RADIATION THERAPY ONCOLOGY GROUP

RTOG 0246

A PHASE II STUDY OF A PACLITAXEL-BASED CHEMORADIOTHERAPY REGIMEN WITH SELECTIVE SURGICAL SALVAGE FOR RESECTABLE LOCOREGIONALLY ADVANCED CARCINOMA OF THE ESOPHAGUS

Study Chairman
Thoracic Surgery/ Surgical Oncology
Stephen G. Swisher, M.D.
M.D. Anderson Cancer Center
1515 Holcombe Boulevard, Box 445
Houston, TX 77030
(713) 792-8659
FAX# (713) 794-4901
sswisher@mdanderson.org

Medical Oncology
Jaffer A. Ajani, M.D.
(713) 792-2828
FAX# (713) 745-1163
jajani@mdanderson.org

Radiation Oncology
Ritsuko Komaki, M.D.
(713) 792-8659
FAX# (713) 794-5573
rkomaki@mdanderson.org

Pathology
Tsung-Teh Wu, M.D., Ph.D.
(713) 745-4977
FAX# (713) 792-4049
twu@mdanderson.org

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RTOG HQ/ Statistical Center
(215) 574-3189
(800) 227-5463 Ext. 4189

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SCHEMA (4/23/04)(4/13/05)

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<th>Induction Chemotherapy (see Section 7.1.1.1)</th>
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<td>G-CSF</td>
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<th>T</th>
<th>Followed by Chemoradiotherapy to Begin on Day 29 of the Last Cycle</th>
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<td>of Induction Chemotherapy (Day 57 of protocol)</td>
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<td>E</td>
<td>RT</td>
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<td></td>
<td>Cisplatin</td>
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Followed by Salvage Therapy

**Eligibility:** (See Section 3.0 for details)
- Histologic proof of primary squamous cell or adenocarcinoma of the esophagus or gastroesophageal junction (no tumor extension beyond 2 cm into stomach);
- Locoregionally advanced resectable carcinoma of esophagus without systemic metastases (except T1NO);
- Celiac adenopathy (≤ 2 cm) is allowed. Palpable supraclavicular nodes must have biopsy proof of “no cancer” before study entry;
- Excludes patients with TE fistula or invasion into mucosa of trachea or major bronchi, systemic metastatic disease, or uncontrolled serious medical or mental illnesses;
- Zubrod Performance Status 0-1;
- Ability to tolerate surgical resection as determined by panel of medical oncologist, radiation oncologist and surgical oncologist;
- Patients ≥ 18 years of age;
- No hypersensitivity to *E. coli* -derived products;
- AGC ≥ 1500/mm³, platelets ≥ 150,000/mm³, Hgb ≥ 10 gm%, serum creatinine ≤ 1.5 mg/dl and/or calculated creatinine clearance ≥ 65 cc/min; serum calcium ≤ 11 gm/dl;
- Patients with prior malignancy are eligible if curable non-melanoma skin cancer or cervical cancer in situ or disease free ≥ 5 years;
- No prior chest or upper abdomen radiotherapy; no prior systemic chemotherapy within the past 5 years; no prior esophageal or gastric surgery;
- No patients receiving photodynamic therapy or other investigational agents as treatment for their esophageal carcinoma;
- No pregnant/lactating women or men unwilling to practice contraception;
- Signed study-specific consent form prior to study entry.

**Required Sample Size: 42**
1. Does the patient have biopsy-proven squamous cell or adenocarcinoma of the esophagus or gastroesophageal junction?

2. Is the tumor confined to the esophagus with no extension beyond 2 cm of the proximal stomach?

3. Has an endoscopic ultrasound been performed?
   Specify the pretreatment EUS stage _______________

4. Has a pretreatment PET scan been performed (optional but encouraged)?
   Specify whether there is increased uptake in primary (SUV > 2)
   Specify whether there is increased uptake in lymph nodes
   Specify whether there is increased uptake in metastatic sites

5. Is there evidence of distant disease excluding celiac or supraclavicular adenopathy?

6. Is there palpable supraclavicular adenopathy?

7. If there is palpable supraclavicular adenopathy, do biopsies confirm no evidence of cancer?

8. Is there evidence of invasion of mucosa of trachea or major bronchi or tracheal esophageal fistula (bronchoscopy mandatory for patients with tumor < 25 cm from incisors)?

9. Does the patient have multiple carcinomas of the esophagus?

10. Is the AGC ≥ 1500/mm³?

11. Is the platelet count ≥ 150,000/mm³?

12. Is the Hgb ≥ 10 gm%?

13. Is the serum creatinine ≤ 1.5 mg/dl?

14. If the calculated creatinine clearance was done, are the results ≥ 65 cc min?

15. Is the serum calcium level ≤ 11 mg/dl?

16. Has the patient had prior chest or upper abdomen radiotherapy; prior systemic chemotherapy within the past 5 years; or prior esophageal or gastric surgery?

17. Has the patient had prior major esophageal surgery?

18. Is the Zubrod Performance Status 0-1?

19. Does the surgical oncologist feel that the patient is an operable candidate?
   (continued on next page)
20. Has the patient had a previous malignancy other than curable non-melanoma skin cancer or cervical cancer in situ?
   ______ (Y) If yes, has the patient been disease free ≥ 5 years?

21. Has the patient had evaluations by a medical oncologist and a radiation oncologist and a surgical oncologist?

22. Does the patient have any hypersensitivity to E. coli–derived products?

23. Is the patient receiving photodynamic therapy or other investigational agents as treatment for their esophageal carcinoma?

24. Were pre-entry CTs (or MRIs) of chest and abdomen completed?

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 signed prior to study entry)

5. Patient’s Initials (Last, First, Middle) [Initials only effective 2/2/02]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)

11. Gender

12. Patient’s Country of Residence

13. Zip Code

14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?

16. Medical Oncologist

17. Surgical Oncologist

18. (Y/N) Tissue/blood used for research in current study?

19. (Y/N) Tissue/blood kept for cancer research?

20. (Y/N) Tissue/blood kept for medical research?

21. (Y/N) Allow contact for future research?

22. Treatment Start Date

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.

Completed by _____________________________ Date ___________________________
The optimal treatment strategy for locoregionally advanced esophageal cancer has not yet been determined. Esophagectomy either alone or in combination with chemotherapy and radiation therapy is associated with long-term patient survival of only 15% to 35%. Additionally, many of these patients suffer from significant weight loss and associated comorbidities and are at high risk for perioperative morbidity and mortality following an extensive surgical procedure such as an esophagectomy. Because of these poor outcomes with surgery, alternative treatment strategies have been proposed by some oncologists to treat locoregionally advanced esophageal cancer with definitive chemoradiation and no surgery. These strategies, especially in squamous cell cancer, can result in long-term survivals of 10% to 30% when 5-fluorouracil and cisplatinum or mitomycin C are combined with radiation therapy. Even though the non-operative approach of definitive chemoradiotherapy avoids surgical resection in many patients, this strategy is associated with a high rate of locally persistent or recurrent disease (>50%).

RTOG protocol 94-05 attempted to reduce this high rate of locoregional tumor recurrence with additional radiation therapy (64.8 Gy of radiotherapy plus concurrent 5-FU and cisplatin) compared against the standard chemoradiotherapy dose (50.4 Gy of radiotherapy plus concurrent 5-FU and cisplatin). 236 patients with cT1-4NxM0 squamous (85%) or adenocarcinoma (15%) of the esophagus without tumor extension to within 2 cm of the stomach were stratified based on weight loss, size, and histology, and were randomized to standard dose CMT using a slight modification of the CMT arms of RTOG 85-01: 50.4 Gy + concurrent 5-FU (1000 mg/m\(^2\) x 96 hr) and cisplatin (75 mg/m\(^2\) bolus day 1) weeks 1 and 5 and repeated 4 weeks after the end of radiation vs. high-dose CMT (64.8 Gy and the same chemotherapy). With the exception of a higher proportion of males in the standard dose arm (78% vs. 65%, p=0.047) the distribution of the pretreatment characteristics was similar. A planned interim analysis using a stochastic curtailment analysis after 230 patients were accrued revealed that the chance of the high dose arm having a statistically superior survival result was only 2.4%. Therefore, the trial was closed before meeting its accrual goal of 298.

<table>
<thead>
<tr>
<th></th>
<th>High dose</th>
<th>Standard dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Entered</td>
<td>114</td>
<td>118</td>
<td>230</td>
</tr>
<tr>
<td>No. Eligible</td>
<td>97</td>
<td>99</td>
<td>196</td>
</tr>
<tr>
<td>Max Gr 3</td>
<td>43 (44%)</td>
<td>33 (33%)</td>
<td>76 (38%)</td>
</tr>
<tr>
<td>Toxicity Gr 4</td>
<td>26 (26%)</td>
<td>31 (31%)</td>
<td>57 (29%)</td>
</tr>
<tr>
<td>Gr 5</td>
<td>9 (9%)</td>
<td>2 (2%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Cancer Death</td>
<td>26 (26%)</td>
<td>33 (33%)</td>
<td>59 (30%)</td>
</tr>
<tr>
<td>Median Survival</td>
<td>12.8 months</td>
<td>17.5 months</td>
<td></td>
</tr>
<tr>
<td>2-Yr Survival</td>
<td>24% (6 at risk)</td>
<td>33% (12 at risk)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment-related deaths (Gr 5) were attributed to hematological, respiratory, infectious, and renal causes. This interim analysis suggests that CMT with 64.8 Gy does not offer a survival benefit compared with 50.4 Gy and is associated with significantly higher treatment-related morbidity. This study suggested that the optimal dose of radiation therapy for definitive chemoradiotherapy was 50.4 Gy and that alternative means of improving locoregional control need to be evaluated.

Another means of addressing relapsed or persistent locoregional esophageal tumor after definitive chemoradiotherapy is selective surgical resection. This strategy has been used successfully on an ad hoc basis in previous definitive chemoradiotherapy trials (RTOG 85-01) and theoretically allows the opportunity of reserving surgical resection only for patients truly needing additional locoregional control. As with anal carcinoma and laryngeal cancer, a strategy of selective surgical salvage in esophageal cancer might preserve the esophagus in selected patients and avoid the morbidity and long-term swallowing dysfunctions of esophageal resection in patients not requiring additional locoregional control. There is a need for this strategy to be evaluated in a prospective fashion because at least one retrospective study suggests that the morbidity of surgery following definitive chemoradiotherapy may be increased compared with planned surgery after neoadjuvant chemoradiotherapy. Additionally, much of the information for
definitive chemoradiotherapy has been obtained in squamous cell carcinoma and may not be relevant for adenocarcinoma, which is currently the predominant histology in esophageal carcinoma. This information would be important in trying to determine the feasibility and safety of a non-operative or selective surgical salvage approach in locoregionally advanced esophageal carcinoma as well as the ability to accrue patients to such a strategy.

1.4 Although definitive chemoradiotherapy may reduce the need for mandatory surgical resection, this approach is still associated with poor long-term survival, which is due in large part to metastatic failure. The use of cisplatinum and 5-FU has made some improvements in survival but other novel agents such as paclitaxel are active and may provide additional benefit. In addition, recent studies with neoadjuvant chemoradiotherapy suggest that the addition of a separate course of chemotherapy prior to concurrent chemoradiation may also be beneficial. Paclitaxel and induction chemotherapy have been studied at several different institutions in patients with carcinoma of the esophagus, and the results have been encouraging.

1.4.1 Paclitaxel for Metastatic Esophageal Carcinoma
A phase II trial of paclitaxel at a dose of 250 mg/m² as a continuous 24-hour infusion in patients with advanced esophageal cancer was conducted at MDACC and MSKCC in patients with advanced untreated carcinoma of the esophagus. Seventeen courses were repeated at 21-day intervals. The trial accrued a total of 50 patients; 32 had adenocarcinoma and 18 epidermoid carcinoma. Toxicities primarily involved leukopenia, myalgia, and alopecia but were identical to those reported by previous investigators. Paclitaxel was an active agent with a 32% response rate, with significant activity in both adenocarcinoma (34%) and squamous cell carcinoma (28%).

1.4.2 Paclitaxel in Combination with Other Agents in Metastatic Esophageal Carcinoma
In preclinical systems, there is evidence of synergism when paclitaxel is combined with cisplatin or 5-fluorouracil. The rationale for the combination of paclitaxel, cisplatin, and/or 5-FU is that the common toxicities of each agent are non-overlapping (paclitaxel: alopecia, myelosuppression, and neuropathy; cisplatin: nausea, vomiting, renal toxicity, and neuropathy; and 5-FU: mucositis, dermatitis, and diarrhea). Phase I Trials have indicated the feasibility of combining paclitaxel given by a 24-hour infusion with cisplatin, either with or without G-CSF support. In the trial of paclitaxel given together with cisplatin without G-CSF support reported by Rowinsky, febrile neutropenia was the dose limiting toxicity and the recommended phase II doses were paclitaxel/cisplatin 135 mg/m²/75 mg/m², respectively.

Paclitaxel has also been combined with cisplatin and 5-FU. In this multi-institutional study of approximately 61 patients, the response rate for patients with adenocarcinoma was approximately 45% and for those with squamous cell carcinoma was approximately 55%. The overall response rate was 48%. Sixty-one percent of patients experienced some form of grade 3/4 non-hematologic toxicity, and 48% of patients required one or more hospitalizations for treatment-related toxicity. The median duration of response was 5.7 months. Seven complete remissions were seen (12%) with a significantly higher complete response rate in squamous cell cancer (20%) compared with adenocarcinoma (3%). While the observed response rate to cisplatin, fluorouracil, and paclitaxel was higher than the observed response rate to paclitaxel alone, or to cisplatin, or to 5-fluorouracil in most prior studies, the toxicity was not trivial. Nevertheless, there were no treatment-related deaths in this study.

1.4.3 Preoperative Paclitaxel and Cisplatin followed by Concurrent Cisplatin, 5-FU, and Radiation Therapy (4/23/04)
The regimen that has been chosen for this protocol is one that has been successfully used as a preoperative regimen at MDACC in an outpatient setting. In this study, a total of 38 patients were treated preoperatively on a Phase II study at MDACC from November 1996 to October of 1998. The patients were predominantly male with distal esophageal or gastroesophageal adenocarcinoma with a median age of 55 years (range: 38-74). Pretreatment clinical staging with endoscopic ultrasound demonstrated locoregionally advanced esophageal tumors with 87% of the primary tumors graded as cT3 tumors and 66% having enlarged lymph nodes (cN1).

Chemotherapy consisted of a combination of 5-fluorouracil, cisplatin, and paclitaxel. 5-Fluorouracil was administered at 750 mg/m²/d as continuous infusion on days 1-5. Cisplatin
was administered at 15 mg/m²/d as intravenous (IV) bolus on days 1-5. Taxol was administered as a 24-hour IV infusion at a dose of 200 mg/m² on day 1. The second cycle of chemotherapy was given to those patients who did not have evidence of local or distant tumor progression and had recovered from all toxic effects (≤ grade 1).

Upon completion of two cycles of induction chemotherapy, patients received concurrent chemoradiation. A total radiotherapy dose of 45 Gy was delivered (1.8 Gy/day for 25 days). The daily fraction size was 1.8 Gy, and 25 fractions were delivered. Patients underwent simulation by standard methods utilizing esophagoscopy, esophagography, and CT information to determine the exact boundaries of the carcinoma. Using megavoltage (≥ 6 MV) equipment, the 2- to 4-field technique was applied. The superior and inferior borders of the field were 5 cm beyond the edges of the carcinoma, while the lateral borders of the field were 2 cm beyond the edges. The concurrent outpatient chemotherapy regimen consisted of 5-fluorouracil and cisplatin. Cisplatin was administered at 15 mg/m²/d on days 1-5 of radiotherapy administration (in the first week only). 5-Fluorouracil was administered at 300 mg/m²/d as a continuous infusion for 5 days per week during the radiotherapy administration. Patients did not receive chemotherapy on weekends.

Chemotherapy- and chemoradiation-related toxicity demonstrated that 30% of patients had a grade 3 or 4 toxicity that was predominantly due to granulocytopenia during the induction chemotherapy.22 Thirty-seven of the 38 patients entered on the trial completed all planned chemotherapy and concurrent chemoradiation. One patient died 9 days after his initial dose of chemotherapy from an acute myocardial infarction and associated pulmonary embolism. Thirty-five of the 37 (95%) patients who completed induction therapy underwent surgical resection. One patient refused surgery because of a complete clinical response, and the other developed metastatic progression in the liver. At the time of surgery, 11/35 (31%) patients had a complete pathologic response and 7/35 (20%) demonstrated only microscopic carcinoma. With an intention-to-treat analysis (38 patients) and a median follow-up of 40 months (range 29 to 53 months), only 12 patients have relapsed with esophageal tumor. Recurrences include one patient with a locoregional recurrence alone (anastomosis), one patient with a locoregional and metastatic recurrence (regional lymphadenopathy and pleural and pericardial disease), and 10 patients with metastatic recurrence alone (1 pleural effusion, 3 bone, 2 brain, 2 lung, 1 liver, 1 clinical progression). The median time to locoregional and metastatic progression has not yet been reached, and the overall survival and disease-free survival rates are 62% and 57%, respectively, at 3 years. Twenty-one of 38 patients (55%) are alive without evidence of disease 29 to 53 months after treatment. These encouraging results are double those that are reported in the literature for patients with locoregionally advanced esophageal cancer treated with surgery alone, induction chemotherapy, or induction chemoradiation.1,2,3,23,25,26 This regimen employed several novel features that may have been beneficial, including a taxane in the induction chemotherapy step and a novel three-step approach with chemotherapy (step 1) followed by concurrent chemoradiation (step 2) and then surgery (step 3). The regimen was well-tolerated and demonstrated improved results; we, therefore, elected to use this regimen for this selective surgical protocol to evaluate the best potential outcome.

1.5 Rationale for the Proposed Trial

Esophageal carcinoma is a cancer for which surgical or radiation-based therapies cure less than 25% of patients due to a high incidence of both local and systemic disease relapse. Random assignment trials have indicated a survival advantage for concurrent chemotherapy plus radiation over radiation alone. However, it has not been possible to administer the desired number of courses of chemotherapy after completion of chemoradiotherapy. Thus, a major consideration must be given to additional chemotherapy prior to definitive chemoradiotherapy. At MDACC and MSKCC, separate trials have been completed to document the feasibility of the approach of giving induction chemotherapy followed by chemoradiotherapy and mandatory surgical resection.15-16 It is hypothesized that induction chemotherapy prior to definitive chemoradiotherapy may: (1) result in delay or elimination of micrometastases, (2) make chemoradiotherapy more effective by diminishing the bulk of primary tumor, and (3) allow patients to receive all intended therapy because of improved tolerance to chemotherapy in the induction setting.
We propose to use the MDACC regimen to evaluate the feasibility of selective surgical salvage. The information obtained from this trial will be important in trying to determine the feasibility and safety of a non-operative or selective surgical salvage approach in locoregionally advanced esophageal carcinoma. Additionally, standard criteria could be developed to identify patients with persistent or recurrent esophageal cancer meriting consideration of surgical salvage. It would also allow a preliminary gauge of the interest and willingness of surgeons and patients to accrue to a selective surgical strategy. If the data from this phase II trial are encouraging, a later phase III trial with a larger number of patients could be designed to test in a randomized fashion the optimum approach to locoregionally advanced esophageal carcinoma (i.e., selective surgical resection vs. mandatory surgical resection). The preliminary data from this trial will allow predictions for the number of patients needed in a phase III trial.

2.0 OBJECTIVES
2.1 Determine feasibility and ability to accrue to a non-operative approach with definitive chemotherapy, concurrent chemoradiation, and selective surgical salvage;
2.2 Determine standard criteria for salvage therapy with serial CT scans (mandatory), serial endoscopy and ultrasound (mandatory), and serial PET scans (optional but encouraged);
2.3 Estimate the overall survival of this selective surgical strategy; other efficacy outcomes, such as disease-free survival, also will be estimated;
2.4 Evaluate the rate of treatment-related toxicity associated with the induction and chemoradiation therapies;
2.5 Assess the tolerance in patients receiving selective surgical strategy;
2.6 Evaluate the morbidity and mortality of selective surgical salvage;
2.7 Collect tissue specimens for the future purpose of associating molecular markers with response and treatment efficacy outcomes.

3.0 PATIENT SELECTION
3.1 Eligibility Criteria (4/23/04)
3.1.1 The patient must have biopsy-proven resectable primary (non-recurrent) squamous cell or adenocarcinoma of the esophagus or gastro-esophageal junction. Disease must be entirely confined to the esophagus or gastro-esophageal junction, and peri-esophageal soft tissue.
3.1.2 A PET scan suggestive of metastatic disease must have other imaging studies or biopsies to prove that there is no metastatic disease.
3.1.3 Pre-entry CTs of chest and abdomen are required (MRIs are acceptable). An imaging study suspicious for liver metastases must be followed with a negative liver biopsy before a patient can be considered eligible to enter the study.
3.1.4 Diagnosis by endoscopic ultrasound is required. The tumor stage must be greater than T1N0.
3.1.5 Bronchoscopy is required if the lesion is < 25 cm from the incisors to exclude TE fistula or invasion.
3.1.6 Zubrod Performance Status 0-1.
3.1.7 AGC must be $\geq 1500/mm^3$, platelet count must be $\geq 150,000/mm^3$, Hgb $\geq 10$ gm%; serum creatinine $\leq 1.5$ mg/dl and/or calculated creatinine clearance $\geq 65$ cc/min; if both serum creatinine and calculated creatinine clearance are done, both tests must be within these limits; serum calcium $\leq 11$ mg/dl.
3.1.8 Palpable supraclavicular nodes must be proven negative for cancer by biopsy before study entry.
3.1.9 Patients $\geq 18$ years of age.
3.1.10 Signed study-specific informed consent prior to study entry.
3.2 Ineligibility Criteria
3.2.1 Prior chest or upper abdomen radiotherapy; prior systemic chemotherapy within the past 5 years; prior esophageal or gastric surgery.
3.2.2 Patients with tumor extension beyond 2 cm into the stomach.
3.2.3 Patients with multiple primary carcinomas of the esophagus.
3.2.4 Patients with cervical esophageal carcinoma or tumors < 5 cm from cricopharyngeus.
3.2.5 Patients with evidence of disseminated cancer.
3.2.6 Tracheoesophageal fistula: bronchoscopy is required to exclude TE fistula if the primary carcinoma is < 25 cm from the incisors. Bronchoscopy is also required when the cancer is at or above the carina by an imaging study.
3.2.7 Celiac adenopathy $> 2$ cm.
3.2.8 Patients with uncontrolled diabetes, heart disease, or hypertension;
3.2.9 Patients who are unable to comprehend the study requirements or who are not likely to comply with the study parameters.
3.2.10 Patients with a hypersensitivity to E. coli-derived products.
3.2.11 Patients receiving photodynamic therapy or other investigational agents as treatment for their esophageal carcinoma.
3.2.12 Due to the embryotoxic effects of chemotherapy, pregnant or lactating women or men unable or unwilling to practice contraception are excluded.
3.2.13 Patients with prior malignancy, other than curable non-melanoma skin cancer or cervical cancer in situ, unless disease-free for ≥ 5 years.

4.0 PRETREATMENT EVALUATION

4.1 Required Evaluations
4.1.1 Complete history and physical examination, including the patient’s weight, with an assessment of the patient’s performance status within four weeks prior to study entry.
4.1.2 All patients must be evaluated by a medical, surgical, and radiation oncologist prior to study entry.
4.1.3 Laboratory Studies (within 2 weeks prior to study entry):
   CBC, ANC, platelets;
   Chemistry including serum creatinine, electrolytes, ALT, AST, LDH, alkaline phosphatase (if alkaline phosphatase is ≥ 1.5 X upper limits of institutional normal, a bone scan is required), total bilirubin, total protein, albumin, uric acid, inorganic phosphorous, calcium, BUN, magnesium; calculated creatinine clearance (optional).
4.1.4 A central venous access (a long line, subclavian catheter, or implantable device) should be established in all patients prior to beginning chemotherapy.
4.1.5 Imaging Studies (within 4 weeks prior to study entry):
   CT Scan of the chest and abdomen (MRIs are acceptable);
   Upper GI endoscopy (endoscopic ultrasound is required);
   PET scan (optional but strongly encouraged); a PET scan suggestive of metastatic disease must have imaging studies or biopsies to prove that there is no metastatic disease.
   Double contrast upper GI radiographs are optional.
   Data on T stage, N stage will be collected. Whenever possible, EUS/FNA of the nodes is highly desirable to improve accuracy.
   Bronchoscopy is required if the lesion is < 25 cm from the incisors to exclude TE fistula or invasion.
4.1.6 Biopsy of supraclavicular node if clinically enlarged (i.e., palpable).
4.1.7 Bone scan (if alkaline phosphatase is elevated ≥ 1.5 x upper limits of institutional normal).
4.1.8 Nutritional Assessment by institutional nutritionist is highly encouraged but not required.
4.1.9 Bilateral audiogram (optional, but encouraged in patients with clinical hearing loss).

5.0 REGISTRATION PROCEDURES

5.1 On-Line Registration
Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. The RA will register the patient by logging onto the RTOG Web site (www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. A username and password is required. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the
DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.2.

5.2 Dial-In Registration
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 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

Note: Intensity Modulated RT (IMRT) Is Not Allowed

6.1 External Beam (4/13/05)

External beam RT with megavoltage linear accelerators (≥ 6 MV) will be used to deliver multiple (> 2) field techniques. Patients will be treated 5 d/wk at 1.8 Gy/d for 28 days for a total dose of 50.4 Gy.

Initial volumes will be based on the pretreatment simulation-esophagram films. The superior and inferior borders of the field will be 3 cm beyond the tumor, and the lateral borders of the field will be 2 cm beyond the lateral borders of the tumor as defined by endoscopic US, esophagram, or CT (whichever is larger). The peri-esophageal nodes will be included. A barium swallow will also be obtained at the time of simulation to confirm the location of the esophagus. If the primary tumor is above the carina (proximal esophagus), the supraclavicular nodes will be included in the AP/PA RT field. At least two fields will be treated each day and portal films will be obtained of at least two fields per week, or more often if needed. Weekly quality assurance check films should be made for review. Treatment may be given with combination of anterior/posterior oblique, or lateral fields, such that the dose of the target volume does not differ from the dose specified at isocenter by >10%. Oblique fields cannot be used for the entire course. If a four-field technique is used, the AP/lateral field can be alternated with the PA/lateral fields. If a three-field technique is used, all three fields must be treated daily. The patient treatment position may be either supine or prone (which may allow a shift in the esophagus in cases where sparing of the spinal cord is difficult). Planning CT is required.

6.2 Technical Factors

6.2.1 Beam Energy: Megavoltage equipment with photon energies ≥ 6 MV is required.

6.2.2 Treatment Distance: The treatment distance to skin should be 100 cm for SSD technique and minimum isocenter distance should be 100 cm for SAD techniques.

6.2.3 Blocking: Primary collimation may be used, and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be radiated. Spinal cord blocking on the AP or PA field is prohibited. The use of off cord oblique or lateral block field arrangements will be necessary to meet the spinal cord normal tissue dose requirements.

6.2.4 Compensating Filters: In case of sloping surfaces such as the thoracic inlet, compensating filters are recommended. If compensating filters are not available, appropriate reductions in field size must be done at prescribed dose levels to meet the dose homogeneity requirements.

6.2.5 Normal Tissue Doses: The spinal cord dose must not exceed 45 Gy maximum. Normal lung (more than 2 cm outside the target volume) must not receive more than 45 Gy. The entire heart dose should be no more than 30 Gy with < 50% of the organ receiving a maximum of 40 Gy.

6.2.6 Fractionation: At least two fields are to be treated daily, or three fields for a three-field technique.

6.3 Treatment Planning

6.3.1 Planning CT must be done for isodose distribution.
6.3.2 Isodose distribution at the mid-transverse plane of the tumor with tumor volumes clearly identified should be submitted. For the purpose of the distribution, it may be assumed that the central axis passes through the midplane of the tumor.

6.3.3 In addition to this distribution, two specific points of calculation are required.

6.3.4 A point 2 cm below the superior margin of the field or the point found to receive the maximum spinal cord dose. Maximum cord dose should be recorded daily on treatment record.

6.3.5 Supraclavicular node dose at 3 cm anterior depth, if applicable. Record daily on the treatment chart. Lower esophageal and gastroesophageal junction cancers should have clinically negative celiac nodes treated. Clinically positive celiac nodes should always be treated regardless of primary tumor location.

6.3.6 Doses are prescribed and calculated without tissue inhomogeneity connection.

6.3.7 Per protocol, the dose delivered to the prescription point must be within ± 5% relative to the doses specified. Doses ≥ 6% to 10% will be scored as a variation, acceptable. Doses ≥ 10% will be scored as a deviation, unacceptable.

6.4 Dose Specifications

6.4.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.4.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.4.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.4.4 For a single beam: on the central ray at the center of the target area.

6.4.5 For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.

6.4.6 Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).

6.5 Localization Methods

6.5.1 Localization films taken on treatment simulators are required using contrast material in the esophagus. For proximal 1/3 lesion, (defined as primary tumors above the carina) a metal marker (BB) should be placed on the lateral extent of the bilateral S/C fossa to be certain that they are included in the lateral and/or oblique fields. Verification portal films taken on the treatment unit are required until satisfactory, then at least weekly. Supraclavicular nodes that are involved should be outlined with a wire on the simulation film.

6.6 Radiation Checklist (4/23/04)

6.6.1 Chemoradiation should begin on Day 29 (day 57 of protocol) of the last cycle of chemotherapy provided the patient’s recovery from all toxicities (grade less than 1 except alopecia and peripheral counts ANC greater than 1500 and platelet count greater than 100,000/mm$^3$) is adequate. During irradiation, patients are seen for a status check at least once a week with notation of tolerance, weight, and blood counts. Blood counts are obtained weekly to minimize the chance of continuing irradiation during unacceptable nadir counts. If the absolute granulocyte falls below 1000 or the platelet count falls below 50,000 during the course of radiation therapy, treatment should be delayed until the counts rise above these levels.

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

6.7 Supportive Therapy

6.7.1 If estimated caloric intake is less than 1200 kilocalories or if weight loss is ≥ 5% of pretreatment weight, oral, enteral, and/or intravenous hyperalimentation should be considered. Institutions may place a feeding jejunostomy prior to initiating EBRT.

6.8 Ancillary Treatment

6.8.1 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-diarrhea agents are allowed.

6.9 Treatment Interruptions or Modifications

6.9.1 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 ≤ 1000; platelet count ≤ 50,000; vomiting ≥ 3/days unresponsive to antiemetics; diarrhea ≥ 5 watery stools/day unresponsive to anti-diarrheals; 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; however, every effort should be made to limit treatment interruptions to 1-2 weeks. If treatment interruptions are longer than 2 weeks, the study chair, Dr. Swisher, must be contacted.

6.9.2 Dose Modifications: Every effort must be made to deliver the full 50.4 Gy to all patients. Toxicity may be encountered that is sufficiently severe to require treatment interruption. Once the toxicity has resolved, the patient’s therapy should resume and full protocol dose should be delivered. The toxicity, which forced any dose reduction, must be documented.

6.10 Toxicity Reporting Guidelines (3/24/10)
6.10.1 Acute radiation effects were evaluated and scored using the revised NCI Common Toxicity Criteria, v. 2.0.
6.10.2 Fatal Events: All deaths with attribution of definite, possible, or probable resulting from protocol radiation therapy must be reported by telephone to the RTOG Headquarters dedicated AE line at 215-717-2762 or 1-800-227-5463 x 4189, to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to the RTOG Headquarters dedicated AE telephone line at 215-717-2762 or 1-800-227-5463 x 4189.
6.10.3 Life Threatening (Grade 4) and Fatal (Grade 5) Events: All life-threatening (an event that in the view of the investigator places the patient at immediate risk of death from the reaction) and Grade 5 events that are related, possibly related, or probably related to protocol treatment must be reported by telephone to the RTOG Headquarters AE telephone line (given above), to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.
6.10.4 Documentation: All applicable data forms and a written report from the site principal investigator, must be submitted to RTOG Headquarters (FAX #215-928-0153) within 10 working days of the telephone report of any fatal adverse event with the attribution of definite, possible, or probable relation to protocol radiotherapy as specified in Section 6.10.3.

7.0 DRUG THERAPY
RTOG institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control Guidelines stated in the RTOG Procedure Manual.
7.1 Schedule of Induction Chemotherapy and Chemoradiotherapy
7.1.1 Induction Chemotherapy (4/23/04)
Patients will receive up to two cycles of chemotherapy prior to chemoradiotherapy depending on response to the first cycle of induction chemotherapy. If clinical progression is suspected, then double contrast barium study may be performed. Central venous access (long line, subclavian catheter, or implantable device) should be established in all patients.
7.1.1.1 Schedule: Induction Chemotherapy (4/13/05)
Outpatient administration of chemotherapy is encouraged. Chemotherapy schedule will be as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Schedule</th>
<th>Cycle 1 Days</th>
<th>Cycle 2* Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>650 mg/m²/d</td>
<td>96-hour continuous infusion by a portable pump</td>
<td>M-F</td>
<td>29-33</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²/d</td>
<td>I.V. in 1-hour</td>
<td>1-5</td>
<td>29-33</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>200 mg/m²/d</td>
<td>2-hour infusion</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>PEG-G-CSF (Neulasta™)</td>
<td>6 mg</td>
<td>Subcutaneous</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>G-CSF</td>
<td>300 µg for patients ≤ 70 kg or 480 µg for patients &gt; 70 kg</td>
<td>Subcutaneous</td>
<td>6-15</td>
<td>34-42</td>
</tr>
</tbody>
</table>
Subsequent dose may be decreased by 20% based on toxicity experienced during the preceding course; however, the dose of chemotherapy drugs will not be increased.

Adequate hydration, electrolyte supplementation, and antiemetic support will be provided when administering cisplatin. Patients will receive at least 1.0 liter of 1/2 NS with magnesium and potassium supplements intravenously on all cisplatin days. All patients will be encouraged to drink at least 2L of fluid daily.

PEG-G-CSF (Neulasta™) will be used at a fixed dose of 6 mg subcutaneously on day 6 and day 34 during the induction chemotherapy phase of the treatment OR G-CSF (either 300 µg for patients < 70 kg or 480 µg for patients > 70kg) will be given subcutaneously from days 6-15 and 34-42. Neulasta™ should not be administered in the period between 14 days prior and 24 hours after administration of cytotoxic chemotherapy.

*The second course of chemotherapy will be repeated on day 29 provided the patient has recovered from all toxicities (grade < 1) except alopecia and provided that peripheral counts (absolute granulocyte count > 1500/mm³ and platelet count > 100,000/mm³) are adequate.

The following decision guidelines will be used for recommending the next step after patients have received at least one cycle of chemotherapy:

<table>
<thead>
<tr>
<th>Event</th>
<th>Action To Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local progression after the first cycle of chemotherapy (by Upper GI barium study or upper GI endoscopy)</td>
<td>Proceed to chemoradiotherapy</td>
</tr>
<tr>
<td>Stable or any response to the first cycle of chemotherapy</td>
<td>Proceed with the 2nd cycle of chemotherapy</td>
</tr>
<tr>
<td>Completed two cycles of chemotherapy</td>
<td>Proceed to chemoradiotherapy</td>
</tr>
<tr>
<td>Development of distant metastases anytime</td>
<td>Salvage therapy; off protocol treatment</td>
</tr>
</tbody>
</table>

### 7.1.1.2 Dose Modification for the Second Cycle of Induction Chemotherapy (4/13/05)
Reduction of chemotherapy dose will be based on the degree of hematologic and non-hematologic toxicities. The goal is not to induce grade 3 or 4 non-hematologic toxicity. If the granulocyte level drops below 1000, counts should be performed every other day until the level rises above 1000.

**Paclitaxel will not be modified for non-hematological toxicity.**

<table>
<thead>
<tr>
<th>Induction Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td>ANC nadir &lt; 500 for ≥ 5 days and/or platelet nadir &lt; 50K</td>
</tr>
<tr>
<td>Infection or bleeding related to myelosuppression</td>
</tr>
<tr>
<td>Serum Creatinine*</td>
</tr>
<tr>
<td>Serum Creatinine*</td>
</tr>
<tr>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Ototoxicity</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Vomiting/diarrhea/ dehydration</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Any other non hematological toxicity except alopecia; nausea/vomiting</td>
</tr>
<tr>
<td>2nd occurrence of any Grade 3-4 nonhematological toxicity (during 1st cycle)</td>
</tr>
</tbody>
</table>

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

### 7.1.2 Chemoradiotherapy (4/23/04)(4/13/05)
Chemoradiotherapy should begin on day 29 (day 57 of protocol) of the last cycle of chemotherapy provided the patient has recovered from all toxicities (grade < 1) except alopecia and peripheral counts (absolute granulocyte count > 1500/mm³ and platelet count > 100,000/mm³) are adequate.

#### 7.1.2.1 Chemotherapy During Radiotherapy (Chemotherapy will be administered for 5 weeks [5 cycles])
Chemotherapy during radiotherapy will consist of 5-FU at 300 mg/m²/d as a continuous 96-hour infusion by a portable pump during radiotherapy. (Typically, 5-FU infusion may be initiated Monday morning and the pump should be disconnected Friday after radiotherapy. Once discontinued on Friday, patients would not receive 5-FU until the following Monday. This would mean that the patient might receive a bit more than 96 hours of 5-FU infusion).

Cisplatin: The dose of cisplatin starting on day 29 (day 57 of protocol) will be 15 mg/m²/d on days 1-5. The hydration and anti-emetic support with cisplatin will be the same as indicated above (Section 7.1.1.1). This will be accomplished in the outpatient setting. The following table demonstrates the drug doses and schedule to be used with radiotherapy.

<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>300 mg/m²/d</td>
<td>24-hour continuous infusion by a portable pump (total 96 hour infusion)</td>
<td>5 days/week, M-F during radiotherapy</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²/d</td>
<td>I.V. in 1-hour</td>
<td>1-5</td>
</tr>
</tbody>
</table>

#### 7.1.2.2 Dose Modification for Cisplatin During Chemoradiotherapy (4/13/05)
Reduction of chemotherapy dose will be based on the degree of hematologic and non-hematologic toxicities. The goal is not to induce grade 3 or 4 non-hematologic toxicity. If the granulocyte level drops below 1000, counts should be performed every other day until the level rises above 1000.
### Chemotherapy Radiation Therapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC nadir &lt; 500 for ≥ 5 days and/or platelet nadir &lt; 50K</td>
<td>Grade 4 ANC and/or Grade 3 Platelets</td>
<td>5-FU/CDDP</td>
<td>Decrease 20%</td>
</tr>
<tr>
<td>ANC &lt; 1000 or platelet &lt; 50K</td>
<td>Grade 3 and/or Grade 3 platelets</td>
<td>RT/Chemo</td>
<td>Hold for 1 week (refer to Section 7.1.2.6)</td>
</tr>
<tr>
<td>Infection or bleeding related to myelosuppression</td>
<td>Present</td>
<td>5-FU/CDDP</td>
<td>Decrease 20%</td>
</tr>
<tr>
<td>Serum Creatinine*</td>
<td>&gt; 1.4 but &lt; 2.0</td>
<td>CDDP</td>
<td>Decrease 50%</td>
</tr>
<tr>
<td>Serum Creatinine*</td>
<td>≥ 2.0</td>
<td>CDDP</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>≥ 3</td>
<td>CDDP</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (≥ 5 day duration)</td>
<td>CDDP</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Mucositis/esophagitis</td>
<td>Grade 4</td>
<td>RT/Chemo</td>
<td>Hold for 1 week (refer to Section 7.1.2.6)</td>
</tr>
<tr>
<td>Vomiting/diarrhea/dehydration</td>
<td>4</td>
<td>CDDP</td>
<td>Decrease 20%</td>
</tr>
<tr>
<td>Any non-hematological or other toxicity/adverse event, except alopecia; nauseavomiting</td>
<td>≥ 3</td>
<td>5-FU</td>
<td>Hold on treatment week and resume at 240 mg/m²/d M-F (96 hours) for the remaining duration of therapy (providing the toxicity has resolved to Grade ≤ 1).</td>
</tr>
</tbody>
</table>

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

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**7.1.2.3 Criteria for Treatment Breaks During Chemoradiotherapy (3/24/10)**

Treatment breaks will be required for all patients demonstrating > Grade 3 mucositis or esophagitis, or myelosuppression as outlined above (i.e., ANC < 1000 or platelets < 50,000). In this situation, both radiation and chemotherapy treatments will be postponed for one week at which time re-evaluation will be performed. A maximum treatment delay of up to two weeks is permissible. If a greater than two-week treatment delay is required because of toxicity, the patient will receive no further protocol treatment and be treated at the discretion of the treating physician. The revised NCI Common Toxicity Criteria, v. 2. was used to determine toxicity during radiation therapy.

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**7.2 5-Fluorouracil (5-FU)**

**7.2.1 Formulation**

5-FU is available in 10-ml vials, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide.

**7.2.2 Administration**

Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

**7.2.3 Pharmacology**

5-FU is a marketed drug available in 500-mg vials. It is a fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a fluorine atom in the 5 position has replaced a hydrogen atom.
There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to the thymidylic acid. In this fashion, 5-FU interferes with the synthesis of DNA and to a lesser extent, inhibits the formation of ribonucleic division and growth; the effect of fluorouracil may be to create a thymidine deficiency, which causes unbalanced growth and death of the cell.

7.2.4 Supplier
5-FU is available commercially.

7.2.5 Storage
Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (49°-86°F). Protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F with vigorous shaking; allow cooling to body temperature before using.

7.2.6 Side Effects and Toxicities
The spectrum of toxicity from 5-FU includes stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea with cramping and/or bleeding, anorexia, nausea, and emesis. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly, the maximal depression may be delayed for as long as 20 days. By the 30th day, the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, angina, lethargy, malaise, headache, allergic reactions, disorientation, confusion, euphoria, dizziness, incoordination, visual changes, photosensitivity (eyes and skin), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, vein pigmentation, biliary sclerosis, or acalculous cholecystitis.

7.3 Cisplatin (CDDP) (4/13/05)

7.3.1 Formulation
Cisplatin (Platinol) is available as 10-mg and 50-mg vials of dry powder, which are reconstituted with 10 ml, and 50 ml of sterile water for Injection USP, respectively. Cisplatin is also available as a 1 mg/ml solution in 50- and 100-mg vials.

7.3.2 Administration
Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. Cisplatin should be given immediately after preparation as a slow intravenous infusion.

7.3.3 Pharmacology
The dominant mode of action of cisplatin appears to involve the formation of a bifunctional adduct resulting in DNA crosslinks. How this kills the cell remains unclear. There are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 18 to 37 minutes followed by a secondary phase ranging from 44 to 190 hours. This prolonged phase is due to protein binding that exceeds 90%. Urinary excretion is incomplete with only 27% to 45% excreted in the first five days. The initial fractions are largely unchanged drugs.

7.3.4 Supplier
Cisplatin is available commercially.

7.3.5 Storage
The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W).

7.3.6 Side Effects and Toxicities
Includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage that appears to be transient), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), hyperuricemia, seizures, rash, ocular toxicities, rare cardiac abnormalities, or possible acute myeloid leukemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrocytopenia, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks
with recovery generally at about three weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, and loss of muscle or nerve function.

7.4 Paclitaxel

7.4.1 Formulation
Paclitaxel is supplied as a fully reconstituted sterile solution in a 30-mg vial at a concentration of 6 mg/ml in 5 ml vials in polyethoxylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%.

7.4.2 Administration
The appropriate dose of paclitaxel should be withdrawn from the vial and further diluted with either 0.9% sodium chloride or 5% dextrose injection. Premedication with decadron, diphenhydramine, and cimetidine has virtually eliminated all adverse hypersensitivity reactions. Premedication will be given during the induction chemotherapy phase of treatment, when a 1-3-hour infusion schedule of paclitaxel is used.

7.4.3 Pharmacology
Paclitaxel is a plant product from the stem bark of Taxus brevifolia, the western yew, a small evergreen native to the Pacific Northwest. Paclitaxel has a unique mechanism of action. In contrast to other known mitotic spindle (Paclitaxel) 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.

7.4.4 Supplier
Paclitaxel is commercially available.

7.4.5 Storage
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. Paclitaxel will be prepared by diluting the total dose in 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP (D5W) in a concentration range of 0.3 mg/ml to 1.2 mg/ml. 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 paclitaxel from plastic tubing or solution bags composed of polyvinyl chloride. The total dose must be administered through a standard 0.22-micron filter.

7.4.6 Side Effects and Toxicities
The following toxicities are anticipated: myelosuppression, myalgias and arthralgias, bradycardia and other cardiac rhythm disturbances, alopecia, stomatitis, nausea, vomiting, allergic reactions, peripheral neuropathy, CNS toxicity-seizures. Urticaria (hives, welts), hemoglobin, leukocytes (total WBC), lymphopenia, neutrophils/granulocytes (ANC/AGC), platelets, conduction abnormalities/atrioventricular block, nodal/junctional arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmia (PVCs/bigominy/trigeminy/ventricular tachycardia), cardiac-ischemia/infarction, hypertension, hypotension, fatigue (lethargy, malaise, asthenia), erythema multiforme, flushing, injection site reaction, nail changes, pruritis, radiation recall reaction, rash/desquamation, colitis, diarrhea, stomatitis/pharyngitis, taste disturbance, typhilitis, alkaline phosphatase, bilirubin, liver dysfunction/failure, AST, ALT, infection, dizziness, lightheadedness, leukoencephalopathy associated with radiological findings, mood alteration-anxiety agitation, neuropathy-motor, neuropathy-sensory, ocular-other (scintillation scotoma), blurred vision, flashing lights/floaters, pneumonitis/pulmonary infiltrates, Stevens-Johnson Syndrome.

7.5 PEG-G-CSF (Neulasta™)

7.5.1 Formulation
Neulasta™ (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is obtained from the bacterial fermentation of a strain of E. coli bearing a genetically engineered plasmid containing the human G-CSF gene. Neulasta™ is supplied in 0.6-ml pre-filled single-dose syringes for
subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

7.5.2 Administration

The PEG-G-CSF will be injected subcutaneously into rotating sites on the abdomen, arms, and legs. PEG-G-CSF should be visually inspected for discoloration and particulate matter before administration. PEG-G-CSF should not be administered if discoloration or particulates are observed. PEG-G-CSF can be self-administered by the patient. Each patient or a designated caregiver will be instructed by the nursing staff in the proper method for the antiseptic subcutaneous administration of PEG-G-CSF. Prior to administration at home, these skills must be competently demonstrated by the patient or caregiver. Patients/caregivers will also receive written instruction concerning medication storage (refrigeration).

7.5.3 Pharmacology

Both filgrastim and pegfilgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function show that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared with filgrastim.

7.5.4 Supply

Neulasta™ is commercially available.

7.5.5 Storage

Neulasta™ should be stored refrigerated at 2° to 8° C (36° to 46° F); syringes should be kept in their carton and protected from the light until time of use. Shaking should be avoided. Before injection, Neulasta™ may be allowed to reach room temperature for a maximum of 48 hours but should be protected from the light. Neulasta™ left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta™ should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta™ should be discarded.

7.5.6 Side Effects and Toxicities

Neulasta™ is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Drugs such as lithium may potentiate the release of neutrophils; patients who are taking lithium should have more frequent monitoring of their neutrophil counts. The predominant toxicity attributed to Neulasta™ in clinical trials was medullary bone pain of mild to moderate severity. Other adverse experiences included nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. Leukocytosis (WBC > 100 x 10^9/L) was observed in less than 1% of subjects. A rare case of hypoxia was also observed. Reversible elevations in LDH, alkaline phosphatase, and uric acid were also observed.

7.6 G-CSF

7.6.1 Formulation

The G-CSF to be used in this study is a recombinant human G-CSF from Amgen. The G-CSF is obtained from the bacterial fermentation of a strain of E. coli bearing a genetically engineered plasmid containing the human G-CSF gene. The G-CSF is formulated as a clear, colorless, particulate-free solution and is provided in vials containing 600 µg of the G-CSF protein in 2 ml of an aqueous buffer (final concentration = 300 µg/ml).

7.6.2 Administration

The appropriate dose of G-CSF is withdrawn into and administered from a plastic syringe. G-CSF solution vials and dilutions should not be shaken. The G-CSF will be injected subcutaneously into rotating sites on the abdomen, arms, and legs. G-CSF (either 300 µg/day for patients ≤ 70 kg and 480 µg/day for patients > 70 kg will be given subcutaneously from days 6-15 and days 34-42). G-CSF can be self-administered by the patient. Each patient or a designated caregiver will be instructed by the nursing staff in the proper methods of sterile removal of G-CSF from the vial and the antiseptic subcutaneous administration of G-CSF. Prior to administration at home, these skills must be competently demonstrated by the patient or caregiver. Patients/caregivers will also receive written instruction on the dose to be
administered, on medication storage (refrigeration), and that each reconstituted vial may only be used once.

7.6.3 **Supplier**

G-CSF is commercially available.

7.6.4 **Storage**

The intact vial should be kept refrigerated at 2-8°C. The 300 µg/ml G-CSF is stable for at least 36 months when stored under these conditions. Exposure of the material to excessive temperatures above or below this range can result in loss of activity. **Do not allow G-CSF to freeze, and do not administer any G-CSF which has been inadvertently frozen.** Vials should be treated as unit-dose containers, and any unused reconstituted solution should be discarded.

7.6.5 **Side Effects and Toxicities**

The predominant toxicity attributable to G-CSF is mild medullary bone pain. Splenomegaly and rare cases of splenic rupture have been reported. Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis. Allergic-type reactions, including anaphylaxis, skin rash and urticaria, occurring on initial or subsequent treatment, have been reported. Severe sickle cell crises have been reported in patients with sickle cell disease; one of these cases was fatal. Mild alopecia has also occurred. Mild transient swelling at injection sites can occur. Spontaneously reversible mild to moderate elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase have occurred.

7.7 **Adverse Drug Reaction Reporting (3/24/10)**

7.7.1 **Beginning April 1, 2010,** the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to grade severity of adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

7.7.2 **This study will be monitored by the Clinical Data Update System (CDUS)** version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.7.3 **Adverse Drug Reaction Reporting – Commercial Agent(s) (4/13/05)**

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses a commercial anticancer agent. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery followed by a FDA Form 3500 (MedWatch) sent to the address on the form and to RTOG Data Management within ten working days. Sites are also responsible for reporting adverse events as specified by their Institutional Review Board:

7.7.3.1 Any ADR that is both serious (*life-threatening* [grade 4] or *fatal* [grade 5]) and unexpected;
7.7.3.2 Any increased incidence of a known ADR that has been reported in the package insert or the literature;
7.7.3.3 Any ADR that results in significant disability or incapacity;
7.7.3.4 Any infant born to a patient that was treated on this protocol and has a congenital anomaly or birth defect;
7.7.3.5 Any hospitalization within 30 days of treatment;
7.7.3.6 Any death on study if clearly related to the commercial agent(s).
7.7.3.7 The ADR report should be documented on FDA Form 3500 (*MedWatch*) and mailed or faxed to the address on the form, as well as to the RTOG Data Management Department: (4/13/05)

RTOG Data Management
1818 Market Street
Suite 1600
Philadelphia, PA 19103
Phone: 215-717-2762
FAX: 215-928-0153
All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included.

7.7.4 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment must be telephoned to the RTOG Headquarters Data Management department within 24 hours of discovery.

7.7.5 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at [http://ctep.info.nih.gov](http://ctep.info.nih.gov). The report must include the time from original diagnosis to development of AML/MDS, and if available, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed/FAXED within 30 days of AML/MDS diagnosis to the Investigational Drug Branch (IDB) and to the RTOG Data Management Department: (4/13/05)

Investigational Drug Branch  RTOG Data Management
(NCI/CTEP)  AML/MDS Report
P.O Box 30012  1818 Market Street
Bethesda, MD 20824  Suite 1600
Fax: 301-230-0159  Phone: 215-717-2762
Fax: 215-928-0153

All AML/MDS forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included.

8.0 SALVAGE THERAPY

8.1 Follow-up Evaluation

8.1.1 Following definitive chemoradiation, patients will be followed closely for evidence of residual or recurrent esophageal tumor at locoregional and distant sites. If the patient has evidence of residual or recurrent esophageal tumor on follow-up, the patient will be evaluated for salvage therapy.

8.1.2 Follow-up investigations to identify residual esophageal carcinoma will include serial endoscopies (endoscopic ultrasound preferred). CT abdomen and chest scans are mandatory. PET scans are optional, but encouraged and should be performed at regularly scheduled time points. Biopsies will be performed as clinically indicated. (See Section 11.1)

8.1.3 This trial will try to determine the diagnostic findings associated with residual and recurrent esophageal cancer as well as the biologic factors. Pathologic specimens will be collected and analyzed whenever possible.

8.1.4 The determination of residual or recurrent esophageal cancer will be made by the medical, radiation and surgical oncologist and will be based on the follow-up studies and clinical judgment.

8.1.5 Diagnostic Findings warranting consideration of residual or recurrent esophageal cancer:

8.1.5.1 CT Chest/Abdomen: increase in size of primary, locoregional, or metastatic disease (biopsy should be performed if clinically indicated).

8.1.5.2 PET: new uptake in primary, locoregional or metastatic sites (biopsy should be performed if clinically indicated).

8.1.5.2.1 Image Interpretation and Grading Guidelines

PET images should be interpreted by an experienced nuclear physician from each participating site, without knowledge of the results of CT or other imaging studies or of surgical staging procedures. All images will be interpreted with the use of the standardized forms specifically developed for this study. Final PET evaluation-combined re-reading of the PET scan will then be done in combination with the CT and other available imaging studies.

8.1.5.2.2 Guidelines for Analysis

Visual analysis will involve the identification of abnormal uptake as being greater than normal activity on the attenuation-corrected images. The abnormalities will be recorded on the standard form. Intensity of uptake in the primary tumor and presence or absence of locoregional nodal involvement and distant metastatic disease will be recorded on a 5-
point scale (4 = definitely abnormal, 3 = probably abnormal, 2 = indeterminate, 1 = probably normal, 0 = definitely normal). For guidance purposes, mediastinal (and hilar, etc.) nodal disease is graded in reference to normal background tissue activity as compared to blood pool activity. That is, 0 = definitely normal (soft tissue) activity, 1 = probably normal (uptake is greater than normal background but less than blood pool activity), 2 = indeterminate (uptake is comparable to mediastinal blood pool activity), 3 = probably abnormal (uptake is slightly greater than mediastinal blood pool activity), and 4 = definitely abnormal (uptake substantially greater than mediastinal blood pool activity).

8.1.5.2.3 Confirmatory Studies for Positive FDG-PET Findings

PET-positive lymph nodes: Lymph nodes should be labeled as shown in Lymph Node Maps. If clinically indicated, supraclavicular, abdominal or mediastinal lymph node abnormalities can be confirmed by open biopsy or FNA. If a liver abnormality is noted, biopsy or FNA cytology can be performed to confirm metastatic disease. MRI and ultrasonography without biopsy may be used to diagnose benign cysts or hemangiomas. However, biopsy is required if noninvasive tests are indeterminate. It is sometimes not practical to biopsy small lesions. PET-positive adrenal lesions, PET-positive bone lesions: osseous abnormalities seen on PET can be further evaluated if clinically indicated by imaging studies (plain radiographs, CT, MRI, or repeat bone scintigraphy, if considered clinically appropriate), by biopsy, or by both in order to exclude metastatic disease. In the event that PET identifies more than one metastatic site that was not detected by another imaging study, and it is deemed clinically inappropriate to subject the patient to biopsies at each site, a positive biopsy of the most technically accessible site will serve as sufficient tissue confirmation of distant metastatic disease. If clinically appropriate, confirmation of all sites of distant metastatic or locoregional disease suspected on PET (and other imaging studies) is desirable. A lesion reported as a probable metastasis on PET, but not biopsied, will be considered a false-positive imaging result if it remains unchanged at the six-month follow-up. In patients who have a lesion (or lesions) detected on imaging studies that are not confirmed by biopsy, repeat standard imaging is required at the six-month follow-up.

8.1.5.3 Endoscopy and ultrasound: increase in mass or lymph nodes on endoscopic ultrasound (biopsy should be performed if clinically indicated); biopsy or fine needle aspirate (lymph nodes or primary) showing viable cancer; undilatable stricture.

8.1.5.3.1 Description of technique: The patient is sedated with appropriate medications. The endoscope is passed through the mouth into the esophagus and stomach. Any masses, strictures or ulceration should be identified and biopsied. The video endoscope can then be withdrawn. A radial echoendoscope (EUS scope) is then passed into the esophagus to the stomach. The water balloon of the echoendoscope is then filled and air is suctioned from the stomach. EUS examination of the celiac axis is performed with careful search for any enlarged celiac lymph nodes. If any enlarged celiac lymph node is identified, its size is measured and its morphologic characteristics are identified. Morphologic criteria that suggest malignancy are 1) size more than 8 mm; 2) round shape (vs ovoid or oblong shape of benign lymph nodes); 3) echotexture – malignant nodes are hypoechoic or same echotexture as the tumor; and 4) sharp margins. The endoscope is withdrawn into the esophagus and the search is made for enlarged mediastinal lymph nodes. Staging of the esophageal lesion is then performed, with careful consideration for preservation of tissue architecture, extent of the tumor into the various layers of the esophageal wall, extension beyond the esophageal wall, and infiltration of surrounding structures including the aorta, azygos vein, crura of diaphragm, pleura, and pericardium. The radial echoendoscope is then withdrawn. If a decision is made to perform FNA of any visualized structure, then a linear echoendoscope (with capabilities for fine needle aspiration) is then passed through the mouth into the esophagus and stomach. The structure to be biopsied is localized into the echoendoscope and maneuvered to an optimal position for FNA. An FNA needle is then inserted through the needle port in the echoendoscope. The needle position is adjusted with an elevator and the needle with the stilette is inserted into the mass or the lymph node. The stilette is then withdrawn. A syringe with suction is then attached to the needle and multiple in and out movements are made with the needle in the mass. The suction is then removed and the needle pulled out of the endoscope. The tissue is then retrieved by passing the stilette back into the needle, the tissue is put on the glass slides and cytology preparations are made by the cytology technician. The slides can then be stained with "Diffquik" and "Papanicolou" stain and analyzed by the cytologist.
8.1.5.3.2 Since mucosal biopsies often miss viable underlying tissue, it is suggested that the primary mass have three FNAs performed as well as any suspicious and accessible enlarged lymph nodes.

8.1.5.4 Bone Scan/MRI Brain: metastatic disease

8.1.5.5 Clinical: Clinical symptoms suggestive of recurrent disease as determined by radiation oncologist, medical oncologist, and surgical oncologist.

8.1.6 The type of salvage therapy will be determined by the medical, surgical and radiation oncologist, and the patient and will depend on the clinical and physiological status of the patient.

8.1.7 Options for salvage therapy will include: surgery (if no systemic disease and patient is physiologically fit), additional chemotherapy, other therapies (i.e., brachytherapy or photodynamic therapy) or observation as clinically indicated.

8.1.8 Surgical salvage will only be considered for patients who have suspected or proven recurrent or persistent esophageal cancer that is present locoregionally. It will not be considered for unresectable or systemic metastatic sites.

8.1.8.1 The determination of locoregionally resectable disease will be made by the surgical oncologist and will be defined as disease limited to the primary and regional nodes that can be resected completely.

8.1.8.2 No systemic metastases can be present to consider surgical salvage (i.e., liver, bone, lung, or brain metastases).

8.1.8.3 Patient must be physiologically fit as determined by the surgical, medical and radiation oncologist to consider salvage esophagectomy.

8.1.8.4 The patient must desire and approve of salvage esophagectomy after all the potential increased risks have been delineated.13

8.1.8.5 Salvage Esophagectomy Procedure:
8.1.8.5.1 The type of surgery will depend upon the location and extent of the primary tumor. Surgery will be performed within 10 to 12 weeks following the completion of chemoradiotherapy. Patients will undergo an esophagectomy with anastomotic reconstruction in the chest or neck through a cervical incision. Complete intrathoracic nodal staging will include stations 7, 8, 9, 15, 16, and 17. Overlying pleural and adjacent soft tissues will be included to insure an adequate radial margin. A feeding jejunostomy will be put in place for postoperative nutritional support. (8/13/04)

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

8.1.8.5.3 If the cancer is found to be unresectable, this strategy will be considered a failure and patients will be followed for survival. Additional therapy will be based on the judgment of the treating physicians.

9.0 OTHER THERAPY

9.1 Therapy for patients with metastatic relapse or physiologically unfit locoregional relapse

9.1.1 Patients with pathologically proven metastatic disease or poor physiologic condition with locoregional disease will be considered for additional therapy based on the judgment of the treating physicians.

9.1.2 Alternative therapies will include but not be limited to additional chemotherapy, novel biologic agents, additional radiation therapy, or simple observation.

9.1.3 The decision for alternative therapies will be made by the medical, radiation, and surgical oncologists and will be made in conjunction with the patient’s choice.

10.0 TRANSLATIONAL RESEARCH/TISSUE BANK
(For patients who have consented to participate in the tissue component of the study; see Appendix IB)

10.1 Translational Research (recommended but not mandatory)
The RTOG has been collecting diagnostic tissue from esophagus cancer protocols over the last ten years. A number of histologic, cell kinetic/proliferation, and molecular markers are under investigation. The results of these ongoing studies will lead to the investigation of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials and 2) developing novel treatment strategies that target the molecular abnormalities identified. A final decision on which markers will be studied
awaits the results of completed RTOG esophagus cancer trials that have reached maturity. The trial described here will not be ready for biomarker analysis for several years.

### 10.2 RTOG Tissue Bank (recommended but not mandatory)

#### 10.2.1 Rationale

The purpose of the RTOG Tissue Bank is to acquire and maintain high-quality specimens from RTOG trials, to provide uniform access of such tissues to investigators for correlative studies, and to preserve tissue from each block through careful block storage and processing. Correlative studies from these specimens are meant to integrate new research findings into future protocol development and to educate RTOG members.

#### 10.2.2 Specimen Collection

Tissue specimens for banking should be taken from pre-treatment diagnostic biopsy and/or salvage esophagectomy. The following must be provided in order for the case to be evaluable for the Tissue Bank:

**10.2.2.1 Pretreatment biopsy:**

- **10.2.2.1.1** One H&E stained slide.
- **10.2.2.1.2** A paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue, punched from the tissue block that contains tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE:** A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. These unstained slides should be placed on either Fisher “superfrost plus” or similar positively charged slides, or on other gap immunohistochemical staining slides. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- **10.2.2.1.3** A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report.
- **10.2.2.1.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; the form must include the RTOG protocol number and patient’s case number.
- **10.2.2.1.5** Submit materials to: (4/13/05)

LDS Hospital  
Dept. of Pathology  
E.M. Laboratory  
8th Ave & C Street  
Salt Lake City, UT 84143  
801-408-5626  
FAX 801-408-5020  
holly.goold@ihc.com

**10.2.2.2 Salvage esophagectomy:**

Typically, pre-existing esophageal carcinomas show extensive ulceration after pre-operative chemoradiation. If residual tumors are grossly identifiable, an effort for tumor banking should be performed. If no residual tumors are grossly identified, areas with ulceration indicating a site of pre-existing carcinoma should be completely sectioned and submitted for histological examinations. Sections for margins, lymph nodes, and representative esophageal and gastric mucosa are performed as regular esophagectomy specimens.

- **10.2.2.2.1** One H&E stained slide.
- **10.2.2.2.2** A paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue, punched from the tissue block that contains tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE:** A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. These unstained slides should be placed on either Fisher “superfrost plus” or similar positively charged slides, or on other gap immunohistochemical staining slides. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- **10.2.2.2.3** A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report.
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LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
801-408-5626
FAX 801-408-5020
holly.goold@ihc.com

10.3 Reimbursement
10.3.1 RTOG will reimburse submitting institutions $300 for fresh or flash frozen tissue or for serum, $200 per case for a block or core of material, or $100 per case for unstained slides. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.4 Confidentiality/Storage (See Appendix IB and the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, and the date the specimens were sent. No clinical information is kept in the database.

10.4.2 The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters (4/23/04)

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<th>Prior to entry (≤ 28days)</th>
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11.0 PATIENT ASSESSMENTS
11.1 Study Parameters (4/23/04)
a. Within 2 weeks prior to study entry
b. Required if tumor is < 25 cm from incisors
c. Encouraged in patient with hearing loss
d. At the time of endoscopy perform mucosal biopsy of primary mass and needle aspirate of any suspicious nodes (if possible)
e. Optional
f. Optional (but highly encouraged)
g. If clinically indicated
h. CT scan should be done after 2nd cycle of induction chemotherapy to ensure there is no progression that would require re-planning radiation therapy
i. Every 3 months x 2 visits, then every 6 months x 2 visits, then yearly
j. Weekly during chemoradiotherapy
k. Highly encouraged, but not required
l. Patient to be evaluated by Medical Oncologist, Surgical Oncologist and Radiation Oncologist
m. Patient to be evaluated by Medical or Radiation Oncologist and Thoracic Surgeon/Surgical Oncologist

11.2 Criteria for Response
These tumors are not measurable; thus response is not an endpoint of this study. The rate of negative endoscopy (if possible, mucosal biopsy and FNA of primary and lymph nodes negative) 6 to 8 weeks after completion of radiation therapy (See Section 11.1) would be the equivalent of a complete response. Residual mass on CT scan or endoscopic ultrasound does not preclude complete response (since fibrosis often remains) as long as all biopsies of primary tumor are negative, and there is not enlargement between sequential examinations.

11.3 Criteria for Progression of Disease
11.3.1 While it is recognized that it is not always possible to obtain pathologic proof of progressive disease, biopsy or autopsy material confirming recurrent cancer is highly desirable, and every reasonable attempt to obtain it is encouraged.
11.3.2 In the absence of histologic or cytologic proof of recurrence, clinical evidence (including new masses on CT scan, new lesions on bone scan, ascites not explained by other causes, or enlarging mass by endoscopic US) can be used in combination with clinical suspicion to determine recurrent or relapsed esophageal cancer. These findings should lead to a search for a mass that can be biopsied.
11.3.3 Patients who develop progression of disease at the primary site while receiving chemoradiotherapy or develop metastatic disease outside the RT field will be considered treatment failures. They may be treated with any form of palliative therapy at the discretion of their physician (including salvage esophagectomy if there is no evidence of metastatic disease and only locoregional resectable progression).
11.3.4 Patients who develop local recurrence only after definitive chemoradiation may be offered surgery; they will be considered treatment failures. Those who develop metastases may be offered chemotherapy; they will be considered treatment failures. The regimen chosen may include a variety of phase II agents under study or conventional chemotherapy.
11.3.5 The dates and sites of all failure patterns must be reported.

11.4 Criteria for Discontinuation of Treatment
11.4.1 Patient’s refusal to continue study participation.
11.4.2 Occurrences of unacceptable toxicity that would necessitate a major modification of treatment. In this event, follow-up and data submission will continue according to protocol.

12.0 DATA COLLECTION (9/5/03)
Data should be submitted to: (4/13/05)
RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

12.1 Summary of Data Submission

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</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints
- To estimate the one-year overall survival rate.
- To determine the frequency of major (grade 4) acute toxicities associated with the chemoradiation and surgical salvage therapy.
- To determine the frequency of patients with persistent or recurrent locoregional esophageal carcinoma who would be eligible for surgical salvage resection.

13.2 Sample Size
Thirty-eight analyzable patients will be required for this study. Based upon the RTOG’s database of esophagus patients treated with chemoradiation in previous studies, a one-year survival rate of approximately 60% has been seen. The regimen will need to have a one-year survival rate of 77.5% or better in order for it to be deemed promising enough for study in a phase III protocol (≈ hazard reduction of 50% with type I error of 0.05 and type II error of 0.20).\textsuperscript{28} Adjusting this figure by 10% to account for patient ineligibility or loss, a total sample size of 42 patients will be required for this study.

13.3 Patient Accrual
In the last RTOG phase III study of the esophagus (RTOG 94-05), a total of 190 patients from RTOG institutions were accrued in four years, for an approximate accrual rate of 4 cases per month. After allowing approximately six months for institutions to obtain IRB approval to open
this study, and assuming a similar accrual rate for this study, accrual should be completed in 18 months. If, after 18 months, accrual is less than two patients a month, the RTOG Gastrointestinal Committee will decide if the study should be closed due to poor accrual.

13.4 Early Stopping Rules

13.4.1 Failure to Deliver Protocol Treatment

A treatment would not be suitable for further study if it were not tolerable by the patients. In order to test the null hypothesis that 80% or more of the patients are able to receive sufficient treatment (as defined by at least three cycles of chemotherapy and 90% of the dose of radiation) with significance level 0.05, we will observe the amount of treatment delivered to the first 25 patients. If nine or more patients have not received the sufficient treatment, we shall conclude that the treatment is unable to be delivered to the patients at an acceptable dose level and recommend that patients no longer be entered onto the study. With 25 evaluable patients, the power to detect differences between the null (0.80) and various alternative values is shown below:

<table>
<thead>
<tr>
<th>True proportion of patients able to tolerate treatment</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>15%</td>
</tr>
<tr>
<td>0.70</td>
<td>32%</td>
</tr>
<tr>
<td>0.65</td>
<td>53%</td>
</tr>
<tr>
<td>0.60</td>
<td>73%</td>
</tr>
<tr>
<td>0.55</td>
<td>87%</td>
</tr>
<tr>
<td>0.50</td>
<td>95%</td>
</tr>
</tbody>
</table>

After reviewing toxicity data, appropriate actions shall be recommended by study chair, disease chair, and statisticians to the RTOG Data Monitoring Committee and the Research Strategy Committee for their approval.

13.4.2 Unacceptable Toxicity

The unacceptable toxicity is defined as grade 5 (fatal) toxicity due to chemotherapy and radiation therapy and will be limited to those toxicities that occur before protocol surgery or within two months after chemoradiation if there is no surgery. The following early stopping rules are proposed to test the null hypothesis that the proportion of unacceptable toxicity is less than or equal to 5% with significance level of 0.05. We will reject the null hypothesis if we observe more than three fatal toxicities (grade 5) out of the first 25 patients who started protocol treatment regardless of protocol eligibility. If we observe three or fewer of fatal toxicities at the designated time, the trial shall proceed as planned. On the other hand, if we observe more than three toxicities, we shall conclude that the proportion of unacceptable fatal toxicity is greater than 5%. With these 25 patients, the power to detect differences between the null (0.05) and various alternative values is shown:

<table>
<thead>
<tr>
<th>True toxic event rate</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>24%</td>
</tr>
<tr>
<td>0.15</td>
<td>53%</td>
</tr>
<tr>
<td>0.20</td>
<td>77%</td>
</tr>
<tr>
<td>0.25</td>
<td>90%</td>
</tr>
<tr>
<td>0.30</td>
<td>97%</td>
</tr>
</tbody>
</table>

After reviewing toxicity data, appropriate actions shall be recommended by study chair, disease chair, and statisticians to the RTOG Data Monitoring Committee and the Research Strategy Committee for their approval.

13.5 Analysis Plan

13.5.1 Interim Reports

Interim reports will be prepared every six months until the final analysis. In general, the interim report includes the patient accrual rate with projected completion date; pretreatment characteristics of patients accrued; rates of treatment delivery with respect to the protocol prescription; and the frequency and severity of toxicities due to chemotherapy and radiation therapy.

13.5.2 Analysis for Reporting the Initial Treatment Results
This major analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are: patients from the analyses with reasons for exclusion; institutional accrual; distribution of the important prognostic baseline variables; patient accrual rate with projected completion date; and observed results with respect to the endpoints described in Section 13.1. Further subgroup analysis will not be undertaken because of the small sizes involved in each subgroup. This study was designed to compare the efficacy against the RTOG historical database.

A statistical analysis will be performed to examine the possible difference between the genders and among the races. The interim analysis will include a tabulation of all cases by gender and racial categories. The analysis for reporting the initial treatment results will include 95% confidence intervals for treatment tolerance and survival. 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:

### Gender and Minority Accrual Estimates

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>11</td>
<td>29</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>12</td>
<td>30</td>
<td><strong>42</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>4</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8</td>
<td>20</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>12</td>
<td>30</td>
<td><strong>42</strong></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX IA
RTOG 0246
SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE
A PHASE II STUDY OF A PACLITAXEL-BASED CHEMORADIO THERAPY REGIMEN WITH SELECTIVE SURGICAL SALVAGE FOR RESECTABLE LOCOREGIONALLY ADVANCED CARCINOMA OF THE ESOPHAGUS

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 cancer of the esophagus.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) chemotherapy given before radiation therapy and followed by chemotherapy given together with radiation therapy has on you and your esophageal cancer and whether certain patients can be treated without the need for surgical resection (removal of all or part of your esophagus).

This research is being done to determine whether this is a safe and effective way of treating esophageal cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 42 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (4/13/05, 6/6/05)
You will receive the following treatment:

<table>
<thead>
<tr>
<th></th>
<th><strong>STEP 1</strong></th>
<th><strong>STEP 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle 1</strong></td>
<td><strong>Cycle 2</strong></td>
<td><strong>One month after last chemo dose</strong></td>
</tr>
<tr>
<td>5-FU</td>
<td>Days 1-5 continuous for 96 hours</td>
<td>Days 29-33 continuous for 96 hours</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Days 1-5 in 1 hour</td>
<td>Days 29-33 in 1 hour</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Day 1 in 2 hours</td>
<td>Day 29 in 2 hours</td>
</tr>
<tr>
<td>RT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Days 6-15 after cycle 1</td>
<td>Days 34-42 after cycle 2</td>
</tr>
<tr>
<td>*Neulasta</td>
<td>Day 6</td>
<td>Day 34</td>
</tr>
</tbody>
</table>

**Step 1:**

**Chemotherapy Alone**

You will receive one or two cycles of chemotherapy called 5-FU, cisplatin, and Taxol. One cycle lasts five days. On the first day, you will receive Taxol given into a vein (intravenous) over 2 hours. You will receive 5-FU on days 1 through 5. This will run continuously for 96 hours over 5 days into your vein by an intravenous pump. The pump will be portable allowing you to get around. Also, on days 1 through 5, you will receive cisplatin. This will be a one-hour intravenous infusion given once a day on days 1 through 5. A second cycle of this chemotherapy will be given on day 29 or three weeks from the end of the first cycle. Your chemotherapy may be given as an in-patient at your institution because it is given continuously for 5 days.

You will receive G-CSF for 1½ weeks after ending each chemo cycle. This would be on days 6 through day 15 after the 1st cycle and days 34 through 42 after the second cycle. G-CSF is an injection or shot. This medicine helps your white blood cells increase after treatment. White blood cells help to fight infection. Your doctor may choose to give you Neulasta™ instead of G-CSF. Neulasta™ is a longer acting form of G-CSF. Neulasta™ is an injection or shot, and you would receive it on day 6 of the first cycle of chemotherapy, and day 34 of the second cycle of chemotherapy.

If, after the 1st cycle of chemotherapy alone, your cancer remains the same or gets better, you will have a second cycle of chemotherapy alone, then go on to chemotherapy and radiation together.

If, after the 1st cycle of chemotherapy alone, your cancer grows more around your esophagus, you will not get a second cycle of


chemotherapy alone and will go on to get the chemotherapy and radiation together.

If, after the 1st cycle of chemotherapy alone, your cancer grows other places in your body, you will go on to other treatment decided by you and your physician.

**Step 2:**  
**Chemotherapy and Radiation Therapy Together:**

Approximately one month from your last chemotherapy cycle, you will start chemotherapy together with radiation therapy. You will receive radiation therapy five days a week, Monday through Friday, for 5 weeks, plus 3 days. The chemotherapy 5-FU will be given into your vein continuously over five days every week during radiation therapy. The chemotherapy drug cisplatin will be given the first five days of radiation therapy. The cisplatin will be given into your vein (intravenous).

You may have to be in the hospital when the chemotherapy treatment is being given because the chemotherapy is given slowly over a number of days.

**Step 3:**  
**Salvage Therapy:**

Approximately one month from your last day of radiation, you will be evaluated with various tests to assess the status of your esophageal cancer. If it is determined that your esophageal cancer is still present, you will be offered a “salvage” therapy by your doctors which may be salvage esophageal resection (surgery), additional chemotherapy, additional radiation therapy, other therapies, or no therapy and continued observation. You will participate in choosing your salvage therapy in conjunction with advice from your doctor regarding the risks and potential benefits of each type of treatment given your physical condition and the status of your esophageal tumor.

**Procedures that will be Done for this Study:**

**Prior to study entry:**
- History and physical examination – a medical and surgical oncologist and radiation oncologist will examine you.
- Blood tests
- Assessment of your calorie intake
- CT scan or MRI of the chest and abdomen
- Upper GI with barium contrast (optional)
• An access device for giving chemotherapy will be necessary. This device will be placed under your skin on the front of your chest with a plastic tube leading to a large vein.
• Upper GI endoscopy and biopsy (an ultrasound is also required).
• Bronchoscopy – if necessary based on the location of your cancer
• Biopsy of a lymph node – if a lymph node is seen as enlarged on the x-rays
• A feeding tube that goes directly into your stomach may be necessary if you are having trouble eating.
• Bone scan – if necessary based on blood tests
• Audiogram – (hearing test) if necessary
• PET scan - if indicated by your physician
• Barium swallow contrast examination (optional)

Prior to each Chemotherapy Cycle:
• Physical examination
• Blood tests
• Audiogram (hearing test), if necessary.

After each Chemotherapy Cycle:
• Physical examination will be done weekly during radiation therapy treatment
• Weekly blood tests during radiation therapy
• Barium swallow contrast examination (optional)
• CT scan after second cycle of chemotherapy
• Upper GI endoscopy and an ultrasound and biopsy – if indicated by your physician.

Approximately 1½ months to 2 months after you have completed all treatment:
• Physical examination
• Blood tests
• CT scan or MRI of the chest and abdomen
• Upper GI endoscopy and biopsy (an ultrasound is also required)
• Biopsy of a lymph node – if a lymph node is seen as enlarged on the x-rays
• PET scan-if indicated by your physician

At each Subsequent Follow-up (every 3 months x 2, then 6 months x 2 and then yearly) (3/24/04)
• Physical examination by a medical or radiation oncologist and thoracic surgeon/surgical oncologist
• Blood Tests
• Barium swallow contrast examination (optional)
• CT scan or MRI of the chest and abdomen
• Upper GI endoscopy and biopsy if indicated by your physician (an ultrasound is also required)
• PET scan - if indicated by your physician.
• Bone scan – if indicated by your physician

**HOW LONG WILL I BE IN THE STUDY? (12/15/03, 3/5/04)**

This study will take approximately 4 to 5 months to complete. Follow-up visits will be scheduled every three months x 2, then every six months x 2, and then yearly.

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?**

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 Esophagus**

*Very Likely*
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Sore throat, which can be painful and make it very difficult to chew and/or swallow foods
- Tanning or redness of the skin in the neck and chest areas being treated
- Fatigue
- Hair loss in the treatment area

*Less Likely, But Serious*
- Esophageal stricture or tightening of the esophagus
Fistula or perforation of the esophagus – an ulceration that can cause a hole in the esophagus. This could lead to the use of a feeding tube.
Radiation pneumonitis or scarring of the lung
Myelitis – nerve damage or inflammation of the spinal cord

Risks Associated with Paclitaxel

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

**Less Likely**
- Muscle aches and/or joint pains
- Nausea and/or vomiting
- Headaches
- Skin or nail darkening
- Skin ulcers

**Less Likely, But Serious**
- Allergic reaction that 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
- Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
- Facial swelling
**Less Likely, But Serious**
Decreasing the kidneys’ ability to handle the body’s waste, which may be permanent.
Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating
Decrease in liver function
Other cancer called Acute Leukemia

**Risks Associated with 5-FU (5-Fluorouracil)**

**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

**Less Likely, But Serious**
Damage to the heart that causes chest pain
Infection at the catheter entry site

**Risks Associated with G-CSF and Neulasta™**

**Very Likely**
Fever
Loss of hair
Fluid retention
Nausea and/or vomiting
Diarrhea
Mild to moderate bone pain
Fatigue
Redness, swelling, itching, pain at injection site

**Less Likely**
Allergic reactions
Change in taste
Muscle pain
Chest pain
Insomnia
Abdominal pain
Mouth sores
Dizziness
Abnormally large number of white blood cells
Inflammation of blood vessels
Increase in uric acid and some enzyme levels in the blood
Headache
Skin rash
Anorexia
Constipation
Sore throat

**Less Likely, But Serious**
Irregularity of heartbeat
Decrease in blood pressure
Difficulty breathing
Enlargement of spleen that may lead to rupture

**Risks Associated with Placement of Venous Access Device**

**Likely**
Bleeding
Possible infection at the access site

**Less Likely, But Serious**
Blood clots forming in the vein
Puncture of the lung

**Risks Associated with Salvage Surgical Therapy (4/13/05)**

**Very Likely**
Postoperative pain
Loss of appetite
Nausea and/or vomiting
Weakness
Changes in bowel habits

**Less Likely**
Fever
Pneumonia or other infection (i.e., wound, urine)
Postoperative complication requiring re-operation (i.e., bleeding, leak at anastomosis)
Weight Loss
Narrowing of anastomosis requiring dilation by endoscopy
Loss of coordination or balance
Blood clot in lung
Damage to the heart that causes chest pain
Heart arrhythmia
Breathing problem requiring ventilator or tracheostomy
Death due to a postoperative complication
Problems with digestion and changes in swallowing function
Hoarseness
Possibility of inhaling food and/or liquids into the lungs that could also result in pneumonia

**Less Likely, But Serious**
Stroke

**Reproductive Risks**

Treatment on this study may cause permanent sterility. This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

**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 esophageal 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; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

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?
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 cancer of the esophagus 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

SIGNATURE

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's Name                               Signature             Date

_____________________                       __________________   _________
Name of Person Obtaining Consent       Signature             Date
ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. We would like to keep some of the tissue that remains for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Your tissue may be helpful for research whether you do or do not have cancer.

If you are considered to be a surgery candidate after treatment on this study, we would also like to keep some of the tissue that is left over from the surgery.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue before it is given to a researcher. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care.**

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee.

In the future, people who do research may need to know more about your health. While _________ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers
your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

**BENEFITS**

The benefits of research using tissue/blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**RISKS**

**Physical Risks**
Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and, rarely, creation of an abnormal opening or passage.

**Social-Economic Risks**
There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _______ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, 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.

**MAKING YOUR CHOICE**

If you have any questions about the research involving your tissue/blood or about this form, please talk to your doctor or nurse, or call the institution’s research review board at _________ (IRB’s phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.**
1. My tissue and/or blood may be used for the research in the current study.

   Yes          No

2. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat cancer.

   Yes          No

3. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).

   Yes          No

4. Someone from _____ (doctor’s office/institution) may contact me in the future to ask me to take part in more research.

   Yes          No

Participant statement:
I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

__________________________  __________________  ____________
Patient’s Name              Signature          Date

Witness statement:
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

__________________________  __________________  ____________
Name of Person Obtaining Consent  Signature          Date
### APPENDIX II

**RTOG 0246**

#### KARNOFSKY PERFORMANCE SCALE

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

#### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (<em>Karnofsky 90-100</em>).</td>
</tr>
<tr>
<td>1</td>
<td>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 (<em>Karnofsky 70-80</em>).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (<em>Karnofsky 50-60</em>).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<em>Karnofsky 30-40</em>).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<em>Karnofsky 10-20</em>).</td>
</tr>
<tr>
<td>5</td>
<td>Death (<em>Karnofsky 0</em>)</td>
</tr>
</tbody>
</table>
**APPENDIX III**


**DEFINITION OF TNM**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adventitia</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Tumors of lower thoracic esophagus</td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis in celiac lymph nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Not applicable</td>
</tr>
<tr>
<td>M1b</td>
<td>Non-regional lymph nodes and/or other distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis in cervical nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
</tr>
</tbody>
</table>

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Code</th>
<th>N Code</th>
<th>M Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
</tr>
</tbody>
</table>
HISTOPATHOLOGIC TYPE
The staging classification applies to all carcinomas (*squamous cell and adenocarcinomas*). Adenocarcinomas arising from Barrett's esophagus are included in the classification.

HISTOPATHOLOGIC GRADE (G)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

**Note:** For this study, metastatic disease is not allowed except for celiac nodes of less than 2 cm.