nodal site location.
• Lateral Field Borders: The borders of the lateral fields (if used) 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 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 bed, the lateral fields may need to be obliqued slightly to spare the spinal cord.
• Anterior Margin: The gastric bed extends anteriorly to the anterior abdominal wall in most patients. Therefore, the anterior abdominal wall is the appropriate anterior border for the majority of patients.

Note: these borders will require individualization.
Radiographs are then obtained for AP:PA and lateral fields. Appropriate skin localization marks are made on the patients to ensure that patients positioning will be identical in all planning steps.

6.1.10 Kidney Volume Definition – CT target planning with or without contrast will be used to define the kidneys.

6.1.11 Definition of Stomach and Duodenum: Oral contrast: the patient drinks oral contrast (barium or gastrografin +/- esophotrast) in order to document the position of the gastric remnant, distal esophagus anastomosis and duodenum. Radiographs are again obtained for the AP:PA and lateral fields.

6.1.12 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, hepatic and cardiac shielding.

6.1.13 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, as least 1/2 of the 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.

6.1.14 **Cardiac Shielding**: With proximal gastric lesions or lesions at the esophagogastric junction, inclusion of 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.

6.1.15 **Dose – Time Factors:**
- The specification of the target dose is in terms of a dose to a point at or near the center of the target volume. ICRU prescription point = isocenter = center of CTV (should also be the center of PTV).
- All fields will be treated each day.
- Isodose distributions on a plane containing the central axis are mandatory.
- Central axis isodose distributions should have no more than +/- 10% dose variation within the target volume.
- Patients receive 1.8 Gy per day to isocenter, five days per week.

6.1.16 **Dose Limiting Structures**
- The spinal cord dose must not exceed 45 Gy.
- The cardiac silhouette must not have greater than 30% of its area exposed to a dose of 40 Gy.
- At least 2/3 of one functioning kidney should receive a dose ≤ 20 Gy.
- The liver must not have more than 60% of its volume exposed to more than 30 Gy.

6.1.17 **Radiation Checklist**
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 neutrophil count falls below 1,000/mm$^3$ or the platelet count falls below 50,000/mm$^3$ during the course of radiation therapy, treatment should be delayed until the counts rise above these levels.

Port films will be taken of each field at the initiation of treatment and at least every other week during treatment. (11/01/02)

**Supportive Therapy**: If estimated caloric intake is less than 1500 kilocalories or if weight loss is ≥ 5% of pretreatment weight, oral, enteral and/or intravenous hyperalimentation should be considered. Institutions may place feeding jejunostomy prior to initiating EBRT.

**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.

6.1.18 **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/mm$^3$; platelet count ≤ 50,000/mm$^3$; vomiting ≥ 3/day unresponsive to antiemetics; diarrhea ≥ 5 watery stools/day unresponsive to antidiarrheals; or weight loss ≥ 10% of pretreatment weight. Rarely, non-treatment 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.

**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 patients’ therapy should resume and full protocol dose delivered. The toxicity which forced any dose reduction must be documented.

6.2 **Quality Assurance of Field Placement/Dose Distribution (11/01/02)**

6.2.1 **Patients will undergo CT planning.**

6.2.2 **THE PLANNING DATA, INCLUDING PLANNING CT SCAN, SIMULATION FILMS, ISODOSE DISTRIBUTIONS (AXIAL, CORONAL, AND SAGITTAL PLANES THROUGH THE PTV) WILL BE SENT TO RTOG HEADQUARTERS FOR RAPID REVIEW BY THE STUDY CHAIR OR HIS DESIGNEE (SEE SECTION 12).**

7.0 **DRUG THERAPY (8/25/03)**

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control Guidelines stated in the RTOG Procedure Manual

7.1 **Arm 1 (Arm 1 closed to accrual May 21, 2003)**
Pre-radiation Chemotherapy (Arm 1) (Arm 1 closed to accrual May 21, 2003)

7.1.1 Patients will need a double lumen central line placed for chemotherapy administration. (2/18/02)

7.1.2 Patients will receive two cycles of chemotherapy prior to chemoradiotherapy. Treatment must begin within 8 weeks of surgery. (11/01/02)

7.1.3 Schedule: Outpatient administration is encouraged. Treatment will be given Days 1-5 and 29-33. Chemotherapy schedule is as follows: (11/01/02)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily Dose</th>
<th>Schedule</th>
<th>On Days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>600 mg/m²/day</td>
<td>24-hr continuous infusion by a portable pump</td>
<td>1-5; 29-33</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²/day</td>
<td>IV in 1 hour infusion</td>
<td>1-5; 29-33</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>175 mg/m²</td>
<td>24-hr infusion</td>
<td>1; 29</td>
</tr>
</tbody>
</table>

*Cycle 1: Days 1-5 5-FU and cisplatin; Day 1 paclitaxel
*Cycle 2: Days 29-33 5-FU and cisplatin; Day 29 paclitaxel

As noted below, subsequent doses of chemotherapy may be decreased by 20% based on toxicity experienced during the preceding cycle.

Adequate hydration, electrolyte supplementation, and antiemetic support will be provided according to institutional guidelines. Decadron premedication will be administered according to institutional guidelines.

Cycle #2 (Days 29-33) will be given provided the patient has recovered from all toxicities and peripheral counts (absolute neutrophil count (ANC) > 1,500/mm³ and platelets > 100,000/mm³). If the counts are below this level, hold chemotherapy for one week (to Day 36). See below for dose modification.

7.1.4 Dose Modification (Pre-chemoradiation Arm 1) (11/01/02)

Reduction of chemotherapy dose for Cycle #2 will be based on the degree of hematologic and nonhematologic toxicities.

If a treatment interruption is for greater than two weeks because of severe toxicity, pre-radiation chemotherapy will be stopped and the patient will proceed to concurrent chemoradiotherapy after toxicity levels have decreased but within six weeks.

Dose modification for Cycle #2 Taxol® and cisplatin will be based on hematologic toxicities.

<table>
<thead>
<tr>
<th>ANC 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>Between 500 and 1,000</td>
<td>and/or Between 50,000 and 75,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>and/or &lt; 50,000</td>
<td>Decrease 20% (applies to both drugs)*</td>
</tr>
<tr>
<td>Infection and/or bleeding related to myelosuppression</td>
<td></td>
<td>Decrease 20% (applies to both drugs)*</td>
</tr>
</tbody>
</table>

* At the discretion of the investigator, colony-stimulating factor may be used.

The following dose modifications for 5-FU, Taxol® and cisplatin based on nonhematologic toxicities will be applicable for Cycle #2:

<table>
<thead>
<tr>
<th>Non-hematologic Toxicity Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>No change</td>
</tr>
<tr>
<td>3-4</td>
<td>Decrease 20% (applies to all three drugs)</td>
</tr>
</tbody>
</table>
The following dose modification for Cycle #2 cisplatin based upon renal insufficiency occurring with Cycle #1 cisplatin will be followed:

<table>
<thead>
<tr>
<th>Maximum serum creatinine (mg/dl) in a well-hydrated state with two readings</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.4</td>
<td>No change in cisplatin dose for Cycle #2</td>
</tr>
<tr>
<td>1.5 to 2.0</td>
<td>Decrease cisplatin dose 50% for Cycle #2</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Discontinue cisplatin</td>
</tr>
</tbody>
</table>

7.1.2 Concurrent Chemoradiotherapy (Arm 1) (Arm 1 closed May 21, 2003)

Concurrent chemoradiotherapy should begin 3-4 weeks after the completion of Cycle #2 of pre-radiation chemotherapy. It should begin no later than 6 weeks after the completion of Cycle #2 of pre-radiation chemotherapy. Concurrent chemotherapy will consist of 5-FU and Taxol®. 5-FU will be given at 300 mg/m²/day as continuous infusion by a portable pump 5 days per week during radiotherapy (5-FU can be initiated Monday morning and can be completed by Friday evening, even though this means that the “Friday dose” will not reach a full 300 mg/m². Once the radiotherapy is completed on Friday, patients should have their infusion pumps disconnected irrespective of the volume of uninfused 5-FU. The uninfused 5-FU should be discarded). Taxol® will be given on Days 1, 8, 15, 22, and 29 of radiotherapy at a planned dose of 45 mg/m² i.v. over 3 hours. If a radiation treatment break is required, all chemotherapy will be held until radiation resumes.

7.1.2.1 Dose modification for Concurrent Chemoradiotherapy (Arm 1) (Arm 1 closed May 21, 2003)

Patients will be examined at least once weekly. 5-FU dose modifications will be based on nonhematologic toxicity observed during chemoradiotherapy. If 5-FU is held, radiotherapy will also be temporarily held. If a treatment interruption is for greater than two weeks because of severe toxicity, the patient will be considered “off study”. The patient will be treated at the discretion of their physician and follow-up data will continue to be submitted.

The dose modification for 5-FU is as follows:

<table>
<thead>
<tr>
<th>Non-hematologic Toxicity Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>No change</td>
</tr>
<tr>
<td>3-4</td>
<td>Hold 5-FU (and radiation) for 5 days (one treatment week) and then resume at 250 mg/m²/day for the remaining duration of therapy provided the toxicity has improved to Grade 2 or less. If the toxicity has not decreased to Grade 2 or less after one treatment week, continue to hold 5-FU, paclitaxel, and RT for another treatment week.</td>
</tr>
</tbody>
</table>
Taxol® doses during radiotherapy will be based on myelosuppression as follows:

<table>
<thead>
<tr>
<th>ANC Nadir</th>
<th>Platelet Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,000 and</td>
<td>&gt; 75,000</td>
<td>No change</td>
</tr>
<tr>
<td>Between 500 and</td>
<td>Between 50,000 and</td>
<td>No change</td>
</tr>
<tr>
<td>1,000</td>
<td>75,000</td>
<td></td>
</tr>
<tr>
<td>&lt; 500*</td>
<td>&lt; 50,000</td>
<td>*Skip the dose of Taxol® (continue radiation) until ANC &gt; 1,000 and/or platelets &gt; 100,000 then resume with 20% reduction</td>
</tr>
</tbody>
</table>

Infection and/or bleeding related to myelosuppression**

**Skip the dose of Taxol® (hold radiation & 5-FU as well) until ANC > 1,000 and/or platelets > 100,000 then resume with 20% reduction

*If Taxol® is held for cytopenias without infection/bleeding for greater than two weeks, radiation/5-FU will continue as planned.

** If infection and/or bleeding occurs and counts have not recovered after two weeks, all treatments will be discontinued and the patient will be taken “off study.”

7.2 Arm 2

7.2.1 Pre-radiation Chemotherapy (Arm 2)

7.2.1.1 Venous access through a central line is required.

7.2.1.2 Patients will receive two cycles of chemotherapy prior to chemoradiotherapy. Treatment must begin within 8 weeks of surgery. (11/01/02)

7.2.1.3 Schedule: Outpatient administration is encouraged. Treatment will be given on Days 1 and 29. Chemotherapy schedule is as follows: (11/01/02)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily Dose</th>
<th>Schedule</th>
<th>On Days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>175 mg/m²/day</td>
<td>3-hr infusion</td>
<td>1 and 29</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
<td>i.v. in 1 hour infusion</td>
<td>1 and 29</td>
</tr>
</tbody>
</table>

*Cycle 1: Day 1 paclitaxel and cisplatin
*Cycle 2: Day 29 paclitaxel and cisplatin

Adequate hydration, electrolyte supplementation, and antiemetic support will be provided according to institutional guidelines. Decadron premedication will be administered according to institutional guidelines.

7.2.1.4 Dose Modification (Pre-chemoradiation Arm 2) (11/01/02)
The dose of chemotherapy will be attenuated as follows: cisplatin and paclitaxel doses will be modified on the basis of the most severe toxicity seen during the previous cycle (previous week) of chemotherapy.

If a treatment interruption is for greater than two weeks because of severe toxicity, pre-radiation chemotherapy will be stopped and the patient will proceed to concurrent chemoradiotherapy after toxicity levels have decreased but within six weeks.

If a patient develops Grade 3-4 peripheral neurologic toxicity, both cisplatin and taxol will be held until resolution to Grade 2 or less. Chemotherapy may be continued for Grade 1-2 neuropathy.

In addition, Cisplatin dose modification will be based on renal toxicity as follows:

<table>
<thead>
<tr>
<th>Maximum serum creatinine (mg/dl) in a well hydrated state with two readings</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.4</td>
<td>No change in cisplatin dose</td>
</tr>
<tr>
<td>1.5 to 2.0</td>
<td>Decrease cisplatin dose 50% (rounded down to 37 mg/m²)</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Hold cisplatin (re-evaluate the following week)</td>
</tr>
</tbody>
</table>
In addition, Taxol® dose modification will be performed based on myelosuppression as follows:

<table>
<thead>
<tr>
<th>ANC Nadir</th>
<th>Platelet Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500 and</td>
<td>&gt; 75,000</td>
<td>No change</td>
</tr>
<tr>
<td>Between 1,000 and 1,500</td>
<td>&gt; 75,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 1,000 and/or &lt; 75,000</td>
<td></td>
<td>Decrease Taxol® dose by 50% (rounded down to 87 mg/m²/day). Continue cisplatin at the same dose.</td>
</tr>
</tbody>
</table>

7.2.2 Concurrent Chemoradiotherapy (Arm 2) (11/01/02)

Concurrent chemoradiotherapy should begin 3-4 weeks after the completion of Cycle #2 of pre-radiation chemotherapy. It should begin no later than 6 weeks after the completion of Cycle #2 of pre-radiation chemotherapy. Concurrent chemotherapy will consist of cisplatin and Taxol®. Cisplatin will be given at 30 mg/m² once weekly during radiation (Days 1, 8, 15, 22, 29). Taxol® will be given as a continuous 96-hour infusion via an implanted venous access device (e.g. Mediport). Taxol® therapy should be started as early as possible on Monday morning. In this way, patients will receive 15 mg/m² of Taxol® each day for 4 consecutive days, so that day #4 of treatment (started on Thursday) is completed on day #5 (Friday) of each week. Because of the stability of Taxol®, the pumps can only hold 30 mg/m² of Taxol®. This is sufficient for the first two days of therapy. Therefore, on Wednesday of each week, the cassette will be changed and the pump refilled with another 30 mg/m² of Taxol®. In this way, the Taxol® should be completely infused by Friday of each week and the patient will have received a total Taxol® dose of 60 mg/m² over the 4 consecutive days (96 hours). The continuous infusion Taxol® will correspond to radiation treatment days (e.g. Monday morning through Friday morning). If a radiation treatment break is required, chemotherapy will be held until radiation resumes. The daily dose of Taxol® will be 15 mg/m²/day (i.e. 60 mg/m²/96 hrs).

Between starting the Taxol® on day 1 of each cycle and prior to the administration of cisplatin, prehydration of 500 to 1,000 cc of normal saline should be given. This can take between one to two hours.

Decadron premedication is not required for the 96-hour infusional Taxol®. However, premedication for the 96-hour infusional Taxol® is at the discretion of the treating physician.

Schedule of Concurrent Chemoradiotherapy (Arm 2)

<table>
<thead>
<tr>
<th>Drugs/Radiation</th>
<th>Daily Dose</th>
<th>Schedule</th>
<th>On Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>1.8 Gy/day</td>
<td>Once daily</td>
<td>1-5; 8-12; 15-19; 22-26; 29-33</td>
</tr>
<tr>
<td>Taxol®</td>
<td>15 mg/m²/day x 4 days (60 mg/96 hr.)</td>
<td>96-hr continuous infusion by a portable pump</td>
<td>1-5; 8-12; 15-19; 22-26; 29-33 (corresponding exactly to radiation days)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>30 mg/m²</td>
<td>1-hr infusion</td>
<td>1; 8; 15; 22; 29</td>
</tr>
</tbody>
</table>

7.2.2.1 Dose Modification for Concurrent Chemoradiotherapy (Arm 2) (11/01/02)

The dose of concurrent chemotherapy will be attenuated as follows: cisplatin and paclitaxel doses will be modified on the basis of the most severe toxicity seen during the previous cycle (previous week) of concurrent chemoradiotherapy. If radiotherapy is held for toxicity (e.g. mucositis, esophagitis), chemotherapy (both cisplatin and Taxol®) will also be held.

If a treatment interruption is for greater than two weeks because of severe toxicity, the patient will be considered “off study.” The patient will be treated at the discretion of their physician and follow-up data will continue to be submitted.

If a patient develops Grade 3-4 peripheral neurologic toxicity, both cisplatin and Taxol® will be held until resolution to Grade 2 or less. Chemotherapy may be continued for Grade 1-2 neuropathy.
In addition, Cisplatin dose modification will be based on renal toxicity as follows:

<table>
<thead>
<tr>
<th>Maximum serum creatinine (mg/dl) in a well-hydrated state with two readings</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.4</td>
<td>No change in cisplatin dose</td>
</tr>
<tr>
<td>1.5 to 2.0</td>
<td>Decrease cisplatin dose 50% (to 15 mg/m²)</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Hold cisplatin (re-evaluate the following week)</td>
</tr>
</tbody>
</table>

In addition, Taxol® dose modification will be performed based on myelosuppression as follows:

<table>
<thead>
<tr>
<th>ANC Nadir</th>
<th>Platelet Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500</td>
<td>and &gt; 75,000</td>
<td>No change</td>
</tr>
<tr>
<td>Between 1,000 and 1,500</td>
<td>and &gt; 75,000</td>
<td>Decrease Taxol® dose by 50% (to 7.5 mg/m²/day x 4 days); continue cisplatin at same dose.</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>and/or &lt; 75,000</td>
<td>Hold Taxol® (re-evaluate the following week). Hold radiation and cisplatin as well.</td>
</tr>
</tbody>
</table>

7.3 Cisplatin

7.3.1 Method of Action

One mode of action appears to be the inhibition of DNA precursors, although RNA and protein synthesis are also inhibited but to a lesser degree. Cisplatin has properties similar to that of a bifunctional alkylating agent producing intrastrand and interstrand crosslinks in DNA.

7.3.2 Procurement and Storage (2/18/02)

Cisplatin is supplied as a 1mg/ml solution for injection or a lyophilized powder in 50 mg vials that is reconstituted in normal saline to a final concentration of not less than 1 mg/ml. The drug is infused via a peripheral running i.v. at a maximum rate of 500 cc over 1 hour. Cisplatin is commercially available.

7.3.3 Toxicities

Toxicities associated with cisplatin include nausea, vomiting, renal toxicity, ototoxicity, myelosuppression, platelet suppression, and delayed erythropoiesis.

7.4 5-Fluorouracil

7.4.1 Method of Action

5-Fluorouracil (5-FU) is a pyrimidine antimetabolite that blocks the methylation reaction of deoxyuridylic acid, interfering with the synthesis of DNA. It is also incorporated into RNA and interferes with its functions. The drug is metabolized by the liver and is partially excreted via the kidneys. 5-FU is active in a number of malignancies including carcinomas of the colon, stomach, ovary and breast.

7.4.2 Procurement and Storage (2/18/02)

5-FU is commercially available as a 50 mg/ml solution for injection. It is stable if protected from light. If a precipitate is present, it is to be gently heated to no greater than 140°F in a water bath. 5-FU should be stored at room temperature. In aqueous solution it is colorless to faint yellow, and is pH adjusted with sodium hydroxide to 8.6-9.0.

7.4.3 Toxicities

Toxicities associated with the systemic administration of 5-FU include nausea and vomiting, stomatitis, phlebitis, diarrhea, myelosuppression, alopecia, rash, photosensitivity, cerebellar ataxia (rare), and very occasionally angina with accompanying EKG changes.

7.5 Paclitaxel

(Paclitaxel) Paclitaxel is a plant product from the stem bark of Taxus brevis, the western yew, a small evergreen that is native to the Pacific Northwest.

7.5.1 Method of Action

Paclitaxel has a unique mechanism of action. In contrast to other known mitotic spindle poisons (vinca alkaloids, colchicine, and podophyllotoxin), which inhibit tubulin polymerization, paclitaxel markedly enhances microtubule assembly. Microtubules formed in the presence of paclitaxel are unusually stable. Studies with purified microtubule protein have demonstrated that paclitaxel promotes the assembly of tubulin into calcium stable microtubules in vitro in the presence or absence of GTP or microtubule-associated proteins. Paclitaxel binds directly to polymerized tubulin with saturation occurring at an approximate 1:1 stoichiometry with tubulin dimers.

7.5.2 Hypersensitivity reactions to vehicle, Cremophor EL (2/18/02) (11/01/02)
Premedication with dexamethasone, diphenhydramine, and H2 blockers such as ranitidine or cimetidine has virtually eliminated all adverse hypersensitivity reactions. **Premedication is not required using a 96-hour infusion schedule (Arm 2); routine premedication will not be required for the low dose 96-hour continuous infusion of paclitaxel that is given with radiation therapy.**

7.5.3 **Product Description (2/18/02)**

Paclitaxel is supplied as a fully reconstituted 6 mg/ml sterile solution for injection in polyethoxylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%.

7.5.4 **Solution Preparation (2/18/02)**

The appropriate dose of paclitaxel should be withdrawn from the vials and further diluted with 0.9% sodium chloride.

7.5.5 **Procurement and Storage Requirements**

Paclitaxel is commercially available. The intact vials will be stored under refrigeration. Doses will be prepared prior to use because of the concentration dependent stability of paclitaxel. This is a physical stability problem and not a chemical one; precipitation may occur if the stability guidelines are exceeded. After further dilution in polyolefin containers, paclitaxel is stable for 48 hours in concentrations up to 1.2 mg/ml; however, the National Cancer Institute recommends that a concentration of 0.6 mg/ml not be exceeded so that the cremaphor diluent will not be administered too rapidly. Because of the 48 hour stability of paclitaxel, treatment cassettes during the 96 hour infusion will be prepared for two 48 hour treatment intervals, i.e. with one treatment cassette change on day 3. All of these solutions will exhibit a slight haze. A small number of particles have been observed after dilution; therefore, in-line filtration is necessary with all paclitaxel infusions. Analysis of solutions filtered through IVEX-2 (Abbott) 0.2 micron filters showed no appreciable loss of potency. Only glass or polyolefin containers and polyethylene-lined nitroglycerin tubing should be used to prevent the leaching of DEHP, a plasticizer, from plastic tubing or solution bags composed of polyvinyl chloride.

7.5.6 **Administration (2/18/02)**

Paclitaxel exhibits concentration dependent precipitation and must be administered within 48 hours after addition to infusion fluids. The total dose must be administered through a standard 0.22 micron filter.

7.5.6.1 A central venous catheter (CVC) is required.

7.5.6.2 There is no premedication for this regimen.

7.5.6.3 Details of Administration: Paclitaxel will be administered over 96-hours (4 days). Because paclitaxel is stable for only 48 hours, pump cassettes will be changed every 48 hours. To prevent problems with precipitation of paclitaxel in the tubing, distal to the filter, the following procedures will be required to each pump change.

Carefully inspect the tubing from the patient’s central venous catheter to the filter for evidence of any precipitation. If a precipitate is seen in the tubing connecting the patient’s CVC to the infusion tubing, change the tubing. If the patient has an implanted CVC (Port-A-Cath) and there is precipitate in the tubing of the Huber needle, remove the Huber needle and re-access the port with a new needle and tubing.

Remove all of the tubing, the filter and the completed bag of paclitaxel. Flush the catheter with heparin. Use a completely new filter and tubing to connect the next bag of paclitaxel.

7.5.7 **Toxicities**

Neutropenia, leukopenia, thrombocytopenia, anemia, infections, bleeding, hypersensitivity reactions, changes in vital signs including bradycardia and hypotension, abnormal ECG, peripheral neuropathy, myalgias, arthralgias, nausea and vomiting, alopecia, bilirubin elevations, alkaline phosphatase elevations, AST elevations, injection site reaction.

7.6 **Toxicity Reporting**

7.6.1 The revised NCI Common Toxicity Criteria (CTC) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities and can be downloaded from the CTEP home page (http://ctep.info.nih.gov). This study will be monitored by the Clinical Data Update System (CDUS) Version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. 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.

7.6.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected (phone report within 24 hours; written report within 10 days).
7.6.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.6.1.3 Any death on study if clearly related to the commercial agent(s).
7.6.1.4 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. For cases that are diagnosed with AML/MDS during or subsequent to protocol treatment, the Secondary AML/MDS Form must be completed within 30 days of AML/MDS diagnosis and mailed to NCI/CTEP at the address listed on the form. A copy must be sent to RTOG Headquarters. The submission of a Secondary AML/MDS Form cancels the need to submit to CTEP a Form FDA 3500 Adverse Event Form for cases of secondary AML/MDS. The AML/MDS Form may be downloaded from the “forms” category on the CTEP website; the web address is given in Section 7.6.1.
7.6.2 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

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY
Not applicable to this study.
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (11/01/02)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Study</th>
<th>Weekly</th>
<th>Prior to RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical</td>
<td>X&lt;br&gt;b</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;d</td>
</tr>
<tr>
<td>CBC, Diff, Platelets</td>
<td>X&lt;br&gt;a</td>
<td>X&lt;br&gt;d</td>
<td>X&lt;br&gt;c</td>
</tr>
<tr>
<td>Screening Profile: Alk Phos, Bilirubin, AST, ALT, BUN, Albumin, LDH, Total Protein, Creatinine, Electrolytes</td>
<td>X&lt;br&gt;a</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
<tr>
<td>Pregnancy Test (if applicable)</td>
<td>X&lt;br&gt;d</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
<tr>
<td>Creatinine Clearance (calculated or actual)</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
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<tr>
<td>Chest x-ray</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
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<tr>
<td>Abdominal &amp; Pelvis CT</td>
<td>X&lt;br&gt;d</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
<tr>
<td>Audiogram (if clinically indicated)</td>
<td>X&lt;br&gt;d</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
</tbody>
</table>

- a. Within two weeks prior to study entry
- b. Within four weeks prior to study entry
- c. Physical exam prior to each induction chemotherapy cycle, and weekly physical exam during chemoradiotherapy only
- d. Weekly CBC with differential during induction chemotherapy and chemoradiotherapy
- e. Creatinine and electrolytes only prior to each weekly cisplatin
- f. Prior to each induction chemotherapy cycle; during chemoradiotherapy weeks 1 and 5 only
- g. Prior to RT ANC ≥ 1500/mm³, platelets ≥ 100,000/mm³; caloric intake ≥ 1500 kCal/day

(2/18/02)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At Treatment Completion</th>
<th>Every 3 months</th>
<th>Every 6 months</th>
<th>Annually</th>
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<tr>
<td>History &amp; Physical</td>
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<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
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<tr>
<td>CBC, Platelets</td>
<td>X</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
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<tr>
<td>Electrolytes, Creatinine- Screening Profile</td>
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<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal &amp; Pelvis CT</td>
<td>X</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
<td>X&lt;br&gt;c</td>
</tr>
</tbody>
</table>

- a. For the first 2 years after treatment completion
- b. For years 3 and 4 after treatment completion
- c. Year 5 and beyond after treatment completion
- d. Every 6 months after treatment completion for 2 years
- e. Only as clinically indicated beyond two years after treatment completion

11.2 Treatment Evaluations (11/01/02)

CBC and platelet count will be required on day 1 of treatment, prior to and weekly during chemotherapy and chemoradiotherapy. Screening profile will be done prior to each induction chemotherapy cycle, prior to chemoradiation, and weeks 1 and 5 during chemoradiation. Creatinine and electrolytes will be done prior to weekly cisplatin and weekly during chemoradiation. Physical examination and assessment of toxicity will be done prior to each chemotherapy treatment during chemotherapy alone; weekly status checks during chemoradiation treatment.

11.3 Therapy at the Time of Recurrence (11/01/02)

In the event that local regional or distant recurrence is found, patients will be offered therapy at the discretion of their attending physician. Therapy on recurrence may include (but is not limited to) conventional or investigational forms of chemotherapy, radiation therapy for local recurrence, or in selected patients re-exploration and attempted resection of local recurrence. Biopsy proof of recurrence if at all possible is strongly urged.
11.4 Criteria for Removal From Protocol Treatment (2/18/02)
Efforts shall be made to account for all patients entered into the study during the evaluation of results. However, in detailed evaluation, the following patients categories will be considered:

11.4.1 At the time of disease progression while undergoing treatment, the patient will be taken off protocol treatment; however, follow-up for evaluation will continue.

11.4.2 Early Deaths: Those patients who died as a result of an event not related to their malignancy or to the study drug within six weeks of beginning therapy.

11.4.3 Lost to Follow-Up: Those patients in whom there is inadequate information to judge tumor response because of loss of contact; repeated attempts to obtain information were unsuccessful.

11.4.4 Major Protocol Violation: Patients who deviate from the protocol treatment program by adding a chemotherapeutic agent, by substantially modifying the dosage and schedule of the study drug, or receive further non-protocol treatment without disease progression.

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

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
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</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
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<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>At completion of induction chemotherapy</td>
</tr>
<tr>
<td>Preliminary Dosimetry Information: (11/01/02)</td>
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<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
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<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Planning CT and CT Report (C1, C3)</td>
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<tr>
<td>Final Dosimetry Information: Treatment Form (TF)</td>
<td>Within 1 week of RT end</td>
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<tr>
<td>Daily Treatment Record (T5)</td>
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<tr>
<td>Isodose Distribution (T6)</td>
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<tr>
<td>Boost Films (simulation and portal) (T8)</td>
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<tr>
<td>Initial Followup Form (FS)</td>
<td>Three months after the start of RT</td>
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<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
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</table>

13.0 STATISTICAL CONSIDERATIONS

13.1 Introduction

13.1.1 This trial is designed to determine if either of the two treatment arms under consideration is promising enough to be pursued in a subsequent phase III study against the recently completed intergroup protocol 0116 (RTOG 90-18) adjuvant arm. That arm had one- and two-year disease-free survival rates of 69% and 52%.13

13.1.2 A secondary objective of the trial is to determine if the treatment arms can be delivered as safely and successfully as the intergroup adjuvant arm. On that protocol, 63% (165/260) of the patients were able to complete treatment as planned. Due to the positive results of the study, we would anticipate that the arms of this study have a higher completion rate. We hypothesize 75%.

13.1.3 An additional objective of the study is to see if the treatment toxicities of the two arms under study are no worse than the adjuvant arm of the intergroup. Of 263 patients with available toxicity information,
there were 103, 85, and 3 grade 3, 4, and 5 toxicities observed, including 77, 8, and 0 respectively of gastrointestinal toxicities and 68, 73, and 0 hematologic toxicities.

13.2 Sample Size Considerations (8/25/03)

With a sample size of 43 analyzable patients, we would have a one-sided 97.5% confidence interval around the hypothesized 67% two-year disease-free survival rate with a lower-bound of 52.9%. In other words, we would have a 5% chance of observing a two-year disease-free survival rate of less than 52.9% if the true rate is 67%.

Utilizing that sample size of 43, we would have 74% power (type I error rate of 0.10) of detecting a 15% increase from the observed 60% rate in the intergroup to our projected 75%.

Of greatest interest to us is the rate of grade 3 or greater toxicities. In the intergroup, grade 3 or worse overall toxicities occurred in 73% of the cases. With 43 analyzable patients and a type I error rate of 0.10, we would have 55% power of detecting a 10% absolute increase in rate of toxicity and 86% power to detect a 15% absolute increase. Limiting to grade 3 or worse hematologic toxicities, we would have 51% power of detecting a 10% absolute increase (54% to 64%) and 77% power of detecting a 15% absolute increase (54% to 69%); looking only at grade 3 or worse GI toxicities, we would have 44% power to detect an increase from 32% to 42% and 70% power of detecting an increase from 32% to 47%. Grade 5 (fatal) toxicities occurred in 1% of patients on INT 0116. We would have 21% power to detect an increase of 1%, 37% power to detect a 2% increase, and 64% power to detect a 5% rate of fatal toxicities.

13.2.1 (May 21, 2003)

Arm 1 is closed to accrual with a total of 30 patients. See Section 13.5.2.1. The total sample size required for the study will be 94 patients. This includes 43 patients per arm, plus an additional 10% to adjust for ineligibility.

13.3 Patient Accrual

In the last intergroup phase III study (INT 0116/RTOG 90-18), the RTOG contributed approximately 20 cases a year. Due to the positive results of the intergroup study, we would anticipate an increased accrual to 30 cases per year, meaning that the accrual portion of the study should take 3 years.

13.4 Randomization Scheme (8/25/03)

Patients will be randomized to one of two combined-modality schedules in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen14 will be used because it balances patient factors other than institution. Additionally, patients will be stratified by T-stage (T1-2 vs. T3 vs. T4) and by the number of involved lymph nodes (none vs. one, two, or three vs. four or more) as was done in INT 0116.

13.4.1 (May 21, 2003)

Arm 1 is closed to accrual. See Section 13.5.2.1. All patients entered onto this study will now be assigned to Arm 2. T-Stage and lymph node status will continue to be recorded at registration but, since the study is only accruing to one arm now, the patients are not being stratified.

13.5 Analyses Plans (8/25/03)

13.5.1 Interim Analyses

Interim reports with statistical analyses are prepared every 6 months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a. Patient accrual rate with a projected completion date for the accrual phase;
b. Quality of submitted data with respect to timeliness, completeness, and accuracy;
c. Compliance rate of treatment delivery with respect to the protocol prescription;
d. Frequencies and severity of the toxicities.

13.5.2 Early Stopping Due to Toxicity (8/25/03)

If, at any interim analysis, one arm has three or more treatment related deaths, the statistician will recommend to the study chair that the arm be closed to further accrual. Additionally, once the first 22 analyzable patients have entered the study, if the rate of grade 3 or worse GI toxicities exceeds 47%, the statistician will recommend to the study chair that consideration be given to closing that arm to further accrual.

13.5.2.1 (May 21, 2003) A review of the toxicities/adverse events (AE) associated with the trial was undertaken per the protocol guidelines (Section 13.5.2 Early Stopping Due to Toxicity) by the Study Chairs, GI Committee Chair, the RTOG Statistical Center, and RTOG Headquarters. The protocol stipulates that evaluation of the first analyzable 22 patients on each arm is to be done. If the rate of grade 3 or worse GI toxicities exceeds 47%, the statistician will recommend to the study chairs that consideration be given to
closing that arm to further patient accrual. A conference call was held on May 14, 2003. For Arm 2 (CDDP/Paclitaxel), the GI grade 3 toxicity rate of 24% (5/21) was reported with no grade 4 or 5 (fatal) GI toxicities. For Arm 1 (5-FU/CDDP/Paclitaxel), the GI grade 3 toxicity rate of 59% (13/22) was reported with one grade 4 toxicity (anorexia) but no grade 5 (fatal) GI toxicities. When all toxicities were considered, the worst reported toxicity was a grade 3 in 9 (41%) patients, a grade 4 in 11 (50%) patients, and no grade 5 (fatal). One grade 4 was an infection/febrile neutropenia occurrence. After discussing these data, it was decided to discontinue any further randomization to Arm 1 (5-FU/CDDP/Paclitaxel) because the rate of GI toxicity would be unacceptably high for an experimental arm in a subsequent phase III trial. All patients entering RTOG G-0114 will now be assigned to Arm 2 to complete the trial so that efficacy can be evaluated per protocol design (Section 13.5.3).

13.5.3 Analysis for Reporting the Initial Treatment Results (2/18/02)
The final analysis will be performed two years after the last patient has been entered in the study. All eligible patients (as per Section 3.0) that begin protocol treatment will be included in the analysis. Patients that are removed from protocol treatment for any reason (including those that have an early death, are lost to follow-up, or are a major protocol violation) will be included. The final analysis will include:

a. Tabulation of all cases entered, and any excluded from the analyses with reasons for exclusion;
b. Institutional accrual;
c. Distribution of the important prognostic baseline variables;
d. Observed results with respect to treatment delivery, toxicity, disease-free survival and overall survival.

These endpoints will be estimated with a binomial distribution along with a two-sided 95% confidence interval. If the estimated disease-free survival rate for either arm is greater than or equal to 52.9%, then it will be strongly considered as a possible arm in a subsequent phase III protocol, assuming treatment delivery and toxicities are judged to be acceptable. Furthermore, should both arms prove to be tolerable and efficacious, the RTOG will use statistical selection theory to choose which arm should be considered for further testing in the follow-up trial. Briefly, its criterion is to select the treatment arm with the highest response regardless of how small or “non-significant” the advantage is over the other treatment arm. With 43 patients in each arm, we would have a greater than 80% probability of correctly selecting the better treatment arm when there is an absolute difference of 15% in disease-free survival rates between the two arms. Further subgroup analysis would not be undertaken because of the small sizes in each subgroup.

13.5.4 Inclusion of Women and Minorities
In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we would anticipate the following distribution of patients on this protocol:

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian</th>
<th>Black or African American</th>
<th>Hispanic or Latino</th>
<th>Native Hawaiian or Pacific Islander</th>
<th>White</th>
<th>Other or Unknown</th>
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<td>Female</td>
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<td>0</td>
<td>63</td>
<td>0</td>
<td>94</td>
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</tbody>
</table>
REFERENCES


13. Personal Correspondence


SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A RANDOMIZED PHASE II COMPARISON OF TWO CISPLATIN-PACLITAXEL CONTAINING CHEMORADIATION REGIMENS IN RESECTED GASTRIC CANCERS

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know”, is available from your doctor.

You are being asked to take part in this study because you have stomach cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) chemotherapy alone followed by chemotherapy given with radiation together have on you and your cancer. We also want to see how many patients can tolerate this treatment without severe side effects.

This research is being done to test the safety and effectiveness of two new treatment regimens and to see how these regimens will affect your cancer. We do not know which of these two treatments is better.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 94 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (8/25/03)

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal, one in two chance of being placed in either group.

Note: This was a randomized study, but patients enrolling after May 21, 2003, will receive Treatment Two. Treatment One has been stopped due to side effects experienced by patients.

If you take part in this study, you will receive Treatment Two.
Treatment One: Stopped May 21, 2003

You will receive two cycles of chemotherapy called 5-FU, Cisplatin, and Paclitaxel. For 5 days, you will receive 5-FU continuously through a tube into your vein (intravenously). You will receive Cisplatin intravenously for 1 hour a day for the same 5 days, while you are still receiving the continuous intravenous 5-FU. Also on the first day of this treatment, you will receive Paclitaxel for 24 hours continuously through a tube into your vein. The second cycle of chemotherapy will be the same as the first cycle of chemotherapy, and will be started 28 days after the first cycle started. Each cycle lasts 5 days.

Between three to six weeks after completing your chemotherapy, you will receive radiation therapy once a day, five days a week, Monday through Friday, for 5 weeks. During your radiation, you will receive 5-FU continuously through a tube in your vein. The 5-FU will be given Monday through Friday during each week you get radiation. On the first day of each week that you receive radiation therapy and 5-FU, you will also receive Paclitaxel. Paclitaxel will last 3 hours and will be given through a tube into your vein. Your chemotherapy may be given as an outpatient or as an inpatient in the hospital, depending on the facility that you are being treated at.

Treatment Two: (11/01/02)

You will receive two cycles of chemotherapy called Cisplatin and Paclitaxel. For one day, you will receive Paclitaxel for 3 hours. This will be given through a tube into your vein (intravenously). On the same day, you will receive Cisplatin for 1 hour through a tube into your vein. The second cycle of chemotherapy will be the same as the first cycle of chemotherapy, and will be started 28 days after the first cycle started. Each cycle lasts 1 day.

Between three to six weeks after completing your chemotherapy, you will receive radiation therapy once a day, five days a week, Monday through Friday, for 5 weeks. During your radiation, you will receive Paclitaxel continuously through a tube in your vein. Paclitaxel will be given continuously for 4 days during each week you get radiation therapy. On the first day of each week that you receive radiation therapy and Paclitaxel, you will also receive Cisplatin. Cisplatin will last 1 hour and will be given through a tube into your vein. Your chemotherapy may be given as an outpatient or as an inpatient in the hospital, depending on the facility that you are being treated at.
If you take part in this study, you will have the following tests and procedures:

Prior to study entry: (2/18/02)

- History and physical exam
- Blood test called CBC, and tests for your liver and kidney function
- Chest X-Ray
- CT Scan of the abdomen and pelvis
- A venous access device (a tube into a large vein) will be put in so you can receive the chemotherapy
- Hearing test (audiogram) if indicated by your physician
- Pregnancy test if applicable
- Additional X-Rays or a bone scan will be done if indicated by your physician

During Chemotherapy Alone:

- Physical exam before each cycle
- Blood tests – done weekly and before treatments

During Chemotherapy and Radiation Therapy together:

- Physical exam weekly
- Blood tests – done weekly and before treatments

At completion of treatment:

- Physical exam
- Blood tests
- CT Scan of the abdomen and pelvis

During follow-up:

- Physical exam – every 3 months from the end of treatment for the first 2 years, every 6 months for the next 3 years, then every year after that.
- Blood tests – every 3 months from the end of treatment for the first 2 years, every 6 months for the next 3 years, then every year after that.
- Chest X-Ray – every year
- CT Scan of the abdomen and pelvis – every 6 months from the end of treatment for 2 years, then as indicated by your physician.
- Additional X-Rays or a bone scan will be done if indicated by your physician.
HOW LONG WILL I BE IN THE STUDY?

This study will take approximately 4 months to complete. Follow up visits will be scheduled every three months for two years, then every six months for three years, and then yearly for the rest of your life.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY? (8/25/03)

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the chemotherapy and radiation are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy to the Stomach

**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.

*Very Likely*
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Reddening or tanning of the skin
- Hair loss in the treatment area
- Nausea and/or vomiting
- Loss of appetite
- Weight loss
- Weakness and fatigue

*Less Likely, But Serious*
- Kidney damage - decreasing the kidneys’ ability to handle the body’s waste which may be permanent.
Risks Associated with Paclitaxel

Very Likely
Decrease in blood counts which can lead to a risk of infection and bleeding.
Hair loss
Fatigue
Nausea and/or vomiting
Mouth sores
Numbness, tingling, or burning in the hands or feet
Skin redness or rash

Less Likely
Muscle aches and/or joint pains
Headaches
Skin or nail darkening
Skin ulcers

Less Likely, But Serious
Allergic reaction which can cause difficulty breathing, irregular heartbeat, low blood pressure, and even be life threatening.
Changes in vision
Decrease in blood pressure
Severe rash called Stevens-Johnson syndrome which can cause fever and red sores in your mouth and eyes

Risks Associated with Cisplatin

Very Likely
Decrease in blood counts which can lead to a risk of infection and bleeding.
Loss of appetite and/or taste; metallic taste in your mouth
Nausea and/or vomiting
Fatigue
Hearing loss or ringing in the ears
Numbness or tingling in the hands or feet

Less Likely
Muscle cramps or spasm
Loss of coordination
Involuntary movements or shaking

Less Likely, But Serious (2/18/02)
Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
Decreasing ability of the kidneys to handle the body’s waste which may
be permanent
Allergic reactions which can cause difficulty in breathing, fast heartbeat, and sweating
Decrease in liver function
Other cancer called Acute Leukemia

Risks Associated with 5-FU (5-Fluorouracil) Treatment with 5-FU stopped May 21, 2003

Very Likely
- Decrease in blood counts which can lead to a risk of infection and bleeding.
- Loss of appetite
- Nausea and/or vomiting
- Diarrhea with cramping or bleeding
- Skin rash
- Fatigue
- Headaches
- Hair loss which is temporary
- Mouth sores
- Sore throat

Less Likely
- Confusion
- Inflammation of the fingers and toes
- Increased sensitivity to sunlight
- Darkening of the skin, nails, or veins
- Loss of coordination or balance
- Inflammation of the veins
- Loss of coordination

Less Likely, But Serious
- Chest pain that may be associated with damage to the heart

Reproductive risks:
Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

Are there benefits to taking part in the study?
If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with stomach cancer in the future.
WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment except medications to make you feel better. With the latter choice, your tumor may continue to grow. 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.

Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute 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). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as 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.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.
WHAT ARE MY RIGHTS AS A PARTICIPANT? (11/01/02)

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in stomach cancer from the RTOG Gastrointestinal Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

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

_________________________  __________________________
Name  Telephone Number

For information about this study, you may contact:

_________________________  __________________________
Name  Telephone Number

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

_________________________  __________________________
Name  Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

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. I may also request a copy of the protocol (full study plan).

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).

<table>
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<th>New York Heart Association Functional Status</th>
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<tr>
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<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class III</td>
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<tr>
<td>Class IV</td>
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</table>

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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
APPENDIX III

AJCC STAGING SYSTEM
STOMACH, 5TH EDITION
(continued)

STAGE GROUPING

<table>
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</table>

HISTOLOGIC GRADE (G)

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated
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
- All deaths within 30 days of termination of the agent.
  As above

- 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