

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0113**

**NON-OPERATIVE THERAPY OF LOCAL-REGIONAL CARCINOMA OF THE  
ESOPHAGUS: A RANDOMIZED PHASE II STUDY OF TWO PACLITAXEL-BASED  
CHEMORADIOTHERAPY REGIMENS**

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## RADIATION THERAPY ONCOLOGY GROUP

RTOG 0113 (8/4/04)

### NON-OPERATIVE THERAPY OF LOCAL-REGIONAL CARCINOMA OF THE ESOPHAGUS: A RANDOMIZED PHASE II STUDY OF TWO PACLITAXEL-BASED CHEMORADIOTHERAPY REGIMENS

#### SCHEMA

<b>S</b>		<b>R</b>	
<b>T</b>	<b><u>Weight Loss</u></b>	<b>A</b>	<b><u>Arm 1 (5-FU-based)</u></b>
	1. < 10%		Induction chemotherapy with 5-FU, cisplatin, paclitaxel
<b>R</b>	2. ≥ 10%	<b>N</b>	(up to 2 cycles) followed by (on day 29 of the last cycle) continuous
			96-hr. infusion 5-FU and weekly paclitaxel with concurrent
<b>A</b>	<b><u>Lesion Size</u></b>	<b>D</b>	radiotherapy* (50.4 Gy) [G-CSF given from days 6-15 and 34-42]
	1. ≤ 5 cm		
<b>T</b>	2. > 5 cm	<b>O</b>	<b><u>Arm 2 (Non-5-FU-based)</u></b>
			Induction chemotherapy with paclitaxel and cisplatin
<b>I</b>	<b><u>Histology</u></b>	<b>M</b>	(up to 2 cycles) followed by (on day 29 of the last cycle) continuous
	1. squamous cell carcinoma		96-hr. infusion paclitaxel and weekly cisplatin with
<b>F</b>	2. adenocarcinoma	<b>I</b>	concurrent radiotherapy* (50.4 Gy). Routine G-CSF administration
			is not planned.
<b>Y</b>		<b>Z</b>	
		<b>E</b>	

**\*Participating institutions must utilize 3-D CT planning and must be able to comply with criteria described in Section 6.0.**

#### **Eligibility:** (See Section 3.0 for details) [1/15/02]

- Histologic proof of primary squamous cell or adenocarcinoma of the esophagus or gastroesophageal junction (*No tumor extension beyond 2 cm into stomach*)
- T1N1M0; T2-4, N any, M0 (*except regional nodes such as supraclavicular and celiac*)
- Zubrod Performance Status 0-1
- Patients' total intake (oral/enteral) must be ≥ 1700 kCal/day (*see Section 4.1.10*)
- Platelets ≥ 150,000, Hgb ≥ 10 gm%, ANC ≥ 1500, serum creatinine ≤ 1.5 mg/dl
- Patients with prior malignancy are eligible if disease free ≥ 5 years
- No prior chest radiotherapy; no prior systemic chemotherapy; no prior major esophageal surgery
- Excludes patients with TE fistula or invasion into mucosa of trachea or major bronchi, metastatic disease (*other than supraclavicular or celiac nodes*), uncontrolled serious medical or mental illnesses
- Signed study-specific consent form prior to study entry

**Required Sample Size: 84**

**RTOG Institution #** \_\_\_\_\_

**RTOG 0113 (8/4/04)**

**ELIGIBILITY CHECK (8/6/02)**

**Case #** \_\_\_\_\_

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- \_\_\_\_\_ (Y) 1. Does the patient have biopsy-proven squamous cell or adenocarcinoma of the esophagus or gastroesophageal junction?
- \_\_\_\_\_ (Y) 2. Is the tumor confined to the esophagus with no extension beyond 2 cm of the proximal stomach?
- \_\_\_\_\_ (Y/N) 3. Has an endoscopic ultrasound been performed?  
\_\_\_\_\_ If yes, specify the EUS stage
- \_\_\_\_\_ (N) 4. Is there evidence of distant disease?
- \_\_\_\_\_ (N) 5. Is there evidence of invasion of mucosa of trachea or major bronchi or tracheal esophageal fistula?
- \_\_\_\_\_ (N) 6. Does the patient have multiple carcinomas of the esophagus?
- \_\_\_\_\_ (Y) 7. Did the patient have a CT of the chest and abdomen (*MRIs are acceptable*)?
- \_\_\_\_\_ ( $\geq 1500$ ) 8. What is the ANC count?
- \_\_\_\_\_ ( $\geq 150$ ) 9. What is the platelet (*x 1000*) count?
- \_\_\_\_\_ ( $\geq 10$ ) 10. What is the HGB level?
- \_\_\_\_\_ (Y) 11. Was a serum creatinine and/or creatinine clearance done?
- \_\_\_\_\_ (Y/NA) 12. If the serum creatinine was done, are the results  $\leq 1.5$  mg/dl?
- \_\_\_\_\_ (Y/NA) 13. If the creatinine clearance was done, are the results  $\geq 65$  cc min?
- \_\_\_\_\_ (Y) 14. Have the required studies in Section 4.1 been done within the protocol time frame?
- \_\_\_\_\_ (N) 15. Has the patient had prior chest radiotherapy or systemic chemotherapy?
- \_\_\_\_\_ (N) 16. Has the patient had prior major esophageal surgery ?
- \_\_\_\_\_ (Y) 17. Is the Zubrod Performance Status 0-1?
- \_\_\_\_\_ (Y) 18. Is the patient's total intake  $\geq 1700$  kCal/day?
- \_\_\_\_\_ (Y/N) 19. 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  $\geq 5$  years?
- \_\_\_\_\_ (Y) 20. Has the patient had evaluations by a medical oncologist and a radiation oncologist?

RTOG Institution # \_\_\_\_\_

RTOG 0113 (8/4/04, 9/3/04)

**ELIGIBILITY CHECK**

Case # \_\_\_\_\_

(page 2 of 2)

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- \_\_\_\_\_ 5. Patient's Name
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Medical Oncologist
- \_\_\_\_\_ 9. Radiation Oncologist
- \_\_\_\_\_ 10. Date of Birth
- \_\_\_\_\_ 11. Race
- \_\_\_\_\_ 12. Social Security Number
- \_\_\_\_\_ 13. Gender
- \_\_\_\_\_ 14. Patient's Country of Residence
- \_\_\_\_\_ 15. Zip Code
- \_\_\_\_\_ 16. Patient's Insurance Status
- \_\_\_\_\_ 17. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 18. Specify patient's weight loss (*< 10% or ≥ 10%*)
- \_\_\_\_\_ 19. Specify lesion size (*≤ 5 cm or > 5 cm*)
- \_\_\_\_\_ 20. Specify histology (*squamous cell carcinoma or adenocarcinoma*)
- \_\_\_\_\_ 21. Treatment Start Date (*must be within 5 days after randomization*)
- \_\_\_\_\_ 22. Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## 1.0 INTRODUCTION

1.1 Definitive chemoradiotherapy of local-regional carcinoma of the esophagus has made significant inroads in the treatment of this cancer.<sup>1</sup> The data from the first intergroup trial compared definitive radiotherapy (50.4 Gy) plus concurrent 5-FU and cisplatin with radiotherapy (60 Gy) alone and has demonstrated significant survival benefit for patients receiving combined modality therapy.<sup>2</sup> The long-term results demonstrate a curative fraction of approximately 20%.<sup>2</sup> This figure is quite comparable to a surgical approach to local-regional carcinoma of the esophagus.<sup>3</sup> Consequently, a significant alternative to surgical resection has been established. The current options for patients who are medically fit to undergo surgery and whose tumors are technically resectable, include surgery or definitive chemoradiotherapy. Patients who have technically unresectable local-regional carcinoma or those having a potentially resectable carcinoma but who are not fit for surgical resection are eligible to receive definitive chemoradiotherapy. One major drawback of the standard approach of definitive chemoradiotherapy, however, is that it is associated with a high rate of locally persistent or recurrent disease ( $\geq 50\%$ ).<sup>2</sup> Thus an intergroup study was developed to address the problem of local-regional failure.

1.2 An attempt was made to reduce the locally recurrent or persistent disease by mounting the RTOG protocol 94-05, which randomized patients to the standard combined modality arm (50.4 Gy of radiotherapy plus concurrent 5-FU and cisplatin) or high dose chemoradiotherapy (64.8 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<sup>2</sup> x 96 hr) and cisplatin (75 mg/m<sup>2</sup> bolus day 1) weeks 1.5 and repeated 4 weeks after the end of radiation vs. high dose CMT (64.8 Gy + the same chemo). 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 were 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.

	<u>High dose</u>	<u>Standard dose</u>	<u>Total</u>
# Entered	114	118	230
# Eligible	97	99	196
Max Toxicity			
Gr 3	43 (44%)	33 (33%)	76 (38%)
Gr 4	26 (26%)	31 (31%)	57 (29%)
Gr 5	9 (9%)	2 (2%)	11 (6%)
Cancer Death	26 (26%)	33 (33%)	59 (30%)
Median Surv	12.8 months	17.5 months	
2-Yr Surv	24% (6 at risk)	33% (12 at risk)	

Treatment related deaths (Gr 5) included hematological, respiratory, infections, and renal. Of 9 treatment related deaths in the high dose arm, only 3 occurred during the high dose portion ( $>50.4$  Gy) of the protocol. Therefore, the excess deaths do not appear to be related to the higher radiation dose but rather to an unexplained imbalance in the arms. This interim analysis suggests that CMT with 64.8 Gy does not offer a survival benefit compared with 50.4 Gy.<sup>4</sup>

1.3 It is felt that new strategies must be investigated to develop an appropriate experimental arm for the next phase III study. The emphasis for the new approach would be on new agent, particularly paclitaxel, and on the use of induction chemotherapy. Paclitaxel and induction chemotherapy has been studied both at Memorial Sloan-Kettering Cancer Center (MSKCC) and M.D. Anderson Cancer Center (MDACC) in patients with carcinoma of the esophagus. Some of the details of those investigations have been listed below.

### 1.3.1 Paclitaxel for Esophageal Carcinoma

A phase II trial of paclitaxel at a dose of 250 mg/m<sup>2</sup> 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.<sup>5</sup> 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 carcinoma (28%). One patient had a complete response, which remains durable off therapy for 40+ months. The median duration of remission was nine months. This response rate was comparable to that observed in patients treated with cisplatin and fluorouracil.

### 1.3.2 Paclitaxel in Combination with Other Agents

In preclinical systems, there is evidence of synergism when paclitaxel is combined with cisplatin or 5-Fluorouracil.<sup>6-9</sup> 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.<sup>10-11</sup> In the trial of paclitaxel given together with cisplatin without G-CSF support reported by Rowinsky,<sup>11</sup> febrile neutropenia was the dose limiting toxicity and the recommended phase II doses were paclitaxel/cisplatin 135 mg/m<sup>2</sup> /75 mg/m<sup>2</sup>, respectively. The use of routine G-CSF administration in the subsequent phase I study reported by Rowinsky<sup>10</sup> permitted a higher dose of paclitaxel to be administered, with phase II doses of 250 mg/m<sup>2</sup> of paclitaxel and 75 mg/m<sup>2</sup> of cisplatin recommended. Although peripheral neuropathy and myalgias were the dose-limiting toxicities on this trial, grade 3-4 neuromuscular toxicity was not seen at paclitaxel/cisplatin doses  $\leq$  250 mg/m<sup>2</sup> / 75 mg/m<sup>2</sup>, respectively. However, severe peripheral neuropathy may be a limiting toxicity after prolonged administration of paclitaxel/cisplatin therapy as indicated in a recent preliminary report of a phase II trial in metastatic breast cancer.<sup>12</sup> This trial employed paclitaxel given by 24-hour infusion at a dose of 200 mg/m<sup>2</sup> in combination with cisplatin 75 mg/m<sup>2</sup> with G-CSF, recycled every 21 days. After a median of 5 cycles, progressive peripheral neuropathy lead to therapy discontinuation in 43% of patients. Cardiac arrhythmia, a toxicity observed in the initial paclitaxel/cisplatin phase I trial, has not been observed in subsequent studies of paclitaxel/cisplatin, including the trial of Rowinsky et al.<sup>11</sup> in which all patients underwent continuous cardiac monitoring during drug administration.

Paclitaxel has also been combined with cisplatin and 5-FU.<sup>13</sup> 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 nonhematologic 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 cancer (20%) compared to 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 fluorouracil in most prior studies, the toxicity was not trivial. Nevertheless, there were no treatment-related deaths in this study.

At MDACC, this combination has been used in previously untreated patients with potentially resectable carcinoma of the esophagus as induction chemotherapy followed by chemoradiotherapy (*with 5-FU and cisplatin*) in approximately 38 patients. Patients having histologic proof of localized adenocarcinoma of the esophagus or gastroesophageal junction underwent full staging including endoscopic ultrasonographic (EUS) staging. Patients first received up to two courses of induction chemotherapy consisting of 5-fluorouracil at 750 mg/m<sup>2</sup>/day as a continuous infusion on days 1-5, cisplatin at 15 mg/m<sup>2</sup>/day as an intravenous (*i.v.*) bolus on days 1-5, and paclitaxel at 200 mg/m<sup>2</sup> as a 24-hour *i.v.* infusion on day 1. The second course was repeated on day 29. This was followed by radiotherapy (45 Gy in 25 fractions) and concurrent administration of 5-fluorouracil (300 mg/m<sup>2</sup>/day as a continuous infusion 5 days/week) and cisplatin (20 mg/m<sup>2</sup> on days 1-5 of radiotherapy). Following chemoradiotherapy, patients underwent surgery. The feasibility of this approach, curative resection rates, patient survival, and patterns of failure were assessed. Thirty-seven of the 38 patients enrolled were evaluable for toxicity and survival. Adenocarcinoma and distal esophageal location of carcinoma were seen frequently. Thirty-five (95%) of the 37 patients underwent surgery, all of whom had an R0 (*curative*) resection. A pathologic complete response was noted in 11 (30%) of the 37 total patients. In addition, five patients (14%) had only microscopic carcinoma. According to EUS staging, 31 (89%) of the 35 patients, who underwent surgery, had a T3 carcinoma whereas, according to pathologic staging, only 3 (9%) had a T3 carcinoma ( $p = <0.01$ ). Similarly, according to EUS staging, 23 patients (66%) had an N1 carcinoma, whereas, according to pathologic staging, only 7 patients (20%) had an N1 carcinoma ( $p = <0.01$ ). At a

median follow-up of 20 months (*minimum follow-up, 13+ months; maximum follow-up, 36+ months*), the median survival duration for the 37 patients had not yet been reached. Additionally, there were 2 deaths related to surgery. These data demonstrated feasibility of induction chemotherapy followed by chemoradiotherapy. (*Ajani et al. manuscript submitted*).

### 1.3.3 Paclitaxel in Cisplatin Combination Chemotherapy in Esophageal Cancer

At MSKCC, the investigators have studied a combination of paclitaxel and cisplatin on the basis of identifying of paclitaxel as an active drug, and the known activity of cisplatin in patients with advanced esophageal cancer. 5-Fluorouracil was eliminated from the combination because of the toxicity concerns. The combination of paclitaxel and cisplatin was studied using a 24-hour infusion schedule of paclitaxel given at a dose of 250 mg/m<sup>2</sup> on day 1, cisplatin at a dose of 75 mg/m<sup>2</sup> on day 2 with G-CSF support. The antitumor response achieved on this trial to date is comparable to our prior paclitaxel/cisplatin/5-FU trial. Less grade 3/4 nonhematologic toxicity was observed. G-CSF use, however, was a requisite on this trial, and despite an overall reduced incidence of grade 3/4 toxicity, hospitalization for toxicity was still required in more than 40% of patients. A surprising incidence of treatment-related mortality (10%) was observed (*secondary mainly to neutropenic septic complications*), and led to a reduction in the starting dose of paclitaxel to 200 mg/m<sup>2</sup>. Use of a 24-hour compared to the previous 3-hour infusion schedule of paclitaxel did not increase the overall major response rate, and no complete responses were observed in patients with adenocarcinoma.

### 1.3.4 Preoperative Paclitaxel and Cisplatin

Based on the high overall and complete response rate observed for paclitaxel/cisplatin combination chemotherapy in metastatic disease, a multicenter trial of paclitaxel/cisplatin as induction chemotherapy prior to surgery in locally advanced esophageal cancer was conducted. The trial, the companion trial to the metastatic disease trial discussed above, is currently ongoing and accrual is near completion. Paclitaxel is given on day 1 at a dose of 200 mg/m<sup>2</sup> followed on day 2 by cisplatin at a dose of 75 mg/m<sup>2</sup>, cycled every 21 days for 3 cycles preoperatively and 2 cycles postoperatively. G-CSF support is given between cycles. To date, 19 patients are evaluable. Significant downstaging has been observed in 43% of patients treated with preoperative therapy, and a major response has been seen in 47% of patients. To date, no pathologic complete responses have been observed in patients at surgery. Also disappointing on this study was the relatively low rate of curative resection (60%), not significantly greater than what has been observed at this center with surgery alone. Therapy, given as an outpatient, has been well tolerated with grade 3/4 nonhematologic toxicity uncommon. Grade 3/4 neutropenia, as expected, has been observed in 44% of patients. Trial accrual for patients with adenocarcinoma has been completed. The induction chemotherapy yielded a high response rate and excellent tolerance but because of the failure to improve the curative resection rate or induce significant rate of complete responses, this regimen was then followed by concurrent chemoradiotherapy with paclitaxel/cisplatin. Because of the unclear advantage and greater hematologic toxicity using a 24-hour compared to a 3-hour infusion schedule of paclitaxel, a 3-hour infusion of paclitaxel with cisplatin was combined during the induction chemotherapy treatment.

### 1.3.5 Paclitaxel as a Radiation Sensitizer

A number of *in vitro* studies have demonstrated that paclitaxel is a radiation sensitizing anti-neoplastic agent. Using hamster cell cultures, Sinclair and Morton demonstrated that the most sensitive cells were those in M and that cells in G1 and late S were most resistant to ionizing radiation.<sup>7</sup> Other studies have clearly demonstrated that the most sensitive period for radiation is at the G2-M interface.<sup>8,14</sup> Studies with paclitaxel have clearly demonstrated that even at low concentrations and after only a few hours, cells are blocked at the G2-M interface. Recently, Liebmman et al.<sup>15</sup> demonstrated the radiation sensitizing effects of paclitaxel in breast cancer and lung cancer adenocarcinomas. Cells were exposed to paclitaxel from 6-72 hours. Even at concentrations as low as 100 nM, >90% of cells were blocked at G2-M; the overwhelming majority of these cells remained at G2-M for at least 72 hours after paclitaxel exposure. Importantly, in one experiment, cells exposed to drug for 48 or 72 hours demonstrated the highest degree of radiation sensitization, with SERs of 1.9 and 2.0 respectively. A cautionary note was shown when one cell line, an adenocarcinoma lung cancer line, was not sensitized to radiation by paclitaxel, even though a G2-M block was established.

Choy et al.<sup>16</sup> reported the results of a phase I trial of escalating doses of paclitaxel plus a standard radiation therapy treatment schedule for patients with advanced non-small cell lung cancer. The study plan involved treatment with weekly doses of paclitaxel given as a three-hour intravenous infusion for a total of six weeks during radiation therapy. Paclitaxel doses were escalated from 10 to 70 mg/m<sup>2</sup>. Radiation therapy involved a dose of 40 Gy in 20 treatment fractions of 2.0 Gy per fraction to the

prescription point over a period of four weeks. A boost dose of 20 Gy in 10 fractions of 2.0 Gy per fraction was given over the next two weeks. The treatment volume consisted of the primary tumor with a margin of 2 cm around the mass and the ipsilateral hilum. Importantly, in regards to the current proposal, the entire width of the mediastinum was included with a margin of 2 cm around radiographically visible areas of involvement as seen on the pretreatment chest x-ray and CT scan. The inferior border was 4 cm below the carina or 2 cm below the radiographically demonstrated tumor mass. Thus, much of the esophagus was treated. 27 patients were treated. Dose-limiting toxicity was achieved at 70 mg/m<sup>2</sup>. The dose-limiting toxicity was esophagitis. The maximum tolerated dose of paclitaxel was determined to be 60 mg/m<sup>2</sup>. Grade 4 esophagitis was seen in two of three patients at 70 mg/m<sup>2</sup> while the third patient developed grade 2 esophagitis. At 60 mg/m<sup>2</sup> four of eight patients had either grade 3 (*one patient*) or grade 2 (*three patients*) esophagitis.

Preliminary reports of the use of paclitaxel alone or in combination with cisplatin in esophageal cancer have indicated that this approach is feasible and apparently has less toxicity than that observed in earlier trials combining radiotherapy with conventional 5-FU and cisplatin. Urba and colleagues<sup>17</sup> treated 43 patients with preoperative paclitaxel, given weekly at a dose of 50 mg/m<sup>2</sup> over a 3-hour infusion, with cisplatin given on day 1 only at a dose of 75 mg/m<sup>2</sup>. Radiation therapy was given concurrently to a dose of 4500 cGy, delivered in 150 cGy fractions given twice daily over 3 weeks. Therapy was well tolerated with significantly less toxicity than that seen in earlier 5-FU/cisplatin based trials. A pathologic complete response rate of 20% was observed, comparable to earlier chemoradiotherapy trials.

### **1.3.6** *Paclitaxel as a Continuous Intravenous Infusion During Concurrent Radiation*

*In vitro* data noted above indicates that paclitaxel blocks cell growth at G2-M, the phase in the cell cycle at which cells have their greatest sensitivity to the cytotoxic effects of radiation therapy. With brief, intermittent cell exposure to paclitaxel, the G2-M block appears to last between 24 and 72 hours. It is possible that by giving paclitaxel as a continuous intravenous infusion, the arrest of cells in the G2-M phase of cycle may be prolonged further. Preclinical data also suggests that the longer the duration of cell exposure to paclitaxel, the greater the potential cytotoxic effect. Prolonging the duration of paclitaxel infusion may also overcome resistance that may develop to a shorter infusion duration. In breast cancer, paclitaxel given as a 96-hour infusion results in responses in patients who have failed to respond to or who have progressed after responding to prior paclitaxel given over a shorter infusion schedule.<sup>18</sup> Therefore, investigators at MSKCC have investigated 96-hour infusion of paclitaxel plus weekly cisplatin and concurrent radiotherapy.

### **1.3.7** *Results of an Ongoing Phase I Trial of Paclitaxel/Cisplatin and Radiotherapy*

A phase I trial in locally advanced esophageal cancer of weekly cisplatin given together with weekly 96-hour infusion of paclitaxel, using escalating doses of paclitaxel, is ongoing at MSKCC to identify the maximum tolerated dose of paclitaxel that can be administered on this schedule. To date this regimen, given has an outpatient, has been well tolerated and the MTD of paclitaxel is 60mg/m<sup>2</sup>/week. Response assessment is preliminary to date, but all patients treated have had major tumor regression and one pathologic complete response has been observed.

### **1.3.8** *Results of Weekly Paclitaxel Plus Continuous Infusion 5-Fluorouracil with Concurrent Radiotherapy in Patients with Upper Gastrointestinal Carcinomas*

Concurrent radiotherapy and cisplatin-based chemotherapy is effective; however, it also results in increased morbidity and mortality. We chose to exclude cisplatin during chemoradiotherapy of upper gastrointestinal tract carcinoma. We studied the toxicity of continuous infusion 5-fluorouracil and weekly paclitaxel with radiotherapy. Patients had histologic proof of upper gastrointestinal tract carcinoma, local-regional disease, Karnofsky's performance status of  $\geq 70$ , and normal liver, renal, and bone marrow functions. Chemotherapy, given during every week of radiotherapy, consisted of continuous infusion of 5-fluorouracil (300 mg/m<sup>2</sup>/day) for five days per week, plus paclitaxel (45 mg/m<sup>2</sup>) given over three hours one day per week. The dose of radiotherapy varied between 45 Gy and 50.4 Gy. Eighteen men and three women with a median age of 59 years were treated. Nine had esophageal carcinoma, five had esophagogastric junction carcinoma, and seven had gastric carcinoma. Grade 1 and 2 toxicity of weight loss, fatigue, nausea, vomiting, and dysphagia were observed. Two patients had grade 3 fatigue. There was no grade 3 - 4 neutropenia or thrombocytopenia. No patient was hospitalized for the management of treatment-related complications. There were no treatment-related deaths. Among the 11 patients who had surgery, there were 2 pathologic CRs, and 4 pathologic PRs (>90% necrosis). Continuous infusion of 5-fluorouracil plus paclitaxel given concurrently with radiotherapy was well tolerated. This regimen needs to be further investigated.<sup>19</sup>

## **1.4** **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. There is also emphasis on the use of new agents in this disease. The interest in the use of 5-Fluorouracil and cisplatin combination is waning (*this is also demonstrated by the closing of an intergroup trial in March 2000 due to unacceptably low accrual*). We have identified paclitaxel as an active single agent in advanced esophageal cancer, and paclitaxel in combination with cisplatin and/or 5-Fluorouracil leads to a major responses in approximately 45% of patients and up to 20% clinical complete responses in metastatic disease. Preoperative chemotherapy-only trials discussed above demonstrate a significant clinical response rate in the primary cancer. It is hypothesized that induction chemotherapy prior to definitive chemoradiotherapy would: (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 randomize two phase II strategies separately developed at MDACC and MSKCC:

The MDACC strategy emphasizes the use of 5-FU in the induction regimen and uses continuous infusion of 5-FU plus weekly paclitaxel during radiotherapy. One goal is to eliminate the use of cisplatin during radiotherapy as it is thought to be the source of major morbidity and mortality from chemoradiotherapy. The above described data suggest the feasibility of this approach, but it needs to be further studied in a group wide setting.

The MSKCC strategy emphasizes elimination of 5-FU in the induction regimen and also during radiotherapy. Instead, it uses continuous infusion of paclitaxel plus weekly cisplatin during radiotherapy and cisplatin/paclitaxel as induction regimen. The rationale for using a 96-hour infusion schedule of paclitaxel during radiotherapy is twofold: to overcome potential tumor resistance to the short infusion schedule of paclitaxel used during induction chemotherapy, and to enhance the potential for paclitaxel-induced cell cycle arrest in G2M (*when radiotherapy has it's greatest cytotoxicity*) by prolonging the exposure to paclitaxel during radiotherapy.

It is felt that one of these two candidate phase II studies can serve as an experimental arm for a future phase III trial; however, their feasibility in a multi-institutional setting and a comparison of the toxicity as well as efficacy would be required first. Therefore, we propose a randomized phase II study in a group-wide setting to assess toxicity and effectiveness.

## **2.0 OBJECTIVES (6/20/01)**

- 2.1 To evaluate, using a random assignment phase II design, two non-operative therapeutic strategies that investigate induction chemotherapy followed by concurrent paclitaxel-based chemotherapy and concurrent radiotherapy (50.4 Gy) in patients with local-regional esophageal and gastroesophageal junction carcinoma. This trial is designed to determine if either of the two treatment arms under consideration is promising enough to be pursued in a subsequent phase III study against RTOG's database of esophagus patients treated with chemoradiation in previous studies. This decision will be based on the evaluation of the following objectives:
- 2.2 To determine whether there is improvement in one-year survival rate relative to RTOG's database of esophagus patients treated with chemoradiation in previous studies.
- 2.3 To determine whether each of the treatment regimens can be delivered safely and successfully.

## **3.0 PATIENT SELECTION**

### **3.1 Eligibility Criteria (1/15/02)**

- 3.1.1 The patient must have biopsy-proven primary (*non-recurrent*) squamous cell or adenocarcinoma of the esophagus or gastroesophageal junction. Disease must be entirely confined to the esophagus or gastroesophageal junction, and peri-esophageal soft tissue. There must be no tumor extension beyond 2 cm into the stomach.
- 3.1.2 Patients with cervical esophageal carcinoma are eligible.

- 3.1.3 There must be no evidence of disseminated cancer (*Patients must have clinical stage T1N1M0; T2-4, N any, M0. The only exception would be for patients with malignant supraclavicular or celiac nodes who are considered eligible irrespective of the site of esophageal primary [Appendix III], but patients with a TE fistula or direct invasion into the mucosa of the trachea or major bronchi are not eligible.*)
  - 3.1.4 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.
  - 3.1.5 Zubrod Performance Status 0-1 (*Appendix II*)
  - 3.1.6 Patients' total intake (oral/enteral) must be  $\geq 1700$  kCal/day (*see Section 4.1.10*)
  - 3.1.7 Platelet count must be  $\geq 150,000/\text{mm.}$ , Hgb  $\geq 10$  gm%, and ANC  $\geq 1500$ .
  - 3.1.8 Serum creatinine  $\leq 1.5$  mg/dl and/or calculated creatinine clearance  $\geq 65\text{cc/min}$ ; if both are done, both must be within these limits.
  - 3.1.9 Bronchoscopy (*with biopsy and cytology if lesion is seen*) is required, to exclude TE fistula if the primary carcinoma is  $< 26$  cm from the incisors. Bronchoscopy is also required when the cancer is at or above the carina by an imaging study.
  - 3.1.10 Patient must not have had a second malignancy, other than curable non-melanoma skin cancer or cervical cancer *in situ*, unless disease-free for  $\geq 5$  years.
  - 3.1.11 Medical and Radiation Oncologist Evaluations should be performed prior to randomization.
  - 3.1.12 All patients must sign the study-specific informed consent prior to randomization.
- 3.2 Ineligibility Criteria**
- 3.2.1 Prior chest radiotherapy; prior systemic chemotherapy; prior major esophageal surgery;
  - 3.2.2 Patients with multiple primary carcinomas of the esophagus;
  - 3.2.3 Failure to perform the studies specified in Section 4.1 with findings consistent with the criteria noted;
  - 3.2.4 Due to the embryotoxic effects of chemotherapy, pregnant or lactating women or men unable or unwilling to practice contraception are excluded.
  - 3.2.5 Patients with an uncontrolled diabetes, heart disease, or hypertension;
  - 3.2.6 Patients who are unable to comprehend the study requirements or who are not likely to comply with the study parameters.

#### **4.0 PRETREATMENT EVALUATION**

##### **4.1 Required Evaluations (8/6/02)**

- 4.1.1 Complete history and exam including weight with an assessment of the patient's performance status;
- 4.1.2 All patients must be evaluated by a Medical and Radiation Oncologist prior to study entry.
- 4.1.3 Laboratory Studies (*within 2 weeks prior to randomization*)  
 CBC, diff, platelets, and CEA  
 SMA-12 (*serum creatinine, electrolytes, SGOT, AST, LDH, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, inorganic phosphorous, calcium, BUN, magnesium*).  
 Calculated creatinine clearance (*optional*)  
 A venous access (*a long line, subclavian catheter, or implantable device*) will be established in all patients.
- 4.1.4 Imaging Studies(*within 4 weeks prior to randomization*)  
 CT Scan of the Chest and Abdomen (*MRIs are acceptable*)  
 Upper GI endoscopy (*Endoscopic ultrasonography and double contrast upper GI radiographs are highly recommended but not required.*)  
 Chest X-ray  
 Data on T stage, N stage will be collected. Whenever possible, EUS/FNA of the nodes is highly desirable to improve accuracy.
- 4.1.5 Bronchoscopy is required if the lesion is  $< 26$  cm from the incisors to exclude TE fistula or invasion.
- 4.1.6 Biopsy of supraclavicular node if clinically or radiographically enlarged;
- 4.1.7 Lymph node biopsy is not mandatory unless the suspect node(s) are outside the radiation field. Nodes  $< 1$  cm need not be biopsied. For nodes 1-2 cm, a biopsy should definitely be considered.
- 4.1.8 EKG; bone scan (*if alkaline phosphatase is elevated  $\geq 1.5$  x normal*);
- 4.1.9 Nutritional Assessment  
 Patients should ingest either more than 1.5 x their Basal Energy Expenditure (*BEE*) as measured by the Harris-Benedict equation or more than 1,000 calories per square meter of body surface area (*1700 calories for the average 1.7 meter individual*). If the patient is not able to ingest this amount by mouth, a gastrostomy or jejunostomy tube to accomplish this is required. Intravenous hyperalimentation is discouraged. The nutritional supplements should amount to a minimum 1.75 x the BEE or 1200 calories

per square of body surface area but no more than 2.25 x the BEE or 1600 calories per meter square of body surface area unless the patient can be shown to be hypometabolic.

Patients should be instructed about food intake during treatment. Instructions should include recommending the avoidance of irritants (*including alcohol, citrus/acidic foods, sharp foods, or foods with extreme temperatures*). Documentation of any nutritional intervention, including oral high-protein nutritional supplements, feeding tubes, and parenteral or enteral nutrition is required.

#### 4.1.10 Harris-Benedict Equation to Measure BEE

##### Men

$$66.4730 + (13.7516 \times wt \text{ in kg}) + (5.0033 \times ht \text{ in cm}) - (6.75 \times age)$$

##### Women

$$655.0955 + (9.5634 \times wt \text{ in kg}) + (1.8496 \times ht \text{ in cm}) - (4.6756 \times age)$$

Daily Caloric Requirement = BEE x 1.75

Daily Protein Requirement = Caloric Requirement x 6.25

150

#### 4.2 Optional Evaluations

4.2.1 Bilateral audiogram (*encouraged in patients with clinical hearing loss*)

### 5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

### 6.0 RADIATION THERAPY

**Participating institutions must utilize 3-D CT planning and must be able to comply with the criteria described below.**

#### 6.1 Dose Specifications

6.1.1 The prescription dose will be specified at the ICRU-50 reference point, which is defined in Section 6.4.1.3. Note: this point will usually be the isocenter (*intersection of the beams*). The isodose curve representing 93% of the prescription dose must encompass the entire planning target volume (PTV), which is defined in Section 6.4.1.2.

6.1.2 The daily prescription dose will be 1.94 Gy at the ICRU reference point. 1.8 Gy (*which corresponds to the 93% isodose curve*) is to be delivered to the periphery of the PTV.

6.1.3 The reported doses shall include the dose to the ICRU reference point. The maximum point dose, minimum point dose, and mean dose to PTV will also be reported.

6.1.4 The total dose for both arms will be 50.4 Gy (*1.8 G/Fx/day*) prescribed to the periphery (*93% isodose curve*) of the PTV.

#### 6.2 External Beam Equipment

6.2.1 Megavoltage equipment is required with effective photon energies  $\geq 6$  MV.

#### 6.3 Treatment Planning Imaging and Localization Requirements

6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV) and planning target volume (PTV). For this study, the local regional nodes (*whether clinically positive or negative*) will be included in the clinical target volume (CTV) (*Appendix VI*). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, 3-5 mm thickness of the regions, harboring gross tumor and grossly enlarged nodes and 8-10 mm thickness of the remaining regions, are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include both lungs, skin, heart, spinal cord, esophagus, and liver. A measurement scale for the CT image shall be included.

6.3.2 For cervical primaries (defined as tumors above the carina), the bilateral supraclavicular nodes need to be included. The preferable method is a 3 field technique (2 anterior obliques and a posterior field). In most cases, this is not possible; therefore, it is acceptable to initially treat AP/PA to approximately 39.6 Gy then switch to obliques to exclude the spinal cord. The supraclavicular field, which is excluded from

the obliques, can be supplemented with electrons to bring the total dose up to 50.4 Gy (calculated 3 cm below the skin surface). For mid-esophageal primaries (at or below the carina), the paresophageal nodes need to be included—not the supraclavicular or celiac. For distal/gastroesophageal primaries, the field should include the celiac nodes.

**6.3.3** Barium swallow during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the outline of the esophagus.

**6.3.4** Optimal immobilization is critical for this protocol. Alpha cradle or approved alternative immobilization system is required; one of the radiation oncology protocol chairs must approve alternative immobilization system (*Dr. Komaki: 713-794-5573; Dr. Minsky: 212-639-6817*). Patients may be placed on the supine or prone position. In general, supine is recommended for proximal and distal primaries whereas prone is recommended for mid-esophageal

**6.4 Volume and ICRU Reference Point Definitions**

**6.4.1** The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.<sup>20</sup>

**6.4.1.1** Gross Tumor Volume (GTV) is defined as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor (*GTV-P*) only. Note: ICRU Report #50 also defines a clinical target volume (*CTV*) that includes the area of subclinical involvement around the GTV. For this protocol, we have chosen to define the CTV a minimum of 4 cm proximal and distal and 1 cm lateral beyond the GTV delineated by CT scan and/or endoscopy (*endoscopy is preferable*). The final CTV may be larger since for cervical primaries, the supraclavicular nodes need to be included, and for distal primaries, the celiac nodes need to be included in the treatment fields.

**6.4.1.2** Planning Target Volume (PTV) will provide margin around the CTV to compensate for variability in treatment setup, breathing, or motion during treatment. A margin around the CTV will define the PTV. The PTV volume must include a minimum of 1 cm and a maximum of 2 cm around the CTV. **Therefore, the superior and inferior margins will be approximately 5 cm beyond the GTV, and the lateral margins will be approximately 2 cm beyond the GTV. Once again, the final PTV may be larger since for cervical primaries, the supraclavicular nodes need to be included, and for distal primaries, the celiac nodes need to be included in the treatment fields.**

**6.4.1.3** The ICRU Reference Point is to be located in the central part of PTV. Typically this point should be located on the beam axis or at the intersection of the beam axis (*isocenter*).

**6.5 3D Planning**

**6.5.1** Normal Tissue Volume and Tolerances

The normal tissues in the table below are to be contoured in their entirety.

**6.5.2** The following organs and doses by volume are guidelines for the 3D treatment plan. Physician/Dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 1.8 Gy/Fx (*uncorrected*).

**Table 1:**

Incidence of Pneumonitis (%)					
Quartile	GTV (cc)	Mean Dose (Gy)	% of Ipsilateral Lung Receiving > 20 Gy	% of Total Lung Receiving > 20 Gy	V <sub>eff</sub>
≥ Grade 2					
1 <sup>st</sup>	32	20	7	8	0
2 <sup>nd</sup>	12	21	10	23	23
3 <sup>rd</sup>	27	25	38	29	25
4 <sup>th</sup>	27	29	42	33	45
≥ Grade 3					
1 <sup>st</sup>	11	10	7	8	0
2 <sup>nd</sup>	6	11	0	0	5
3 <sup>rd</sup>	3	8	21	19	14
4 <sup>th</sup>	20	24	25	27	26

**Table 2:**

<b>Tolerance Dose</b>			
<b>Organ</b>	<b>Volume</b>	<b>TD 5/5</b>	<b>End Point</b>
Lung ( <i>See Table 1</i> )	( <i>Table 1</i> )	( <i>Table 1</i> )	Clinical Pneumonitis
Spinal Cord	5 cm	50 Gy	Myelitis
	10 cm	50 Gy	Myelitis
	20 cm	47 Gy	Myelitis
Heart	1/3	50 Gy	Clinical Pericarditis
	2/3	45 Gy	Clinical Pericarditis
	3/3	40 Gy	Clinical Pericarditis
Liver	1/2	35 Gy	Clinical Hepatitis
	2/2	30 Gy	Clinical Hepatitis

**6.5.3** It is expected that the dose to the lungs, heart, spinal cord, and liver will be the primary dose-limiting structures. Every effort should be made to keep the total lung dose to a minimum.

**6.5.4** When planning the beam arrangement to the PTV, the lungs, heart, spinal cord, and liver should be out of the field to the greatest extent possible. The dose per fraction to the lungs, heart, and spinal cord should be maintained at 2 Gy or less per fraction to the greatest extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangements should be used.

**6.6 Treatment Verification**

**6.6.1** First day port films or portal images of each field must be obtained and sent to the Quality Assurance Center. Twice weekly (*at least 48 hours apart*) verification films or images of orthogonal views (*anterior to posterior and lateral projection*) must be reviewed by the treating physician. The required accuracy of patient positioning and the use of multi-leaf collimator apertures suggests the daily use of on-line imaging may be desirable.

**6.7 Quality Assurance of Field Placement/Dose Distribution (8/6/02)**

**6.7.1** Patients will undergo 3-D CT planning shortly after registration to the study (before or during their first cycle of induction chemotherapy).

**6.7.2** The planning data, including planning CT scan, simulation films, isodose distributions (axial, coronal, and sagittal planes through the PTV) will be sent to RTOG Headquarters within 4 weeks after registration, for rapid review by the study chair or his designee (See Section 12).

**6.7.3** Dose Heterogeneity

Maximum dose to PTV should not exceed the prescription dose by >7%. The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

**6.8 RTOG 3D-CRT Summary of 1993 ICRU Reports on Recommendations for Prescribing, Recording, and Reporting External Beam Radiation Therapy<sup>20</sup> (Appendix VI)**

**6.8.1** Complete descriptions of volumes to be treated have been included in the 3D-CRT protocols in order to minimize the institutional variation of tumor and target volume delineation for protocol cases. Please consult the ICRU 1993 document for complete descriptions of the various target volumes defined.

**6.8.2** The gross tumor volume (GTV) includes the known disease as determined by physical examination, imaging studies and other diagnostic information.

**6.8.3** The clinical target volume (CTV) includes the area of subclinical involvement around the GTV. The CTV is the GTV plus the margin for clinical negative or positive local regional nodes.

**6.8.4** The planning clinic volume (PTV) is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the GTV. This margin accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues that contain the GTV (e.g., respiration), and size variations in the tissue containing the GTV. The PTV is a geometric concept.

**6.9 Therapy Interruptions**

**6.9.1** If interruption of therapy (*up to two weeks*) becomes necessary, radiation therapy should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported. If an interruption of more than two weeks is necessary, resumption of treatment is at the discretion of the radiation oncology chairs. The patient will be considered a major deviation, but follow-up will be continued.

**6.9.2** If the patient develops  $\geq$  grade 3 RT-related toxicity, radiation therapy and chemotherapy should be withheld. Treatment can resume once grade 3 RT-related toxicity is no longer present. If a patient develops grade 3 esophagitis in the last week of treatment (*i.e. with 5 or fewer radiation treatments remaining*), radiation therapy (*but not chemotherapy*) may continue at the discretion of the treating physician.

**6.10 Criteria for Toxicity**

- 6.10.1** Acute and late toxicity related to radiation therapy include fatigue, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, carditis, myelitis, acute radiation pneumonitis and late pulmonary fibrosis, and esophageal stricture.
- 6.10.2** Acute toxicity monitoring: Acute ( $\leq 90$  days from RT start) side effects of radiation therapy will be documented using the revised NCI Common Toxicity Criteria, Version 2.0, which can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>).
- 6.10.3** Late toxicity monitoring: Late ( $> 90$  days since RT start or persisting beyond 90 days) post-treatment complications will be evaluated and graded according to the RTOG Late Effects Radiation Morbidity Criteria in Appendix IV.
- 6.10.4** All fatal toxicities (*grade 5*) resulting from this protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management, and to the Study Chairman within 24 hours of discovery.
- 6.10.5** All life-threatening (*grade 4*) toxicities from protocol treatment must be reported by telephone to Group Chairman, ACR Headquarters Data Management Staff, and to the Study Chairman within 24 hours of discovery.
- 6.10.6** Appropriate data forms, and, if requested, a written report, must be submitted to Headquarters within 10 working days of the telephone report.

**7.0 CHEMOTHERAPY AND CHEMORADIOTHERAPY**

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

Treatment should begin within 5 business days of registration. (6/20/01)

**7.1 Arm 1 (5-FU-based)**

**7.1.1 Induction Chemotherapy**

Patients will receive up to two cycles of chemotherapy prior to chemoradiotherapy depending on response to the first cycle of induction chemotherapy.

**7.1.1.1 Schedule: Arm I Induction Chemotherapy (1/15/02)**

Outpatient administration of chemotherapy is encouraged. Patients will need a double lumen central line placed for chemotherapy administration. Chemotherapy schedule will be as follows:

DRUGS	Daily DOSE	Schedule	On days
5-FU	700 mg/m <sup>2</sup> /d	24-hour continuous infusion by a portable pump	1-5
Cisplatin	15 mg/m <sup>2</sup> /d	i.v. in 1-hour	1-5
Taxol	200 mg/m <sup>2</sup> /d	24 hour infusion	1
G-CSF*	300 mcg for patients $\leq$ 70 kg or 480 mcg for patients $>$ 70 kg	subcutaneously	6-15 and 34-42

\* Neulasta™ (*pegfilgrastim*) may be substituted for G-CSF; 6 mg administered once per chemotherapy cycle, on day 6. Neulasta™ should not be administered in the period between 14 days prior and 24 hours after administration of cytotoxic chemotherapy. (8/6/02)

Subsequent dose may be decreased by 20% based on toxicity experienced during the preceding course; however, the doses of chemotherapy drugs will not be increased.

Adequate hydration, electrolyte supplementation, and anti-emetic 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.

Premedications for Taxol will include Decadron 20 mg, cimetidine 300mg, and Benadryl 25 mg; all administered intravenously 30 minutes prior to Taxol. (6/20/01)

G-CSF (either 300µg for patients ≤ 70 kg or 480µg for patients >70kg) will be given subcutaneously from days 6-15 and 34-42. Neulasta™ (pegfilgrastim) may be substituted for G-CSF. The recommended dosage of Neulasta™ is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle, on day 6. Neulasta™ should not be administered in the period between 14 days prior and 24 hours after administration of cytotoxic chemotherapy. (8/6/02)

The second course 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 ≥ 1,500/µL and platelet count ≥ 100,000/µL) are adequate.

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

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

#### 7.1.1.2 Dose Modification for the Second Cycle of Chemotherapy

Reduction of chemotherapy dose will be based on the degree of hematologic and nonhematologic toxicities. The goal is not to induce grade 3 nonhematologic toxicity or grade 4 hematologic toxicity. If the granulocyte level drops below 1000, counts should be performed every other day until the level rises above 1000.

Dose modification for Taxol and cisplatin will be based on hematologic toxicities

Granulocyte Nadir		Platelet Nadir	Dose Modification
>1,000	AND	>75,000	No Change
≥ 500 but <1,000	AND/OR	≥50,000 but <75,000	No Change
<500 for more than ≥5 days	AND/OR	<50,000	decrease 20% (applies to both drugs)
Infection or bleeding related to myelosuppression			decrease 20% (applies to both drugs)

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

Toxicity Grade	Dose Modification
0-2	No Change
3* or 4	Decrease 20%

\* Does not apply to alopecia or grade 3 nausea and vomiting

#### 7.1.1.3 Dose modification for cisplatin based upon renal insufficiency will be as follows:

Serum Creatinine*(mg/dL)	Daily Dose
≤ 1.4	No change
> 1.4 but < 2.0	Decrease 50%
≥ 2.0	Discontinue

\*In a well-hydrated state (2 readings necessary when abnormal)

**7.1.1.4** Anaphylaxis (Cisplatin)

Severe allergic reactions to cisplatin are not uncommon. Patients who exhibit anaphylactic-type allergic reactions should not receive further cisplatin.

**7.1.1.5** Nonhematologic Toxicity

The following toxicities are anticipated: nausea, vomiting, diarrhea, mucositis, phlebitis, fatigue, anorexia, myelosuppression, thrombocytopenia, renal dysfunction, ototoxicity, peripheral neuropathy, and dry skin.

This study will utilize the CTC version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>).

**Paclitaxel will not be modified for nonhematologic toxicity.**

The dose levels of cisplatin are outlined in the following table:

Dose levels, cisplatin	mg/m <sup>2</sup>
Starting	15
20% decrease	12

Dose Modification of Cisplatin

Dose reductions for neurotoxicity, mucositis, fatigue (*grade 4 only*), oto-, and renal toxicity are outlined in the following table:

Neurotoxicity/ Fatigue*/ Mucositis	Ototox.	Creatinine Clearance		Creatinine	Dose Level, Cisplatin
		≥ 60 ml/min	Or	≤ 1.5	Starting dose- 15 mg/m <sup>2</sup>
		50 ≤ clearance < 60	Or	1.5 < creatinine < 2	Decrease 20% to 12 mg/m <sup>2</sup>
		< 50 ml/min	Or	≥ 2	Hold cisplatin
Initial Grade 3-4					Decrease 20% to 12 mg/m <sup>2</sup>
	Severe	Any		Any	Hold cisplatin

\*Modification for grade 4 fatigue only and of ≥ 5 days duration.

Dose reductions for cisplatin will be made on the basis of the serum creatinine on the day of treatment, or on the development of grade 3-4 neurologic or ototoxicity, fatigue (*grade 4 only and of ≥ 5 days duration*), mucositis, diarrhea (*grade 4 only*), or nausea/vomiting/dehydration (*grade 4 only*). A creatinine clearance (*optional*) may be obtained to evaluate a rise in serum creatinine and may also be used to adjust the cisplatin dose. However, a creatinine clearance is not mandatory. If the serum creatinine on the day of treatment is > 1.5 mg/dl but < 2.0 mg/dl, and the serum creatinine is used to adjust the dose, the patient should be euvolemic and the value must be confirmed by a second serum creatinine. Modification for grade 4 diarrhea or grade 4 nausea/vomiting/dehydration (*hospitalization required*) will be made for cisplatin only; no modification of paclitaxel will be made for these toxicities.

**With the 1<sup>st</sup> cycle of chemotherapy, reduction of cisplatin will not be based on nausea, vomiting, diarrhea, or dehydration but on stated level of neurotoxicity or mucositis (*grade 3-4*) or fatigue (*grade 4 only*).**

**With the 2<sup>nd</sup> cycle of chemotherapy, dose modifications will be based on other grade 3-4 toxicities, including nausea, vomiting, dehydration, or diarrhea.**

Toxicity Grade (Nausea/Vomiting/Diarrhea/Dehydration)	Cisplatin Dose Modification
0-3	No Change
Initial Grade 4 (Hospitalization)	Decrease 20%

If more than one grade 3-4 nonhematologic toxicity attributable to cisplatin occurs during the 1<sup>st</sup> cycle, then a single dose modification of cisplatin for the greatest toxicity observed will be made for the 2<sup>nd</sup> cycle.

**7.1.2** Arm 1: Radiation Plus Concurrent Chemotherapy

Chemoradiotherapy should begin on day 29 of the last cycle of chemotherapy provided the patient has recovered from all toxicities (*grade < 1*) except alopecia and peripheral counts (*absolute granulocyte count > 1,500/μL and platelet count > 100,000/μL*) are adequate.

**7.1.2.1** Chemotherapy During Radiotherapy

Will consist of 5-FU at 300 mg/m<sup>2</sup>/d as continuous 96-hour infusion by a portable pump during radiotherapy (*typically, 5-FU infusion can be initiated Monday morning and would be terminated Friday after radiotherapy. Once discontinued on Friday, patients would not receive 5-FU until the following Monday.*)

**Taxol:** will be given on days 1, 8, 15, 22, and 29 of radiotherapy at a dose of 50 mg/m<sup>2</sup> i.v. over 3 hours. It is preferred that radiotherapy be initiated on a Monday or Tuesday. During chemoradiotherapy, patients will receive Taxol as premedication with i.v. steroids, H-2 blockers, and diphenhydroxy HCl (*as described above with the induction chemotherapy*).

**7.1.2.2** Dose Modification During Chemoradiotherapy

Potential toxicities of chemoradiotherapy include nausea, loss of appetite, vomiting, malaise, mucositis, hand-foot syndrome, and rarely myelosuppression and neuropathy. Major toxicities include mucositis, hand-foot syndrome, and rarely diarrhea. Patients will be observed weekly.

5-FU doses will be modified as follows based on the level of toxic effects observed during chemoradiotherapy:

Toxicity Grade	Dose Modification
0-2	No change
3 or 4*	Hold 5-FU for 5 days ( <i>one treatment week</i> ) and resume ( <i>at 250 mg/m<sup>2</sup>/d dose 5x/week for the remaining duration of therapy</i> ) provided the toxicity has substantially resolved ( <i>grade ≤1</i> ). If grade 3 or 4 toxicity recurs, call the study chair.

\*Does not apply to alopecia or grade 3 nausea and vomiting

Taxol doses during radiotherapy will be modified based on myelosuppression.

Granulocyte Nadir		Platelet Nadir	Dose Modification
>1,000	AND	>75,000	No Change
≥ 500 but <1,000	AND/OR	≥50,000 but <75,000	No Change.
<500	AND/OR	<50,000	Skip dose until AGN >1,000 and/or plt >100K then resume with 20% dose reduction.
Infection or bleeding related to myelosuppression			Skip dose until AGN >1,000 and/or plt >100K then resume with 20% dose reduction.

**7.2** Arm 2 (non-5-FU-based)

All patients will receive induction chemotherapy (*up to 2 cycles, depending on response to the first cycle of chemotherapy*) prior to chemoradiotherapy.

**7.2.1** Induction Chemotherapy (4/1/02)

Treatment will be delivered every 21 days for 2 induction cycles. Outpatient chemotherapy is encouraged. Patients will need a single lumen central line placed for chemotherapy administration. Paclitaxel will given on day 1 at a dose of **175 mg/m<sup>2</sup>** by 3-hour infusion, followed by **cisplatin** on day 1

at a dose of **75 mg/m<sup>2</sup>**. Subsequent dose may be decreased by 20% based on toxicity experienced during preceding cycle; however, the doses of chemotherapy drugs will not be increased. Routine G-CSF administration is not planned.

**7.2.1.1** Paclitaxel

Premedication for 3-hour infusion of paclitaxel: To minimize the risk of anaphylactoid reactions, all patients will be premedicated with Dexamethasone 20 mg ivpb, Cimetidine 300 mg ivpb, and Diphenhydramine hydrochloride 50 mg ivpb thirty minutes prior to paclitaxel administration.

**Paclitaxel** at a starting dose of **175 mg/m<sup>2</sup> for induction chemotherapy**, will be administered over 3 hours beginning on day 1.

**7.2.1.2** Cisplatin

Cisplatin will be administered on day 1 by intravenous bolus injection at a dose of 75 mg/m<sup>2</sup> for the two induction cycles.

Adequate hydration, electrolyte supplementation, and anti-emetic support will be provided when administering cisplatin. Patients will receive at least 1.5 liter of 1/2 NS with magnesium and potassium supplements intravenously prior to cisplatin and 1.0 liter of the same after cisplatin. All patients will be encouraged to drink at least 2L of fluid daily.

All patients will receive Zofran 10 mg plus Ativan 1 mg (*plus Decadron as specified in premedication for paclitaxel*). Patients will also receive anti-emetic support to reduce delayed nausea and vomiting.

The following schema will be followed in all patients for making treatment decisions after the administration of the 1<sup>st</sup> cycle of induction chemotherapy:

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

**7.2.1.3** Treatment Delay

Up to 2-week delay of treatment will be permitted if, on the day of treatment, the patient has failed to achieve an **adequate hematologic recovery** (***absolute granulocyte count > 1500/mm<sup>3</sup>, platelets > 100,000***) or has not recovered from nonhematologic toxicity to a least < Grade 2 (*mucositis and diarrhea must be < grade 1*). **If the full 2-week period is required for hematologic (*neutrophil*) recovery, then G-CSF will be added to treatment.** If recovery from toxicity has still not occurred by the allowable 2-week delay, the patient will not receive the second cycle of chemotherapy but will instead proceed to receive chemoradiotherapy as described in Section 7.2.2.

If a treatment delay is required, all drugs will be held until recovery has occurred.

**7.2.1.4** Cycle Length

All courses will be repeated every 21 days or as soon as hematologic and non-hematologic recovery have occurred after 21 days. **Patients must have an absolute granulocyte count > 1.5 and platelet count >100,000/mm<sup>3</sup> before starting second course.**

**7.2.1.5** Duration of Therapy

**Prior to radiotherapy patients will receive 2 induction cycles, depending on response to the first cycle of chemotherapy.**

**7.2.1.6**      Use of G-CSF  
Hematologic Toxicity:

Granulocyte Nadir		Platelet Nadir	Dose Modification of paclitaxel
>500 but <1,000	AND/ OR	Between >50,000 and < 75,000	No Change
<500 for ≤4 days	AND	>50,000	No Change
<500 for ≥5 days ( <i>First episode</i> )	AND	Any	Add G-CSF* to subsequent cycles
Failure to Recover Neutrophil Counts by day 28 ( <i>First Episode</i> )			Add G-CSF* to subsequent cycles
Nadir fever as a consequence of myelosuppression ( <i>First Episode</i> )			Add G-CSF* to subsequent cycles
Bleeding as a consequence of thrombocytopenia			Decrease paclitaxel to 150 mg/m <sup>2</sup>

\*See Section 7.1.1.1 for G-CSF dose/schedule

**7.2.1.7**      Nonhematologic Toxicity

The following toxicities are anticipated: nausea, vomiting, diarrhea, mucositis, phlebitis, fatigue, anorexia, myelosuppression, thrombocytopenia, renal dysfunction, ototoxicity, peripheral neuropathy, and dry skin. This study will utilize the CTC version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>).

**Paclitaxel will not be modified for nonhematologic toxicity.**

The dose levels of cisplatin are outlined in the following table:

Dose levels, cisplatin	mg/m <sup>2</sup>
Starting	75
20% decrease	60

Dose Modification of Cisplatin

Dose Reductions for neurotoxicity, mucositis, fatigue (*grade 4 only*), oto-, and renal toxicity are outlined in the following table:

Neurotoxicity/ Fatigue*/ Mucositis	Ototox.	Creatinine Clearance		Creatinine	Dose Level, Cisplatin
		≥ 60 ml/min	<b>Or</b>	≤ 1.5	Starting dose- 75 mg/m <sup>2</sup>
		50 ≤ clearance < 60	<b>Or</b>	1.5 < creatinine < 2	Decrease 20% to 60 mg/m <sup>2</sup>
		< 50 ml/min	<b>Or</b>	≥ 2	Hold cisplatin
Initial Grade 3-4					Decrease 20% to 60 mg/m <sup>2</sup>
	severe	Any		Any	Hold cisplatin

\*Modification for grade 4 fatigue only and of ≥ 5 days duration.

Dose reductions for cisplatin will be made on the basis of the serum creatinine on the day of treatment, or on the development of grade 3-4 neurologic or ototoxicity, fatigue (*grade 4 only and of  $\geq 5$  days duration*), mucositis, diarrhea (*grade 4 only*), or nausea/vomiting/dehydration (*grade 4 only*). A creatinine clearance (*optional*) may be obtained to evaluate a rise in serum creatinine and may also be used to adjust the cisplatin dose. However, a creatinine clearance is not mandatory. If the serum creatinine on the day of treatment is  $> 1.5$  mg/dl but  $< 2.0$  mg/dl, and the serum creatinine is used to adjust the dose, the patient should be euvolemic and the value must be confirmed by a second serum creatinine. Modification for grade 4 diarrhea or grade 4 nausea/vomiting/dehydration (*hospitalization required*) will be made for cisplatin only; no modification of paclitaxel will be made for these toxicities.

**With the 1<sup>st</sup> cycle of chemotherapy, reduction of cisplatin will not be based on nausea, vomiting, diarrhea, or dehydration but on stated level of neurotoxicity or mucositis (*grade 3-4*) or fatigue (*grade 4 only*).**

**With the 2<sup>nd</sup> cycle of chemotherapy, dose modifications will be based on other grade 3-4 toxicities, including nausea, vomiting, dehydration, or diarrhea.**

Toxicity Grade ( <i>Nausea/Vomiting/Diarrhea/Dehydration</i> )	Cisplatin Dose Modification
0-3	No Change
Initial Grade 4 ( <i>Hospitalization</i> )	Decrease 20%

If more than one grade 3-4 nonhematologic toxicity attributable to cisplatin occurs during the 1<sup>st</sup> cycle, then a single dose modification of cisplatin for the greatest toxicity observed will be made for the 2<sup>nd</sup> cycle.

**7.2.2** Arm 2: Radiation Plus Concurrent Chemotherapy

**7.2.2.1** Chemotherapy During Radiotherapy (1/15/02)

Will consist of paclitaxel/cisplatin weekly x 6 weeks with concurrent radiotherapy; Chemoradiotherapy should begin on day 29 of the last cycle of chemotherapy provided the patient has recovered from all toxicities (*See Section 7.1.2*).

**7.2.2.2** Cisplatin

Cisplatin will be given at a fixed dose of 30 mg/m<sup>2</sup> with pre-hydration and antiemetic prophylaxis. Cisplatin will be given once weekly through radiation. **Cisplatin will be given on days 1, 8, 15, 22, 29, and 36; if a treatment break prolongs the duration of radiotherapy beyond 6 weeks, a maximum of 6 weeks of chemotherapy will be given.** Outpatient therapy is encouraged. 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.

**7.2.2.3** Paclitaxel

Paclitaxel will be given as a continuous 96 hour infusion via a central venous device (*longline, subclavian catheter or implanted device*). **The dose of paclitaxel will be 60 mg/m<sup>2</sup> per week. No premedication will be necessary for paclitaxel administered over 96 hours.** Paclitaxel should be started before cisplatin is administered. The paclitaxel infusion will be maintained by an ambulatory pump. The infusion will be continued throughout the radiation period, on Days 1-4 of each week, i.e. Monday-Friday. If a treatment break is required, chemotherapy will be discontinued and neither paclitaxel nor cisplatin will be given. **Paclitaxel will be start on days 1, 8, 15, 22, 29, and 36; if a treatment break prolongs the duration of radiotherapy beyond 6 weeks, a maximum of 6 weeks of chemotherapy will be given.** Therapy can be given in the outpatient department.

**7.2.2.4** Dose Modification

The dose of chemotherapy will be modified as follows: Cisplatin or Paclitaxel doses will be modified on the basis of the most severe toxicity seen during chemoradiotherapy according to the criteria for dose adjustment presented below. **Patients receiving concomitant chemotherapy/radiation therapy who have the chemotherapy treatment held because of toxicity will not receive radiation therapy at that time.** Patients will be re-evaluated in one week for possible re-treatment, and the doses will be modified according to the criteria for dose adjustment presented below. **If the**

treatment break is greater than two weeks because of severe toxicity, the patient may be taken off the trial at the discretion of the primary physician.

**7.2.2.4.1** Dose Modification for Cisplatin (NCI Common Toxicity Scale) (8/4/04)

Patients should be euvolemic for the determination of serum creatinine. If the value of serum creatinine is higher than 1.6 mg%, the value should be confirmed by a second serum creatinine after hydration. Creatinine clearance will not be used.

Neurotoxicity/ Fatigue/ Mucositis	Ototox.	Creatinine Clearance		Creatinine	Dose Level, Cisplatin
		≥ 60 ml/min	<b>Or</b>	≤ 1.5	30 mg/m <sup>2</sup>
		50 ≤ clearance < 60	<b>Or</b>	1.5 < creatinine < 2	20 mg/m <sup>2</sup>
		< 50 ml/min	<b>Or</b>	≥ 2	Hold cisplatin
Grade 3					20 mg/m <sup>2</sup>
Grade 4	severe	Any		any	Hold cisplatin

**(7/31/03)**

Toxicity	Dose Level, Cisplatin
ANC ≥ 1.5	30 mg/m <sup>2</sup>
< 1.5 but ≥ 1.0	25 mg/m <sup>2</sup>
< 1.0	20 mg/m <sup>2</sup>
Platelets ≥ 75,000	30 mg/m <sup>2</sup>
≥ 25,000 but < 75,000	20 mg/m <sup>2</sup>
< 25,000	Hold

**7.2.2.4.2** Dose Modification for Paclitaxel (NCI Common Toxicity Scale)

Toxicity	Dose Level, Paclitaxel
ANC ≥ 1.5	60 mg/m <sup>2</sup> over 96 hours
< 1.5 but ≥ 1.0	40 mg/m <sup>2</sup> over 96 hours
< 1.0	Hold
Platelets ≥ 75,000	60 mg/m <sup>2</sup> over 96 hours
≤ 75,000	Hold
Neuropathy Grade 0-2	60 mg/m <sup>2</sup> over 96 hours
Neuropathy Grade 3 or greater	Hold

**7.2.2.4.3** Dose Modification of Paclitaxel for Neutropenic Fever (6/20/01)

Neutropenic fever (*temperature of 38.5° C with ANC < 1000*) is an expected potential complication of concurrent chemotherapy and radiotherapy. Because of the six week length of therapy, **if neutropenic fever is experienced during therapy and occurs prior to completion of 4 weeks of therapy**, that is, **after completion of only 1, 2, or 3 weeks of therapy and with 3 or more weeks of therapy** still remaining, then on subsequent treatment weeks, **paclitaxel will be reduced 20%**. If a neutropenic fever event occurs after completion of at least 4 weeks of therapy, that is, during week 4, 5, or 6 of therapy with 2 or fewer weeks of therapy remaining, then no dose reduction of paclitaxel will be made.

**7.2.2.5** Expected Toxicity

Toxicity will be graded according to the revised NCI Common Toxicity Criteria (CTC) version 2.0 (3/98) and the RTOG Radiation Morbidity Scoring Criteria.

**7.2.2.5.1** Cisplatin and Paclitaxel

The following toxicities are anticipated: nausea, vomiting, diarrhea, mucositis, phlebitis, fatigue, anorexia, alopecia, myelosuppression, renal dysfunction, ototoxicity, peripheral neuropathy.

**7.2.2.5.2** Criteria for Treatment Breaks During Radiation Therapy with Concurrent Chemotherapy  
Treatment breaks will be required for all patients demonstrating >3+ mucositis or esophagitis, or myelosuppression as outlined above (*i.e.* ANC < 1000 or platelets < 75,000). 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 be taken off study at the discretion of the treating physician.** The revised NCI Common Toxicity Criteria, version 2.0 will be used to determine toxicity during radiation therapy.

### **7.3** 5-Fluorouracil (5-FU)

#### **7.3.1** Formulation

5-FU is available in 10-ml ampules, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

#### **7.3.2** Pharmacology

5-FU is a marketed drug available in 500 mg vials. It is fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a hydrogen atom has been replaced by a fluorine atom in the 5 position.

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 provides unbalanced growth and death of the cell.

#### **7.3.3** Supplier

5-FU is available commercially.

#### **7.3.4** 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 to cool to body temperature before using.

#### **7.3.5** Side Effects and Toxicities

The spectrum of toxicity includes stomatitis and esophagopharyngitis (*which may lead to sloughing and ulceration*), diarrhea with cramping and/or bleeding, anorexia, nausea and emesis are commonly seen during therapy. 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, uncoordination, visual changes, photosensitivity (*eyes and skin*), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, vein pigmentation, biliary sclerosis, or acaculous cholecystitis.

### **7.4** Cisplatin (CDPP)

#### **7.4.1** 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.

#### **7.4.2** 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, and a secondary phase ranging from 44 to 190 hours. This prolonged phase is due to protein binding which exceeds 90%. Urinary excretion is incomplete with only 27 to 45% excreted in the first five days. The initial fractions are largely unchanged drugs.

#### **7.4.3** Supplier

Cisplatin is available commercially.

#### 7.4.4 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 D<sub>5</sub>NS, NS, or D5-1/2NS (*ppt. occurs in D<sub>5</sub>W*). 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.

#### 7.4.5 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 which 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 erythrosuppression, 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.

### 7.5 **Paclitaxel**

#### 7.5.1 Method of Action

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

#### 7.5.2 Hypersensitivity reactions to vehicle, Cremophor EL

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 **3-hour infusion** schedule of paclitaxel is used. **Premedication is not required**, however, **using a 96-hour infusion** schedule. Routine premedication will not be required on this trial.

#### 7.5.3 Product Description

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

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%.

#### 7.5.4 Supplier

Paclitaxel is commercially available.

#### 7.5.5 Solution Preparation

The appropriate dose of paclitaxel should be withdrawn from the vial and further diluted with either 0.9% sodium chloride or 5% dextrose injection.

#### 7.5.6 Stability and Storage Requirements

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 (*D<sub>5</sub>W*) in a concentration range of 0.3 mg/ml to 1.2 mg/ml. **Because of the 48-hour stability of paclitaxel, treatment cassettes during the 96-hour infusion will be prepared for two 48-hour treatment intervals, i.e. with one treatment cassette change on day 3.** All of these solutions will exhibit a slight haze. A small number of particles have been observed after dilution; therefore, in-line filtration is necessary with all paclitaxel infusions. Analysis of solutions filtered through IVEX-2 (*Abbot*) 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.

### 7.5.7 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, wheals*), 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, typhlitis, alkaline phosphatase, bilirubin, liver dysfunction/failure, SGOT, SGPT, 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.

## 7.6 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 clear, colorless, particulate-free solution and is provided in vials containing 600 mcg of the G-CSF protein in 2 ml of an aqueous buffer (*final concentration = 300 mcg/ml*).

### 7.6.2 Solution Preparation

G-CSF may be withdrawn into a syringe for direct use. G-CSF solution vials and dilutions should not be shaken.

### 7.6.3 Supplier

G-CSF is commercially available.

### 7.6.4 Administration

The appropriate dose is withdrawn into and administered from a plastic syringe. The G-CSF will be injected subcutaneously into rotating sites on the abdomen, arms, and legs. The **G-CSF dose will be 300 mcg/day (weight < 70 kg) and 480 mcg/day (weight ≥70 kg)**. 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. These skills must be competently demonstrated by the patient or caregiver prior to administration at home. 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.

### 7.6.5 Stability and Storage Requirements

The intact vial should be kept refrigerated at 2-8°C. The 300 mcg/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.

### 7.6.6 Toxicities

The predominant toxicity attributable to G-CSF is mild medullary bone pain. Splenomegaly and mild alopecia have 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 Toxicity Reporting

7.7.1 The revised NCI Common Toxicity Criteria (*CTC*) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (*≤ 90 days*) toxicities and can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). This study will be monitored by the Clinical Data Update System (*CDUS*) Version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol, which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

- 7.7.1.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected (*phone report within 24 hours; written report within 10 days*).
- 7.7.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.7.1.3 Any death on study if clearly related to the commercial agent(s).
- 7.7.1.4 Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
- 7.7.2 The ADR report should be documented on Form FDA 3500 and mailed to:

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

**8.0 SURGERY**

Not applicable to this study.

**9.0 OTHER THERAPY**

Not applicable to this study.

**10.0 PATHOLOGY**

**10.1 RTOG Tissue Bank (9/3/04)**

- 10.1.1 Patients entered on this study must submit materials to the RTOG Tissue Bank.
- 10.1.2 The following must be provided:
  - 10.1.2.1 One H&E stained slide.
  - 10.1.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
  - 10.1.2.3 Pathology report documenting that submitted block or slides contain tumor.
  - 10.1.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
- 10.1.3 RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).
- 10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.2 Materials will be sent to:

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

**11.0 PATIENT ASSESSMENTS (6/20/01, 4/1/02, 8/6/02)**

**11.1 Study Parameters**

Parameter	Prior to Randomization ( $\leq 28$ days)	Prior to each chemo cycle	After each cycle chemo	42 days after RX Completion	At Follow-up
History & Physical	X	X		X	X
CBC, diff, platelets	X(f)	X(a)		X	X(e)
CEA	X(f)	X(o)			X(e)
SMA-12 <sup>k</sup>	X(f)	X		X	X(e)
Chest X-ray	X			X	X(e)
Bronchoscopy (i)	X				
Audiography	X(b)	X(b)			
Double Contrast Barium UGI	X(c)		X(m)		X(c)
Abdominal & Chest CT (MRIs are acceptable)	X		X(n)	X	X(e)
EKG	X				
Endoscopy and Ultrasound (ultrasound recommended but optional)	X		X(m)	X	X(l)
Bone Scan	X(d)				
PFTs (Spirometry + DLCO)	X(c)				X(g)
Biopsy	X			As needed	X(j)
Toxicity		X		X(h)	X(e)

- a. must be done weekly during chemotherapy (4/1/02)
- b. if clinically indicated
- c. optional (but highly desirable)
- d. if serum alkaline phosphatase elevated  $\geq 1.5$  times normal
- e. q 4 months for 1 year then q 6 months for 2 years then yearly
- f. within 2 weeks prior to randomization
- g. at 8 months only
- h. weekly during RT
- i. if tumor is < 26 cm from the incisors.
- j. at the time of x-ray evidence of local recurrence
- k. SMA-12 = serum creatinine, electrolytes, SGOT, AST, LDH, Alk phos, total bilirubin, total protein, albumin, uric acid, phos, calcium, BUN, mg
- l. Follow-up endoscopy must be done in symptomatic patients; follow-up EUS is not required.
- m. After 1<sup>st</sup> cycle of chemotherapy, UGI barium or UGI endoscopy must be done to rule out/confirm progression (1/15/02)
- n. CT scan should be done after 2<sup>nd</sup> cycle of induction chemotherapy to ensure there is no progression that would require re-planning radiation therapy.
- o. Every 2 months during treatment (4/1/02)

**11.2 Criteria for Response**

These tumors are not measurable and thus, response is not an endpoint of this study. The rate of negative endoscopy at Day 42 (See Section 11.1) would be the equivalent of a complete response.

**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 such 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 U/S), although highly suspicious of recurrent disease will not result in change in the patient's management. These findings should lead to a search for a mass that could be biopsied.

- 11.3.3** Patients who develop progression of disease at the primary site while receiving RT + chemotherapy 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.
- 11.3.4** Patients who develop local recurrence only 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 Removal From Study Analysis**

Efforts shall be made to account for all patients entered into the study during the evaluation of results. However, in detailed evaluation, the following patient categories will be considered.

- 11.4.1** Early Deaths: Those patients who died within six weeks of beginning therapy as a result of an event not related to esophageal cancer or to the study drugs.
- 11.4.2** Lost to Follow-up: Those patients in whom there is inadequate information to judge tumor response because of loss of contact in which repeated attempts to obtain information are unsuccessful.
- 11.4.3** Major Protocol Violations: Patients who receive further therapy or deviate from the treatment program by either adding a chemotherapeutic agent or by substantially modifying the dosage and schedule of the study drugs (*as defined in Section 7.0*) or radiation (*as defined in Section 6.0*).

**12.0 DATA COLLECTION (8/6/02, 9/3/04)**

*(RTOG, 1818 Market Street, Suite 1600, Philadelphia, PA 19103, FAX #215/928-0153)*

**12.1 Summary of Data Submission** (6/20/01, 3/23/04)

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Pathology Slides (P2)	Within 2 wks of study entry
<u>Preliminary Dosimetry Information:</u> RT Prescription ( <i>Protocol Treatment Form</i> ) (T2) Films ( <i>simulation and portal</i> ) (T3) Calculations (T4) Planning CT and CT Report (C1, C3)	Within 4 wks of study entry
Induction Chemotherapy Form (FO)	Within 2 wks of end of each cycle of induction chemotherapy
<u>Final Dosimetry Information:</u> Daily Treatment Record (T5) Isodose Distribution (T6) Boost Films ( <i>simulation and portal</i> ) (T8)	Within 1 week of end of RT
Treatment Summary Form (TF)	Within 2 wks of end of chemo/RT
Initial Follow-up Form (FS) [acute; < 90 days]	Within 8 wks of completion of chemo/RT
Follow-up Form (F1) [ $\geq$ 90 days post RT]	Every 4 months from end of treatment for 1 year; q 6 months x 2 years, then annually from year 5; Also at progression/relapse and at death
Autopsy Report (D3)	As applicable

### **13.0 STATISTICAL CONSIDERATIONS**

#### **13.1 Study Endpoints (6/20/01)**

- To estimate the one-year overall survival rates for each of the regimens.
- To determine the frequency of protocol treatment prescription successfully delivered with each of the regimens.
- To determine the frequency of major ( $\geq$  grade 4) late toxicities associated with each of the regimens.

#### **13.2 Sample Size**

Thirty-eight analyzable patients will be required on each arm of 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. An experimental arm would 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 ( $\approx$  hazard reduction of 50% with type I error of 0.05 and type II error of 0.20).<sup>23</sup> Adjusting this figure by 10% to account for patient ineligibility or loss, **a total sample size of 84 will be required for the 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 of month. Assuming a similar accrual rate for this study, accrual should be completed in 21 months.

#### **13.4 Randomization Scheme**

Patients will be randomized to one of two combined modality schedules in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen<sup>24</sup> will be used because it balances patient factors other than institution. Based upon analyses of past RTOG esophagus studies, patients will be stratified by percentage of weight lost ( $<10\%$  vs.  $\geq 10\%$ ), histology (*adenocarcinoma* vs. *squamous*), and lesion size ( $<5$  cm vs.  $\geq 5$  cm).

#### **13.5 Early Stopping Rules**

##### **13.5.1 Failure to Deliver Protocol Treatment**

A treatment would not be suitable for further study if it was 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 of each arm. If nine or more patients have not received the sufficient treatment on an arm, 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 randomized to the treatment arm. With 25 evaluable patients, the power to detect differences between the null (0.80) and various alternative values is shown below:

True proportion able to tolerate	Power
0.75	15%
0.70	32%
0.65	53%
0.60	73%
0.55	87%
0.50	95%

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.

##### **13.5.2 Unacceptable Toxicity**

The unacceptable toxicity is defined as grade 5 (*fatal*) toxicity due to chemotherapy and radiation therapy. 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, in each arm, more than three fatal toxicities (*grade 5*) out of the first 25 analyzable patients. 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 25 evaluable patients, the power to detect differences between the null (0.05) and various alternative values is shown below:

True toxic event rate	Power
0.10	24%
0.15	53%
0.20	77%
0.25	90%
0.30	97%

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.

### **13.6 Analysis Plan**

#### **13.6.1 *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; the quality of submitted data with respect to timeliness, completeness, and accuracy; rates of treatment delivery with respect to the protocol prescription; and the frequency and severity of toxicities due to chemotherapy and radiation therapy.

#### **13.6.2 *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. The study was not designed to compare the efficacy of the two treatment programs against one another but rather each program will be tested against the RTOG historical database. However, should both experimental arms demonstrate an improvement in survival as compared to the RTOG historical database, and the other factors (*i.e. toxicity and tolerability*) are not dissimilar, the decision as to which arm should be pursued in a follow-up phase III will be determined by statistical selection theory.<sup>25</sup> Briefly, its criterion is to select the treatment arm with highest response regardless of how small or “nonsignificant” its advantage over the other treatment is. With 38 patients in each arm, we would have a greater than 80% probability of correctly selecting the better treatment when there is an absolute difference of 15% in disease-free survival rates between the two arms. This study was designed to evaluate the tolerance to two treatment regimens under the assumption of the same tolerance rate across the genders and the across the races.

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:

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	0	6	1	0	17	0	24
Male	0	1	19	2	0	38	0	60
Total	0	1	25	3	0	55	0	84

## REFERENCES

1. Herskovic A, Martz LK, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *New Engl J Med.* 326:1593-1598, 1992.
2. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 281:1623-1627, 1999.
3. Kelsen DP, Ginsberg R, Pajak T, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med.* 339:1979-1984, 1998.
4. Minsky, B., Berkey, B., Kelsen, D., et al. Preliminary Results of Intergroup INT 0123 Randomized Trial of Combined Modality Therapy (CMT) for Esophageal Cancer: Conventional vs. High Dose Radiation Therapy. Proc of Am Soc Clin Oncol (ASCO), New Orleans, LA, *J Clin Oncol*, 19 239a, 2000.
5. Ajani JA, Ilson DH, Daugherty K, et al. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst.* 86:1086-1091, 1994.
6. Rowinsky E, K., Citardi M, J., Noe D, A., et al. Sequence-dependent cytotoxic effects due to combinations of cisplatin and the antimicrotubule agents, taxol and vincristine. *J Cancer Res Clin Oncol.* 119:727-733, 1993.
7. Sinclair WK, Morton RA. X-ray Sensitivity During the Cellgeneration Cycle of Culture Chinese Hamster Cells. *Radiation Research.* 29:450-474, 1966.
8. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by Taxol. *Nature.* 277:665-667, 1979.
9. Patel G, F, Ren QF, Grem J. Interaction of fluorouracil and paclitaxel in MCF-7 human breast carcinoma cells. *Proc Amer Assoc Cancer Res.* 35:3301994 (Abstract).
10. Rowinsky E, Chaudhry V, Forastiere A, et al. Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony-stimulating factor: neuromuscular toxicity is dose-limiting. *J Clin Oncol.* 11:2010-2020, 1993.
11. Rowinsky E, K., Gilbert M, R., McGuire W, P., et al. Sequences of taxol and cisplatin: a phase I and pharmacologic study. *J Clin Oncol.* 9:1692-1703, 1991.
12. Wasserheit C, Frazein A, Oratz R, et al. Phase II Trial of Paclitaxel and Cisplatin in Women With Advanced Breast Cancer: An Active Regimen With Limiting Neurotoxicity. *J Clin Oncol.* 14:1993-1999, 1996.
13. Ilson DH, Ajani JA, Bhalla K, et al. A phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. *J Clin Oncol.* 16:1826-1834, 1998.
14. Terasima R, Tolmach LJ. X-ray Sensitivity and DNA Synthesis in Synchronis Populations of Hela Cells. *Science.* 140:490-492, 1963.
15. Liebmann JE, Cook JA, Fisher J, et al. *In Vitro* Studies of Paclitaxel as a Radiation Sensitizer in Human Tumor Cells. *J Natl Cancer Inst.* 86:441-445, 1994.
16. Choy H, Akerley H, Safran J, et al. Phase I trial of outpatient weekly paclitaxel and concurrent radiation therapy for advanced non-small cell lung cancer. *J Clin Oncol.* 12:2682-2686, 1994.
17. Grino B, Urba S. A Phase II Trial of Preoperative Taxol and Cisplatin with Radiation therapy in patients with loco-regional esophageal carcinoma. Bristol-Myers Squibb Clinical Investigators Conferences Atlanta, Ga., 1994 (Abstract).
18. Seidman AD, Hochhauser D, Yao TJ. 96 hour paclitaxel after prior short taxane infusion: Phase II pharmacodynamic study in metastatic breast cancer. *Proc Amer Soc Clin Oncol.* 15:1, 1995.
19. I. Schnirer, R. Komaki, J. Yao, et al. A study of concurrent 5FU/paclitaxel and radiotherapy in patients with carcinoma of the upper gastrointestinal tract. Proceeding ASCO 2000.

20. ICRU Report #50: Prescribing, recording and reporting photon beam therapy. *International Commission on Radiation Units and Measurements*, Bethesda, MD.
21. Goitein M, Abrams M. Multi-dimensional treatment planning: I. Delineation of anatomy. *Int J Radiat Oncol Biol Phys.* 9:777-787, 1983.
22. McCloud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: Analysis of staging in the mediastinum and CT by correlative lymph node mapping and sampling. *Radiology.* 182:319-323, 1992.
- 23\*. Dixon DO, Simon, R. Sample size considerations for studies comparing survival curves using historical controls. *J. Clin. Epidemiol.* 41:1209-1213, 1988.
24. Zelen, M. The randomization and stratification of patients to clinical trials. *J. Chron. Dis.* 27:365-375, 1994.
25. Simon R, Wittes RE, Ellenber SS. Randomized Phase II Clinical Trials. *Cancer Treat. Rep.* 69:1375-1381, 1985.

\*Renumbered 6/20/01)

**APPENDIX I (6/20/01)**

**RTOG 0113 (8/4/04)**

**SAMPLE CONSENT FOR RESEARCH STUDY**

**STUDY TITLE**

**NON-OPERATIVE THERAPY OF LOCAL-REGIONAL CARCINOMA OF THE  
ESOPHAGUS: A RANDOMIZED PHASE II STUDY OF TWO PACLITAXEL-BASED  
CHEMORADIOTHERAPY REGIMENS**

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 chemotherapy together has on you and your esophageal cancer.

This research is being done to compare two types of treatment that give chemotherapy before chemotherapy and RT together and how you tolerate the treatment.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 84 people will take part in this study.

**WHAT IS INVOLVED IN THE STUDY? (8/6/02)**

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer selects which group you are put in. Neither you nor the researcher will choose what group you will be in. You will have an equal/one in two chance of being placed in any group.

You will receive one of the following treatment plans:

<b><u>Arm 1</u></b>	<b><u>Cycle 1</u></b>	<b><u>Cycle 2</u></b>	<b><u>One month after last chemo dose</u></b>
5-FU	Days 1-5	Days 29-33	Day: M-F of RT x 5 ½ weeks
Cisplatin	Days 1-5	Days 29-33	-
Paclitaxel	Day 1	Day 29	Day 1,8,15,22,29
RT	-	-	M-F x 5 ½
G-CSF	days 6-15 after cycle 1	days 34-42 after cycle 2	
*Neulasta™	Day 6	Day 6	

\*may be given by your doctor instead of G-CSF (8/6/02)

<b><u>Arm 2</u></b>	<b><u>Cycle 1</u></b>	<b><u>Cycle 2</u></b>	<b><u>One month after last chemo dose</u></b>
Paclitaxel	1	1	Day: 1-4 of RT x 6 weeks
Cisplatin	1	1	Day 1,8,15,22,29,36
RT	-	-	M-F x 5½ weeks

**Arm 1: (8/6/02)**

**Chemotherapy Alone**

You will receive one or two cycles of chemotherapy called 5FU, cisplatin, and taxol. One cycle lasts five days. A double access device for giving chemotherapy will be placed under your skin on the front of your chest with a plastic tube leading to a large vein. On the first day you will receive taxol given into your vein (intravenous). This will last 24 hours and end on day 2. You will receive 5FU on days 1 through 5. This will run continuously for 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 chemo 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 day 6 through day 15 after the 1<sup>st</sup> 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. 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 each chemo cycle.

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

### **Chemotherapy and Radiation Therapy Together:**

Approximately one month from your last chemotherapy cycle, you will start chemotherapy with radiation therapy. You will receive radiation therapy five days a week, Monday through Friday for 5½ weeks. The chemotherapy 5FU will be given into your vein continuously five days a week every week during radiation therapy. The chemotherapy taxol will be given the first day of each week during radiation therapy for five weeks. This will be given into your vein (intravenous).

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

### **Arm 2: Chemotherapy Alone (4/1/02)**

You will receive one or two cycles of chemotherapy called taxol and cisplatin. A single access device for giving chemotherapy will be placed under your skin on the front of your chest with a plastic tube leading to a large vein. The taxol will be given into your vein (intravenous) over three hours. Cisplatin will be given on that day after the taxol is completed. The cisplatin will be given into your vein and will last one hour. Your chemo will be given as an outpatient at your institution.

A second cycle will be given on day 21, or three weeks from the end of the first cycle.

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

## **Chemotherapy and Radiation Therapy Together:**

Approximately one month from your last chemotherapy cycle, you will start chemotherapy with radiation therapy. You will receive radiation therapy five days a week Monday through Friday, for 5 ½ weeks. The chemotherapy cisplatin will be given once a week during radiation. This will be given into your vein and will last about one hour. Taxol will be given over 4 days continuously into your vein. This will be given every week during radiation therapy.

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

## **Procedures That Will Be Done for This Study: (8/6/02)**

### **Prior to study entry:**

- History and physical exam – a medical oncologist and radiation oncologist will examine you.
- Blood tests – called CBC and SMA-12
- CT scan or MRI of the chest and abdomen
- Upper GI with barium contrast (optional but recommended)
- Chest x-ray
- An access device for giving chemotherapy will be placed under your skin on the front of your chest with a plastic tube leading to a large vein.
- Upper GI endoscopy (an ultrasound is also recommended)
- EKG – electrocardiogram of your heart
- Bronchoscopy – if necessary based on where your cancer is
- Biopsy of a lymph node – if a lymph node is seen as enlarged on the x-rays
- 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.
- PFT or pulmonary function tests – breathing tests if needed
- Audiogram – (hearing test) if necessary

### **Prior to each Chemotherapy Cycle:**

- Physical exam
- Blood tests called CBC and CEA. These blood tests will be done on the first day of each chemo cycle and during two weeks during chemotherapy
- Audiogram (hearing test), if necessary.

### **After each Chemotherapy Cycle:**

- Physical exam will done weekly during radiation therapy treatment.

- Blood test called SMA-12. This will be done weekly during radiation therapy.
- After the first cycle of chemotherapy, an upper GI with barium contrast or upper GI endoscopy to rule out or confirm progression

**Approximately 1 ½ months or 42 days after you have completed all treatment:**

- Physical exam
- Blood tests called CBC, CEA, SMA-12
- Chest x-ray
- CT scan or MRI of the chest and abdomen
- Upper GI endoscopy (an ultrasound is optional but recommended)
- Biopsy – if needed

**At each Followup:**

- Physical exam
- Labs – CBC, CEA, SMA-12
- Upper GI with barium contrast
- CT scan or MRI of the chest and abdomen
- Upper GI endoscopy if indicated
- PFT's- only during the 8<sup>th</sup> month of follow-up and as indicated by your physician
- Biopsy – as needed

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

**HOW LONG WILL I BE IN THE STUDY?**

This study will take approximately 2 to 3 months to complete. Follow up visits will be scheduled every four months for one year, then every six months for two years, and then yearly for the rest of your life.

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

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

## **WHAT ARE THE RISKS OF THE STUDY?**

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 which can cause difficulty breathing, irregular heartbeat, low blood pressure, and even be life threatening.

Changes in vision

Decrease in blood pressure

Severe rash called Stevens-Johnson syndrome which can cause fever and red sores in

your mouth and eyes

**Risks Associated with Cisplatin**

Very Likely

Decrease in blood counts which can lead to a risk of infection and bleeding.

Loss of appetite and/or taste; metallic taste in your mouth

Nausea and/or vomiting

Fatigue

Hearing loss or ringing in the ears

Numbness or tingling in the hands or feet

Less Likely

Muscle cramps or spasm

Loss of coordination

Involuntary movements or shaking

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

Chest pain which may cause damage to the heart  
Infection at the catheter entry site

**Risks Associated with G-CSF and Neulasta™ (8/6/02)**

Very Likely

Fever  
Loss of hair  
Fluid retention  
Nausea and/or vomiting  
Diarrhea  
Bone pain  
Fatigue

Less Likely

Chest Pain  
Headache  
Skin rash  
Anorexia  
Constipation  
Sore throat  
Heart arrhythmia or decrease in blood pressure

**Risks Associated with Placement of Venous Access (4/1/02)**

Likely

Bleeding  
Possible infection at the access site

Less Likely, But Serious

Blood clots forming in the vein  
Puncture of the lung

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

### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with 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? (1/15/02)**

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

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

A Data Monitoring Committee, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this 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**

Visit the NCI's Web sites for comprehensive clinical trials information  
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ  
<http://cancernet.nci.nih.gov>.

**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 Signature (*or legal Representative*)

\_\_\_\_\_  
Date

**TISSUE AND BLOOD TESTING (RTOG 0113 (8/4/04))**

I agree to the use of my tissues/other samples for research studies related to my cancer.

Yes       No

\_\_\_\_\_  
Patient Signature (*or legal Representative*)

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

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

### **ZUBROD PERFORMANCE SCALE**

0	Fully active, able to carry on all predisease activities without restriction <i>(Karnofsky 90-100).</i>
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work <i>(Karnofsky 70-80).</i>
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours <i>(Karnofsky 50-60).</i>
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours <i>(Karnofsky 30-40).</i>
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair <i>(Karnofsky 10-20).</i>

## APPENDIX III

### ESOPHAGUS , AJCC 5th Edition, 1997

#### DEFINITION OF TNM

##### **Primary Tumor (T)**

<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>Tis</b>	Carcinoma <i>in situ</i>
<b>T1</b>	Tumor invades lamina propria or submucosa
<b>T2</b>	Tumor invades muscularis propria
<b>T3</b>	Tumor invades adventitia
<b>T4</b>	Tumor invades adjacent structures

##### **Regional Lymph Nodes (N)**

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Regional lymph node metastasis

##### **Distant Metastasis (M)**

<b>MX</b>	Presence of distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
	For tumors of lower thoracic oesophagus
M1a	Metastasis in celiac lymph nodes
M1b	Other distant metastasis
	For tumors of upper thoracic oesophagus
M1a	Metastasis in cervical lymph nodes
M1b	Other distant metastasis
	For tumors of mid-thoracic oesophagus
M1a	Not applicable
M1b	Non-regional lymph node or other distant metastasis

#### HISTOPATHOLOGIC TYPE

The staging classification applies to all carcinomas (*squamous cell and adenocarcinomas*). Adenocarcinomas that arise in Barrett's esophagus are also included in the classification.

#### HISTOPATHOLOGIC GRADE (G)

<b>GX</b>	Grade cannot be assessed
<b>G1</b>	Well differentiated
<b>G2</b>	Moderately differentiated
<b>G3</b>	Poorly differentiated
<b>G4</b>	Undifferentiated

**APPENDIX III**

**ESOPHAGUS , AJCC 5th Edition, 1997**

*(continued)*

**STAGE GROUPING**

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

## APPENDIX V

### ADVERSE EVENT REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
  - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

#### B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

### **C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS**

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

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

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

#### **Commercial and Non-Investigational Agents**

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions ( $\geq$  *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities ( $\geq$  *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

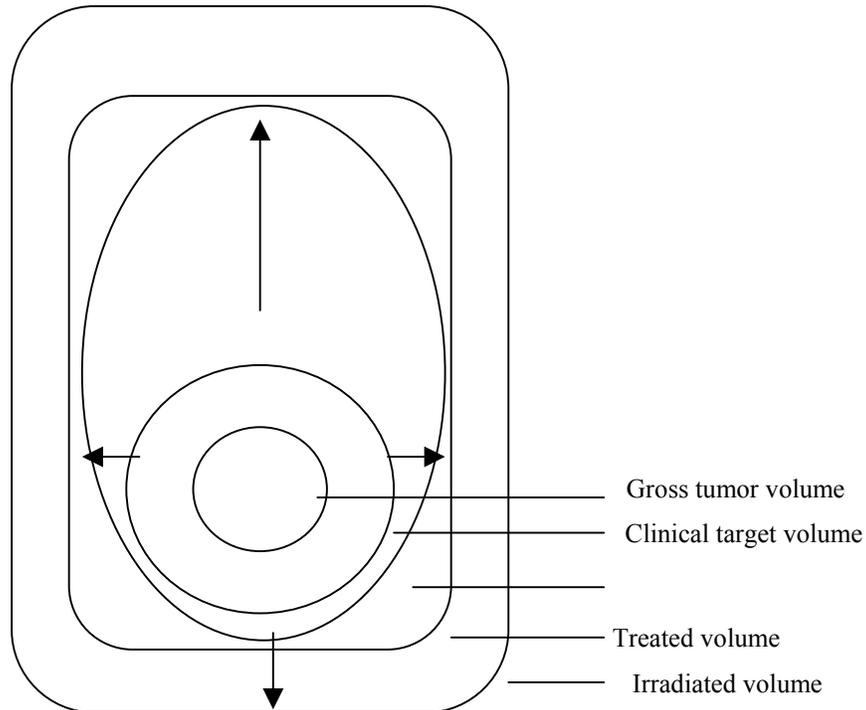
#### **Investigational Agents**

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

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

## APPENDIX VI

### Excerpts from ICRU-50



#### **Schematic illustration of the different volumes**

*Gross Tumor Volume (GTV)* denotes the demonstrated tumor.

*Clinical Target Volume (CTV)* denotes the demonstrated tumor (*when present*) **and also volumes with suspected (subclinical) tumor** (*e.g. margin around the GTV, and e.g. regional lymph nodes, N[\*]/, considered to need treatment*). The CTV is thus a pure anatomic-clinical concept.

*Planning Target Volume (PTV)* consists of the CTV(s) and a margin to account for variations in size, shape, and the position relative to the treatment beam(s). The PTV is thus a geometrical concept, used to ensure that the CTV receives the prescribed dose, and it is (*like the patient/tissues concerned*) defined in relation to a fixed coordinate system. Note that in the example, the magnitude of foreseen movements of the CTV is different in different directions.

*Treated Volume* is the volume that receives a dose that is considered important for local cure or palliation.

*Irradiated Volume* is the volume that receives a dose that is considered important for normal tissue tolerance (*other than those specifically defined for organs at risk*).