

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0017

A PHASE I STUDY OF GEMCITABINE, CARBOPLATIN OR GEMCITABINE, PACLITAXEL AND RADIATION THERAPY FOLLOWED BY ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0017 (4/27/04)

A PHASE I STUDY OF GEMCITABINE, PACLITAXEL OR GEMCITABINE, CARBOPLATIN AND RADIATION THERAPY FOLLOWED BY ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

SCHEMA (9/11/03)

Sequence A*			Sequence B* Closed 5/22/03		
Gemcitabine Dose (mg/m ² /wkly)	Carboplatin Dose (AUC)	Number of Patients	Gemcitabine Dose (mg/m ² /wkly)	Paclitaxel Dose (mg/m ² /wkly)	Number of Patients
Arm 1: 300	--	6	Arm 2: 300	30	6
Arm 3: 300	2	6	Arm 4: 450	30	6
Arm 5: 450	2	6	Arm 6: 450	40	6
Arm 7: 600	2	6	Arm 8: 600	40	6
Arm 9: 750	2	6	Arm 10: 600	50	6
Arm 11: 900	2	6	Arm 12: 750	50	6
			Arm 14: 900	50	6

*Both sequences will be followed by two cycles of adjuvant Gemcitabine-Carboplatin administered q 21 days commencing 3 weeks after the end of the chemoradiation phase.

(11/17/04)

	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
(Arm 1) RT	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Chemo	G	G		G	G		G
(Arms 2-14) RT	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
Chemo	G/C or G/P	G/C or G/P		G/C or G/P	G/C or G/P		G/C or G/P
All Arms following RT	Day 71	Day 78	Day 85	Day 92	Day 99	Day 106	
Chemo	C + G	G		C + G	G		

Radiation therapy at 1.8 Gy/ 5 days a week, x 5 weeks followed by 2 Gy/ 5 days a week for 9 fractions. Total dose will be 63 Gy.

(9/11/03) Gemcitabine and paclitaxel (closed 5/22/03) or gemcitabine and carboplatin will be delivered in the outpatient setting as an intravenous infusion on days 1, 8, 22, 29, and 43 of the planned radiation therapy course. Gemcitabine doses will be escalated per schema until DLT (dose-limiting toxicity) is determined.

This will be followed 21 days after the radiotherapy is completed by 2 cycles of adjuvant chemotherapy. Gemcitabine (1000 mg/m² weekly 2 out of 3 weeks) and Carboplatin (AUC 5.5) on the first week will be delivered intravenously on an outpatient basis q 21 days.

ELIGIBILITY (See Section 3.0 for details)

- Medically inoperable stage IIIA or unresectable stages IIIA & IIIB non-small cell lung cancer
- Measurable disease on the planning CT
- Zubrod Status 0 and 1
- Weight loss ≤10% in 3 months prior to diagnosis
- FEV₁ > 1000 cc
- Serum creatinine ≤ 1.5, Hgb ≥ 8.0, absolute granulocyte count (AGC) ≥ 2000, platelets ≥ 100,000
- Bilirubin ≤ 1.5 mg/dl; SGOT ≤ 1.5 x institutional upper limit
- No pleural effusion on CXR, unless after thoracotomy or invasive thoracic procedure
- No distant metastasis, prior chemo- or thoracic or neck radiation therapy
- No recurrent disease or prior complete tumor resection
- No prior invasive malignancy unless ≥ 3 years and currently disease-free
- Signed study-specific consent form prior to registration

Required Sample Size: Dose Tolerance Dependent; Maximum Size=78

Institution # _____

RTOG 0017

ELIGIBILITY CHECK (4/27/04)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have histologic proof of non-small cell lung cancer documented by biopsy or cytology?
- _____(IIIA-IIIB) 2. What is the tumor stage?
- _____(Y) 3. Is there measurable disease on 3D planning CT?
- _____(N) 4. Has the patient had a weight loss of $> 10\%$ in the 3 months prior to diagnosis?
- _____(N) 5. Is there evidence of metastatic disease?
- _____(N) 6. Prior total or subtotal surgical resection of the lung tumor?
- _____(N) 7. Has the patient had any prior invasive malignancy within the past 3 years other than non-melanomatous skin cancer?
- _____(N) 8. Has the patient received any prior chemotherapy or radiation to the thorax or neck?
- _____(N) 9. Does the patient have a post-resection intrathoracic tumor recurrence?
- _____(Y/N) 10. Is there evidence of pleural effusion on chest x-ray?
_____(Y) If yes, did it appear only after a thoracotomy or other invasive thoracic procedure was attempted?
- _____(N) 11. Has the patient had a myocardial infarction within the last 6 months or symptomatic heart disease, including angina, CHF, or uncontrolled arrhythmia?
- _____(> 1000) 12. Report the FEV 1 (*cc*).
- _____(≤ 1.5) 13. Report the serum creatinine (*mg/dl*).
- _____(≥ 8.0) 14. Report the hemoglobin (*mg%*).
- _____(≥ 2000) 15. State the absolute granulocyte count (*AGC*).
- _____(≥ 100) 16. Report the platelet count ($\times 1000$).
- _____(Y/N) 17. Is the bilirubin ≤ 1.5 mg/dl and SGOT ≤ 1.5 times the institutional upper limits of normal?
_____(Y) If no, is the serum bilirubin and/or SGOT abnormality caused by documented benign disease?

(continued on next page)

Institution # _____

RTOG 0017

ELIGIBILITY CHECK (4/27/04)

Case # _____

(page 2 of 2)

_____(N/NA) 18. If female, is the patient pregnant or lactating?

_____(Y/NA) 19. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?

_____(0-1) 20. What is the Zubrod Performance Status?

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. Date of Birth

_____ 9. Race

_____ 10. Social Security Number

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Treatment Start Date

_____ Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background

Lung cancer is the most common non-cutaneous neoplasm diagnosed in the United States. Approximately 164,000 new cases are estimated to be diagnosed in 2000. It is also the leading cause of cancer deaths with over 156,900 deaths estimated in 2000.¹ Upon initial presentation, fewer than one-half of patients will have surgically resectable lung cancer with the potential for cure. Approximately one-quarter of patients will present with locally advanced disease involving either the ipsilateral mediastinal or subcarinal lymph nodes (*AJCC T1-3 N2 MO, Stage IIIA*), or contralateral mediastinal hilar or ipsilateral or contralateral scalene or supraclavicular nodes (*AJCC any T N3 MO, Stage IIIB*).² A smaller number of patients will have a centrally located primary tumor involving mediastinal structures (*AJCC T4 any N MO, Stage IIIB*). These patients are generally not considered candidates for surgical resection. They usually receive definitive radiation therapy, with or without chemotherapy. While the response rates are high (50-80%), the overall survival is quite poor with a median survival of only 9-12 months and a five year survival of approximately 5%.³ Recently, there has been increased interest in the use of combined modality therapy for Stage III non-small cell lung cancer. Some investigators have focused on neoadjuvant chemotherapy while others have used the combination of chemotherapy and radiation therapy, either sequentially or concomitantly. Various trials of chemotherapy agents and radiosensitizing agents (*including hydroxyurea, bleomycin, 5-fluorouracil, cisplatin*), as well as the radiosensitizer misonidazole, have been performed in small numbers of patients.⁴⁻⁹

Combination chemotherapy and radiation therapy has been introduced to clinical trials of lung cancer and other malignancies. Various agents have been used either sequentially or concurrently in clinical trials of combined chemoradiotherapy for advanced non-small cell lung cancer (*NSCLC*).¹⁰⁻¹² CALGB 8433 was the first major randomized clinical trial¹² to demonstrate a significant survival advantage for the combination of sequential chemotherapy and radiation for patients with inoperable stage III NSCLC. The treatment consisted of 6000 cGy in 200 cGy fractions with or without 2 cycles of prior cisplatin and weekly vinblastine for 5 weeks. Response rates were 56% for patients receiving combination therapy and 43% for patients receiving radiation alone with median survivals of 13.7 and 9.6 months respectively. (*P* = .0066). Re-analysis of this trial at 7 years showed these findings to persist with 5-year survivals of 17% versus 6% respectively. The trial has also been confirmed independently in an intergroup trial by the Radiation Therapy Oncology Group (*RTOG*) and Eastern Cooperative Oncology Group (*ECOG*) with similar findings of improved 1-year and median survivals of 60% and 13.8 months for combined therapy versus 46% and 11.4 months for radiation alone.¹¹ Concomitant chemo- radiotherapy offers an alternative strategy for combined therapy. Its potential advantages over sequential therapy is the immediate treatment of both local and distant sites of disease simultaneously and the opportunity for synergy between the modalities to enhance local control. Recent meta-analysis¹³ revealed that combined modality therapy resulted in a mean gain in life expectancy of approximately 2 months by the end of 3-years and median survival improvement from 10.3 to 12 months. New treatment strategies, perhaps with newer, more active chemotherapeutic agents with radiation enhancing properties, are needed.

Recently, a number of new drugs with promising single agent activity in the refractory solid tumors have been identified. These include paclitaxel, docetaxel, irinotecan, gemcitabine, and vinorelbine. The great majority of these new agents, unlike currently used chemotherapeutic agents, have also been found to act as "radiation enhancers".

Despite substantial gains in the induction of remissions with the use of combination chemotherapy and radiation therapy, the survival of patients is still unacceptably low. Clearly, new treatment strategies are needed.

1.2 Gemcitabine

Gemcitabine (*difluorodeoxycytidine*) is an analog of cytosine arabinoside.¹⁴ It possesses a wide spectrum of activity against solid tumors (*head and neck, breast, small-cell lung, bladder, pancreas, and cisplatin-refractory ovarian cancer*). Gemcitabine has been studied extensively as a single agent in small cell and non-small cell lung cancer. Doses for gemcitabine ranged from 800-1250 mg/m² administered on days 1, 8, and 15 of each 28-day cycle. Toxicities noted were mild and primarily hematologic. Grade 3-4 neutropenia was seen in less than 25% of treated patients and grade 3-4 thrombocytopenia in less than 2%. Non-hematologic toxicities included reversible transaminitis, skin rashes, and fatigue. With over 600 evaluable patients, responses in each individual trial ranged from 20-27%.¹⁵⁻¹⁸

Crino and his colleagues from Italy conducted a randomized phase III study to compare gemcitabine and cisplatin (*GC*) versus mitomycin, ifosfamide, and cisplatin (*MIC*) chemotherapy in patients in advanced NSCLC.¹⁹ Three hundred seven patients were randomized to receive either gemcitabine 1,000 mg/m² on

days 1, 8, and 15 plus cisplatin 100 mg/m² on day 2, every 28 days, or mitomycin 6 mg/m², ifosfamide 3,000 mg/m², and mesna on day 1 plus cisplatin 100 mg/m² on day 2, every 28 days. The whole-blood cell count was repeated on day 1 in both arms and weekly in the GC arm before each gemcitabine administration. Crino et al. report an increased response rate for the GC when compared with the MIC regimen in the treatment of advanced NSCLC.

1.3 **Gemcitabine and RT**

Gemcitabine has been shown to be a potent radiosensitizer, even at noncytotoxic concentrations.²⁰ Plasma levels as low as 20 micromolar a dose, which is 200 times lower than those currently utilized for cytotoxicity, produces radiation-enhancement ratios of 1.6. Reduction in the dATP pool may be one mechanism of radiosensitization. Its pharmacokinetics, clinical efficacy, toxicity, and administration have been characterized. The parent nucleoside drug requires intracellular activation by sequential cellular kinases to its active 5'-triphosphate, metabolite dFdCTP. This cytotoxic triphosphate metabolite is retained for long periods within the cell, with terminal elongation rates of 16 to 72 hours. Therefore, it theoretically maintains its effects for many hours or even days after administration, making it an interesting compound to use simultaneously with daily radiotherapy.

Scalliet and his colleague from the European consortium conducted a phase II trial using weekly gemcitabine (1000 mg/m²/week) with concurrent thoracic radiation therapy in stage III NSCLC.²¹ This study was closed early with only 8 patients due to significant toxicities. It appears that the gemcitabine dose of 1000 mg/m² weekly for 6 weeks with thoracic RT was too high, and radiation planning treatment volume was too large (4500 cm³ for initial volume and 2000 cm³ for boost volume). Vokes and his colleagues conducted the second phase II study with gemcitabine/RT from CALGB.²² This was a randomized phase II trial evaluating new agent-cisplatin doublets both as induction therapy and as radiation sensitizing treatment. The cisplatin dose was fixed throughout at 80 mg/m². Patients were randomized to one of three arms containing gemcitabine, paclitaxel, or vinorelbine. The dose of gemcitabine was 1250 mg/m² at week 1, 2 and, 4, 5 (induction phase) and 600 mg/m² weeks 7, 8 and 10, 11 (concurrent phase). There were 63 patients in gemcitabine group, which had 24% thrombocytopenia and 53% esophagitis. Median survival rate was 17.2 months, and the one-year survival rate was 63%. This study demonstrated induction of cisplatin and gemcitabine (80 mg/m² q 3 week X 2 /1250 mg/m² week 1,2 and 4, 5) followed by additional cisplatin at same dose with reduced gemcitabine dose (600 mg/m²) with concurrent radiotherapy is feasible, and the median and 1-year survival rate were encouraging. However, the optimal dose of gemcitabine in concurrent with thoracic radiation therapy has not been defined.

Currently, phase I trials using gemcitabine concomitantly with radiation in non-small cell patients are being undertaken. The study from MD Anderson by Zinner²³ investigates weekly gemcitabine with limited volume thoracic RT and with a starting dose of gemcitabine of 150 mg/m². The current dose level is at 175 mg/m², and they are hoping to continue further dose escalation. The other phase I study is from England by Anna Gregor.²⁴ The current weekly gemcitabine dose in this study is at 475 mg/m² with radiation therapy (limited planning treatment volume: 1500 cm³ for initial volume and approximately 650 cm³ for boost volume) without reaching dose limiting toxicity.

1.4 **Paclitaxel**

In an ECOG trial, for patients with advanced, previously untreated NSCLC, paclitaxel by 24-hour infusion was the most active single agent, with a response rate of 25%²⁵ and a one-year survival rate of 41%. This finding was corroborated by an MD Anderson study that reported a major response rate of 24%.²⁶ A number of investigators have demonstrated comparable activity and survival for 3-hour paclitaxel infusion in advanced NSCLC^{27,28} (Table 1).

Table 1. Activity and Survival for 3-hour paclitaxel infusion in NSCLC

Study (1 st Author)	Dose (mg/m ²)	Duration (hr)	N	OR	1 Y OS (%)
ECOG (Chang) ²⁵	250	24	24	23%	40
MDA (Murphy) ²⁶	200	24	24	24%	38.5
Gatzemeier ²⁷	225	3	43	21%	
AEMC (Tester) ²⁸	200	3	20	30%	
CANNON (Greco) ²⁹	135→200	1	56	26%	

1.5 Paclitaxel and RT

Paclitaxel interferes with mitotic spindle function. In addition to its direct cytotoxic effect, paclitaxel has been found *in vitro* and *in vivo* studies to potentiate the effects of radiation. The exact mechanism of this interaction is unclear; however, several theories have been postulated.^{30,31} One of the initial phase I studies of paclitaxel with radiation in NSCLC used paclitaxel at a starting dose of 10 mg/m² weekly for 6 weeks as a 3-hour infusion. Twenty-seven patients were treated, and the principal dose limiting toxicity was esophagitis with a MTD of 60 mg/m²/week.³² On the basis of these phase I studies, several phase II studies of paclitaxel and radiation have been performed. One of the earliest of these studies used paclitaxel at 60 mg/m² intravenously, over 3 hours, every week for 6 weeks during radiation therapy. Overall esophagitis was the most common grade 3 or 4 toxicity, occurring in 38% of patients. The median survival was 20 months, with a two-year survival of 33%. The overall response rate of 86 % was encouraging.³³

1.6 Gemcitabine and Paclitaxel

Considering the activity of both paclitaxel and gemcitabine in a wide variety of solid tumors, their differing mechanism of action, and their different toxicity profile, it is logical to attempt to combine these agents. In particular, weekly paclitaxel with its relative lack of myelosuppression appeared well suited to combination chemotherapy.^{34,35} As noted previously, gemcitabine is also well tolerated as a single agent with minimal bone marrow toxicity. Moreover, these agents exert their effect on different pathways of cell synthesis with paclitaxel affecting the microtubular system and gemcitabine disrupting DNA synthesis.

Investigators at Indiana University conducted a phase I trial evaluating weekly paclitaxel with gemcitabine in patients with refractory solid tumors.³⁶ Patients were to have received no more than one prior chemotherapy regimen for metastatic disease, and no prior paclitaxel and gemcitabine. Each agent was administered on days 1, 8, and 15 of each 28 day cycle. Paclitaxel was administered as a 3-hour infusion with a starting dose of 60 mg/m². The starting dose for gemcitabine was 600 mg/m². Twenty-eight patients were evaluable for toxicity. Non-hematologic toxicity was mild with no Grade 3 or 4 toxicities. Grade 3 and 4 hematologic toxicities were noted: anemia - 2 patients, thrombocytopenia - 1 patient, neutropenia - 13 patients. Six patients experienced grade 4 toxicity, and there was one episode of neutropenic fever. Partial responses were seen in four of 24 (17%) evaluable patients. Of note, three of the four responses were in NSCLC. The recommended phase II dose from this study was paclitaxel at 110 mg/m² and gemcitabine at 1000 mg/m².³⁷

Giaccone et al. have looked at the combination of gemcitabine (1000 mg/m²) on days one and eight with escalating doses of paclitaxel (150, 175, 200 mg/m²) on day one in advanced non-small cell lung cancer. Cycles were repeated every three weeks for three cycles in the phase I portion of the trial. They then extended the 200 mg/m² paclitaxel and 1000 mg/m² gemcitabine schedule to treat a further thirty patients. The regimen was well tolerated and produced a 24% response rate.³⁸ Kosmidis et al. have presented early results on their randomized trial of gemcitabine and paclitaxel versus carboplatin and paclitaxel in advanced non-small cell lung cancer. While there was a no obvious increased response rate in either group, the toxicities of the gemcitabine/paclitaxel combination were manageable in this patient population. This suggests that it is reasonable to proceed to look at the combination in a phase I trial in stage III disease.³⁹

(9/11/03) As of May 2003, three out of six patients developed dose limiting toxicities (DLTs) at the starting dose of gemcitabine and paclitaxel (Sequence B, Arm 2, 300 mg/30 mg). These DLTs included possible esophageal perforation, which may have resulted in the death of one patient. Based on the experience with these six patients, the gemcitabine/paclitaxel combination may be too toxic to be added to thoracic radiation in locally advanced non-small cell lung cancer patients. Therefore, Sequence B will be stopped as of 5/22/03, and there will be no further accrual to this regimen.

1.7 Gemcitabine and Carboplatin

Overall, the meta-analysis from Pritchard et al. suggests that traditional platinum-based chemotherapy combined with radiotherapy adds an average of 2 months to patient survival.⁴⁰ In a randomized trial by the EORTC, the carboplatin-etoposide regimen produced equal activity to a cisplatin-etoposide regimen.⁴¹ Several phase I and II trials have looked at the combination of gemcitabine and carboplatin in NSCLC⁴² and while the q4week dosing schedule appears to be toxic, the experience with q3week dosing is much more positive. Edelman et al. developed a regimen of gemcitabine 1000 mg/m², day 1 and 8, and carboplatin AUC=5.5, day 1, repeated on a q3weekly basis, followed by single agent paclitaxel, which was well tolerated with a 31% response rate and a ten-month median survival.⁴³ Ongoing study of this regimen is occurring in SWOG and in the National Coalition phase III trial in NSCLC.⁴²

In this trial, we hope to build on our own experience of using systemic chemotherapy as a radiation sensitizer by combining gemcitabine and carboplatin or gemcitabine and paclitaxel with thoracic radiation

in a phase I setting for locally advanced NSCLC. We will follow this treatment with two cycles of gemcitabine-carboplatin chemotherapy at standard systemic doses.

2.0 OBJECTIVES

- 2.1 Primary:** To determine the maximal tolerated dose (*MTD*) of gemcitabine when administered with carboplatin and thoracic radiation therapy followed by adjuvant chemotherapy for patients with NSCLC.
- 2.2 Primary:** To determine the maximal tolerated dose (*MTD*) of gemcitabine and paclitaxel when administered with thoracic radiation therapy followed by adjuvant chemotherapy for patients with NSCLC.

3.0 PATIENT SELECTION

3.1 ELIGIBILITY

- 3.1.1** Patients with unresected loco-regionally advanced non-small cell lung cancer without evidence of hematogenous metastases, Stages IIIA, or IIIB (*See Appendix III*).
- 3.1.2** Patients must have measurable disease on the planning CT
- 3.1.3** Zubrod performance status 0-1 (*Appendix II*).
- 3.1.4** Weight loss $\leq 10\%$ in three months prior to diagnosis.
- 3.1.5** FEV₁ > 1000 cc
- 3.1.6** No pleural effusion on CXR unless it appeared only after a thoracotomy or other invasive thoracic procedure was attempted.
- 3.1.7** Serum creatinine ≤ 1.5 mg/dl, hemoglobin ≥ 8.0 mg%, absolute granulocyte count $\geq 2000/\mu\text{l}$, platelets $\geq 100,000/\mu\text{l}$.
- 3.1.8** Serum bilirubin ≤ 1.5 mg/dl; SGOT must be ≤ 1.5 times the institutional upper limits of normal unless the abnormality is caused by documented benign disease.
- 3.1.9** Patients must sign a study-specific consent form prior to registration.

3.2 Conditions for Patient Ineligibility

- 3.2.1** Evidence of small cell histology; Stage I, II or stage IV non-small cell cancer.
- 3.2.2** Patients who have undergone complete (*or subtotal*) tumor resection.
- 3.2.3** Patients with post-resection intrathoracic tumor recurrence.
- 3.2.4** Patients with a synchronous (*except for non-melanomatous skin cancer*) or prior invasive malignancy, unless disease-free for ≥ 3 years.
- 3.2.5** Patients with prior chemotherapy or thoracic or neck RT.
- 3.2.6** Patients with myocardial infarction within the preceding six months or symptomatic heart disease, including angina, congestive heart failure, uncontrolled arrhythmia.
- 3.2.7** Pregnant women are ineligible as the treatment involves unforeseeable risks to the participant and to the embryo or fetus. Patients with childbearing potential must practice appropriate contraception.

4.0 PRETREATMENT EVALUATIONS

- 4.1** A complete medical history & physical examination to include Zubrod performance status, neurologic assessment, recent weight loss, usual weight, concurrent non-malignant disease and therapy.
- 4.2** CBC with differential, platelet count, SMA-12, electrolytes, and Mg++ within 14 days prior to randomization.
- 4.2.1** SMA-12: Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT, and SGPT within 14 days prior to study entry.
- 4.3** Chest x-ray; CT scan of the chest, liver, and adrenal glands within 4 weeks prior to study entry.
- 4.4** CT scan or MRI of the brain and radionuclide bone scan within 6 weeks prior to study entry.
- 4.5** EKG and pulmonary function tests including FVC, FEV₁, and DLCO within 2 months prior to study entry.
- 4.6** Location, type, and size of measurable lesion prior to treatment must be recorded.
- 4.7** Pregnancy test as applicable within 14 days prior to study entry.

5.0 REGISTRATION PROCEDURES

- 5.1** See Section 12.2 for data submission pre-requirements for this study. 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

6.1 Radiation Dose

- 6.1.1** Radiation therapy will commence first day of the chemotherapy dose schedule. Total dose to the involved areas will be 63 Gy. This will be administered at 1.8 Gy daily, 5 days a week for total of 25 fractions (45 Gy) to the primary and mediastinum (primary planning target volume: 1^o PTV) followed by a boost to the primary and involved nodes (secondary planning target volume: 2^o PTV) to 2 Gy daily in 9 fractions (18 Gy). The total dose will be 63 Gy in 34 fractions in 7 weeks.
- 6.1.2** A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV), and planning target volume (PTV). 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, CTV, 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.
- 6.1.3** I.V. contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessel. If not, i.v. contrast should be given during the planning CT.
- 6.1.4** Optimal immobilization is critical for this protocol. Alpha cradle or approved alternate immobilization system is required. Alternate immobilization systems must be approved by the protocol chairman.

6.2 Technical Factors

6.2.1 Beam Energy

- 6.2.1.1** Megavoltage equipment is required with effective photon energies ≥ 6 MV.
- 6.2.1.2** 3-D conformal radiotherapy capabilities is required but not limited to the RTOG 3-D approved centers

6.2.2 Treatment Distance

Minimal treatment distance to skin should be ≥ 100 cm for SSD technique and minimum isocenter distance should be 100 cm for SAD techniques.

6.2.3 Blocking

Primary collimation and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.

6.2.4 Compensating Filters or Wedges

In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a two-dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

6.2.5 Therapy Interruptions

- 6.2.5.1** If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.
- 6.2.5.2** If more than one-week interruption is required, resumption of the treatment is at the discretion of the radiation oncologist.
- 6.2.5.3** Radiotherapy interruptions or delays will be permitted only for any \geq grade 3 non-hematologic toxicity or any grade 4 hematologic toxicity
- 6.2.5.4** If neutropenic fever occurs and radiation is withheld, G-CSF may be initiated to expedite neutrophil recovery. However, G-CSF may not be used on days that radiation is being administered.

6.3 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

- 6.3.1** Gross Tumor Volume (GTV) is defined by the physician as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor (GTV-P) and abnormally enlarged regional lymph nodes > 1.0 cm (*short axis measurement*) (GTV-N). These volume(s) may be disjoint. Note ICRU Report #50 also defines a clinical target volume (CTV) which includes the area of subclinical involvement around the GTV.

- 6.3.2** Planning Target Volumes (PTV) will be divided into primary planning target volume (1^o PTV) and secondary planning target volume (2^o PTV).

- 6.3.2.1** Primary planning target volume (1^o PTV) will provide margin around the CTV to provide subclinical regional nodal RT. A margin around the CTV will define the 1^o PTV. The 1^o PTV volume must include a minimum 2.0 cm margin and a maximum 2.5 cm margin around the CTV.

- 6.3.2.2** Secondary planning target volume (2^o PTV) will provide margin around the GTV to compensate for variabilities in treatment setup, breathing, or motion during treatment. A margin around the GTV will

define the 2° PTV. The 2° PTV volume must include a minimum 2.0 cm margin and a maximum 2.5 cm margin around the GTV.

6.3.2.3 Regional Nodal RT

The following lymph node regions must be included even in the absence of clinical or radiological involvement (to 45 Gy)

6.3.2.3.1 Elective treatment of supraclavicular nodes is not allowed.

6.3.2.3.2 Ipsilateral hilar lymph nodes - always (2 cm margin)

6.3.2.3.3 Superior mediastinal lymph nodes (above carina) - always (ipsilateral 2 cm margin).

6.3.2.3.4 Subcarinal lymph nodes (include the contralateral main stem bronchus and extend field at least to 3 cm below the carina) -always.

6.3.2.3.5 Inferior mediastinal nodes to the diaphragm (to bottom of T10) for patients with lower lobe lesions or inferior mediastinal involvement.

6.3.2.3.6 Contralateral hilar lymph nodes - for patients with contralateral mediastinal, or contralateral hilar involvement - (1 cm margin).

6.3.3 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). This is the point at which the doses used in this protocol will be prescribed. Every effort should be made to achieve dose homogeneity across PTV.

6.4 3D Planning

6.4.1 Planning Volume (PTV) - The PTV is to be treated with any combination of coplanar or noncoplanar three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D- planning to produce the optimal conformal plan in accordance with volume definitions.

6.5 Normal Tissue Volume and Tolerances

6.5.1 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 3-dimensional treatment plan. Physician/dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 2 Gy/fx (uncorrected).

ORGAN	VOLUME	TOLERANCE DOSE TD_{5/5}	END POINT
Lung	Ipsilateral whole lung Contralateral lung (only if necessary)	25 Gy 20 Gy	Clinical Pneumonitis
Esophagus	1/3 2/3 3/3	65 Gy 58 Gy 55 Gy	Clinical Stricture and Perforation
Brachial Plexus	point dose	60 Gy	Clinically Manifested Nerve Damage
Spinal Cord	5 cm 10 cm 20 cm	50 Gy 50 Gy 47 Gy	Myelitis Myelitis Myelitis
Heart	1/3 2/3 3/3	66 Gy 50 Gy 40 Gy	Clinical Pericarditis Clinical Pericarditis Clinical Pericarditis
Liver	1/2 2/2	35 Gy 30 Gy	Clinical Hepatitis Clinical Hepatitis

6.5.3 It is expected that the dose to the lungs will be the primary dose-limiting structure. Every effort to keep the total lung dose to a minimum should be performed. Since most lung tumors are localized to one lung, efforts to keep the contralateral lung at a minimum should also be performed. The patient's overall lung function is evaluated by the FEV₁ and DLCO should also be evaluated in determining an individual's lung function reserve and thus the ability to radiate.

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

6.5.5 Total lung volume is defined as the lung volume of both lungs minus the PTV.

6.6 **Localization Films**

All fields treated require filming on simulator units. Portal verification must be done for all treated fields. Copies of both simulator and portal fields must be submitted to RTOG Headquarters as specified in Section 12.0.

6.7 **Dosimetry Monitoring**

The American Association of Physicists in Medicine (*Radiological Physics Center, Houston, TX*) may conduct a field survey of equipment.

6.8 **Compliance Criteria**

Total Dose Criteria	Field Borders	Score
≤ 5%	2 cm to < 2.5 cm	Per Protocol
> 5% to ≤ 10%	1 to < 2cm OR 2.5 to 3.5 cm	Variation, Acceptable
> 10%	< 1 cm OR > 3.5 cm	Deviation, Unacceptable

7.0 **DRUG THERAPY**

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

7.1 **Gemcitabine (*Gemzar*)**

7.1.1 Formulation: Vials of Gemzar contain either 200 mg or 1 gm of gemcitabine HCl (*expressed as free base*) formulated with mannitol (200 mg or 1 gm, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. (*Gemzar PI*).

7.1.2 Preparation: To make a 40-mg/ml final concentration, add 5 ml Normal Saline to the 200 mg size vial or 25 ml Normal Saline to the 1000-mg size vial.

7.1.3 Administration:

- Administer over 30 minutes.
- If the patient reports burning at the injection site, the infusion of gemcitabine is slowed to run in up to one hour. Infusion of gemcitabine should not last beyond one hour.
- Rash can be treated with topical therapy or the administration of diphenhydramine and dexamethasone prior to administration.
- Flu-like symptoms can be treated with acetaminophen.
- There may be some local irritation due to the low pH of the gemcitabine infusion (*pain at injection site*). Gemcitabine is not a vesicant; extravasation should be handled according to your local hospital policy concerning the extravasation of drugs.

7.1.4 Storage: Unreconstituted drug vials are stored at controlled room temperature. Reconstituted solutions should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

7.1.5 Adverse Effects:

- Hematologic - leukopenia, thrombocytopenia, and anemia.
- Gastrointestinal - nausea and vomiting.
- Others - changes in liver function, flu-like symptoms, swelling, tiredness, blood and protein in the urine, and in rare instances, pneumonia.

7.1.6 Supplier: Commercially available.

7.2 **Paclitaxel (*Taxol*) [9/11/03] Note: Sequence B (*Gemcitabine/Paclitaxel*) closed 5/22/03**

7.2.1 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.2.2 Preparation: A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (*Cremophor EL*) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D₅W,

USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (*DEHP*) plasticizer from polyvinyl chloride (*PVC*) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (*NOTE: acceptable limits established by the USP Particular Matter Test for LVP's*) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (*e.g.: Millex-GV Millipore Products*) into the i.v. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.2.3 Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion following gemcitabine. The paclitaxel is mixed in 500 or 1000 cc of D₅W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI%₀ with 0.22 m in-line filter. In order to maximize radiosensitization of paclitaxel, patients will proceed with thoracic radiation ½ to 1-½ hours after paclitaxel infusion has been completed. Paclitaxel will be administered via an infusion control device (*pump*) using non-PVC tubing and connectors, such as the i.v. administration sets (*polyethylene or polyolefin*) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

7.2.4 Storage: Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

7.2.5 Adverse Effects:

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhilitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (*SGOT, SGPT, bilirubin, alkaline phosphatase*) hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (*MI*), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory (*taste*), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions (*acute*), flushing, rash, pruritis.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (*erythema, induration, tenderness, rarely ulceration*), radiation recall reaction.

7.2.6 Supplier: Commercially available.

7.3 Carboplatin (Paraplatin)

7.3.1 Formulation: is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.3.2 Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

<u>Vial Strength</u>	<u>Diluent Volume</u>
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that Paraplatin solutions be discarded eight hours after dilution.

7.3.3 Administration (11/17/04): Carboplatin, at the appropriate dose and dilution, will be given over 30 minutes, immediately after gemcitabine. Dose of carboplatin (*mg*) = target AUC x (*GFR* + 25) with a creatinine clearance calculated by the Cockcroft-Gault Formula substituted for GFR,

$$\text{i.e.: } \frac{\text{GFR}}{(\text{serum creatinine})} = \frac{(140 - \text{age})(\text{kg wt})}{(72)} \times 0.85 \text{ (female) or } \times 1.0 \text{ (male)}$$

For example, a 60-year-old man with a serum creatinine of 1.0 and a weight of 72 kg will have a calculated GFR of 80 mg/min. On day 22 (*AUC* = 6.0), his dose of carboplatin would be 630 mg. NOTE: Aluminum reacts with Paraplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Paraplatin.

- 7.3.4** Storage: Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.
- 7.3.5** Adverse Effects: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte imbalance, hypomagnesemia, hypercalcemia and allergic reaction.
- 7.3.6** Supplier: Commercially available.

7.4 Chemotherapy Plan (9/11/03) Note: Sequence B (Gemcitabine/Paclitaxel) closed 5/22/03

- 7.4.1** General: This protocol will investigate the combined use of gemcitabine, carboplatin or gemcitabine, paclitaxel and radiation therapy followed by 2 cycles of chemotherapy. All patients will be pre-dosed with steroids, H-1 and H-2 blockers. See Section 7.4.7 for premedication.

Sequence A*			Sequence B* Closed 5/22/03		
Gemcitabine Dose (mg/m ² /wkly)	Carboplatin Dose (AUC)	Number of Patients	Gemcitabine Dose (mg/m ² /wkly)	Paclitaxel Dose (mg/m ² /wkly)	Number of Patients
Arm 1: 300	--	6	Arm 2: 300	30	6
Arm 3: 300	2	6	Arm 4: 450	30	6
Arm 5: 450	2	6	Arm 6: 450	40	6
Arm 7: 600	2	6	Arm 8: 600	40	6
Arm 9: 750	2	6	Arm 10: 600	50	6
Arm 11: 900	2	6	Arm 12: 750	50	6
			Arm 14: 900	50	6

*Both sequences will be followed by 2 cycles of adjuvant Gemcitabine-Carboplatin administered q 21 days commencing 3 weeks after the end of the chemoradiation.

- 7.4.2** Gemcitabine will be given at a starting dose of 300 mg/m²/week for both sequences. Conference calls will be regularly held with study chair, co-investigators, and other participating institutions. The gemcitabine and carboplatin or gemcitabine and paclitaxel will be delivered in the outpatient setting as an intravenous infusion on days 1, 8, 22, 29, and 43 of the planned radiation therapy course. Gemcitabine and paclitaxel doses will be escalated per schema until DLT (*dose-limiting toxicity*) is determined.
- 7.4.3** The treating medical oncologist has the option of delivering the weekly chemotherapy on Tuesdays, i.e., days 2, 9, 23, 30, and 44. Similarly, when there is Monday holiday, the weekly chemotherapy will be administered on Tuesdays. A one-day shift in the weekly chemotherapy will thus be allowed, as needed.

7.4.4 Gemcitabine

Gemcitabine will be administered by infusion over 30 minutes followed by carboplatin or paclitaxel on days 1, 8, 22, 29, and 43.

7.4.5 Paclitaxel (9/11/03) Note: Sequence B (Gemcitabine/Paclitaxel) closed 5/22/03

Paclitaxel will be given at a starting dose (*for first three patients*) of 30 mg/m²/week, i.v. by 1-hour continuous infusion (*on an outpatient basis*) on days 1, 8, 22, 29, and 43 following gemcitabine.

7.4.6 Carboplatin (11/17/04)

Carboplatin will be given at a dose of AUC 2.0 over 30 minutes immediately after gemcitabine on days 1, 8, 22, 29, and 43.

7.4.7 Premedications

The patient will be premedicated 30 minutes prior to paclitaxel with 1) dexamethasone-20 mg i.v. immediately (*or dexamethasone 20 mg orally 12 and 6 hours pre-paclitaxel*) in conjunction with 2) diphenhydramine-50mg i.v. and 3) ranitidine-50mg i.v. or cimetidine-300 mg i.v. or Pepcid at investigator's discretion. Patients may receive Compazine 10 mg i.v. or p.o. q 4 hr prn during paclitaxel infusion, or other antiemetic regimens at treating physician's discretion. Prior to carboplatin administration, the choice of antiemetics will be left to individual physician's discretion. Some suggestions include: ondansetron at a dose of 32 mg i.v. prior to carboplatin is recommended. Alternatively, a combination of lorazepam 1 mg; metoclopramide 1mg/kg; dexamethasone 10-20 mg; diphenhydramine 25-50 mg, repeated at reasonable intervals is appropriate. Prophylaxis against delayed nausea and vomiting is a consideration, e.g., a tapering dose of dexamethasone, with or without lorazepam, metoclopramide, or diphenhydramine.

7.4.8 Adjuvant Gemcitabine-Carboplatin

Three weeks after the end of the chemoradiation phase, patients will begin their adjuvant chemotherapy. They will receive two cycles of intravenous gemcitabine-carboplatin. The delivery schedule is as follows: gemcitabine (G) 1000 mg/m² i.v. days 71, 78 + carboplatin (AUC=5.5) i.v. day 71. This will be repeated once q 21 days.

7.5 Dose Modification, Toxicity & Management (2/11/03)

7.5.1 During Concurrent Chemoradiotherapy

7.5.1.1 Toxicities will be graded per the NCI Common Toxicity Criteria Version 2.0.

7.5.1.2 Patients who develop grade 4 myelosuppression or \geq grade 3 non-hematologic toxicity such as diarrhea, nausea, or vomiting should have the gemcitabine/carboplatin or gemcitabine/paclitaxel and radiation held for a week. If the toxicity does not resolve to \leq grade 1, the treatments will be held for an additional week. When resumed, the gemcitabine/ carboplatin or gemcitabine/paclitaxel will be reduced to the previous dose level and radiation will resume as initially planned. Every effort should be made to limit treatment interruptions to 1-2 weeks, and therapy should be restarted when toxicity \leq grade 1. Patients who develop grade 4 hematologic and \geq grade 3 non-hematologic toxicity which persists despite treatment interruptions and dose reductions, will be removed from protocol treatment.

7.5.1.3 For hemoglobin \leq 8 g/dL, patients should be transfused, but neither chemotherapy nor radiation should be interrupted. Erythropoietin may also be used to support the hemoglobin.

7.5.1.4 A dietician should be consulted if caloric intake declines and is associated with a weight loss of \geq 5% of the pre-treatment weight. If weight loss \geq 10% of pre-treatment weight occurs, then adequate nutritional intake must be ensured by dietary supplements, enteral alimentation, or i.v. nutrition. If radiotherapy is interrupted due to \geq grade 3 GI toxicity, gemcitabine/carboplatin or gemcitabine/paclitaxel should be held until radiotherapy can be resumed.

7.5.1.5 Radiation therapy may be interrupted for periods of up to one week for $>$ grade 3 esophagus toxicity, i.e., inability to tolerate liquids, whenever weight loss ($>$ 10% over 2 months) occurs and/or supplemental feedings are necessary. If radiotherapy is interrupted for any reason, gemcitabine/carboplatin or gemcitabine/paclitaxel should be held.

7.5.2 During Adjuvant Gemcitabine-Carboplatin

7.5.2.1 Toxicities will be graded per the NCI Common Toxicity Criteria Version 2.0.

7.5.2.2 Dose adjustments are based on Day of Treatment counts; see tables below:

Hematological Toxicity Dose Modifications (CTC Version 2.0)

ANC (cells/ μ L)		Platelet count (cells/ μ L)	Gemcitabine	Carboplatin
\geq 1,000	and	\geq 50,000	No change	No change
$<$ 1000	or	$<$ 50,000	Hold*	Hold*

*Repeat counts and resume chemotherapy at the -1 dose level (*see table below*) when ANC $>$ 1,000 and platelets $>$ 50,000. Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation courses.

Dose Levels of Gemcitabine and Carboplatin

	Starting Dose (mg/m ²)	Dose Level -1 (mg/m ²)
Gemcitabine	1000	750
Carboplatin	5.5	4

7.5.2.3 Carboplatin Dose Modifications for Renal Toxicity

A $>$ 25% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

7.5.2.4 Other Toxicities

For all other toxicities, which are grade \geq 3 (*except alopecia, nausea, vomiting, fatigue, and anorexia*), reduce carboplatin and gemcitabine by one dose level for subsequent doses within a cycle. Use CTC scale, Version 2.0 to score.

7.6 Toxicity Reporting

7.6.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

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.

7.6.2 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.6.2.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected.

7.6.2.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.6.2.3 Any death on study if clearly related to the commercial agent(s).

7.6.2.4 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.

7.6.3 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 (24 hours)
fax (301) 230-0159**

7.6.4 Special Reporting for this Study (fax 215/928-0153)

7.6.4.1 All grade ≥ 3 non-hematologic toxicities must be reported to RTOG within 24 hours.

7.6.4.2 All grade ≥ 4 hematologic toxicities must be reported to RTOG within 24 hours.

7.6.4.3 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Procedure	Pretreatment (see Section 4.0 for timing)	Weekly During Chemo/RT	After RX^a
History & Physical	X	X	X
Neurological Assessment	X	X	X
Height, Weight & KPS	X	X	X
Tumor Measurement	X		X
Chest x-ray, PA & LAT, EKG	X		X
Chest CT scan (<i>liver & adrenals</i>)	X		X ^b
CBC, diff, platelets	X	X	X
SMA-12 ^d , electrolytes, Mg ⁺⁺	X	X ^f	X
FVC, FEV ₁ , DLCO	X		X ^g
Pregnancy Test (<i>as applicable</i>)	X		
Metastatic Evaluation (<i>bone, brain</i>)	X		X ^c
Toxicity Evaluation		X ^e	X ^e

a. After completing radiation therapy, patients will be seen 3-6 weeks later, then every 3 months for one year, then every six months for 2 years, then annually. The follow-up intervals are calculated from start of RT.

- b. < 3 weeks post RT before the adjuvant chemotherapy begins to assess response to chemoradiotherapy and every 6 months for 2 years from start of RT, then annually. Note: When a chest CT scan is ordered, the chest x-ray can be omitted.
- c. When appropriate for new symptoms or findings.
- d. SMA-12: Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT and SGPT.
- e. See Section 12.0 for acute effects reporting on the FS form. Late effects will be reported on each Follow-up Form (F1).
- f. At least every 4 weeks or as frequently as needed to define drug toxicity.
- g. Every 6 months for 2 years from start of RT, then annually.

11.2 Evaluation During Study

- 11.2.1 An interval history and physical examination with particular attention to drug-induced side effects along with documentation of the patient's weight and performance status on each visit.
- 11.2.2 Weekly CBC, platelet count, differential AGC count, and serum creatinine.
- 11.2.3 An SMA-12, electrolytes, and MG++ shall be performed at least every 4 weeks or as frequently as needed to define drug toxicity.
- 11.2.4 Tumor measurements, response of each lesion, site and overall response shall be evaluated with every chest CT obtained at < 3 weeks post treatment and every 6 months for 2 years, then annually. Follow-up timing is based on the start of RT.
- 11.2.5 All relevant information regarding drug dosage, tumor response, laboratory examinations, and treatment-related toxicities must be recorded before each treatment is given.
- 11.2.6 After completing radiation therapy, patients will be seen according to the schedule in Section 11.0. Required studies for follow-up are listed in Section 11.0.
- 11.2.7 Assessment of late radiation effects will be made on all patients. This evaluation will be scored on the Follow-up Forms using the RTOG/EORTC Late Radiation Morbidity Scheme.

11.3 Criteria for Response

- 11.3.1 This study will use the NCI's Response Evaluation Criteria in Solid Tumors (*RECIST*). All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (*those with the longest diameter*) and their suitability for accurate repeated measurements (*by imaging techniques*). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.⁴⁶
- 11.3.2 Complete Response (CR): the disappearance of all target lesions.
- 11.3.3 Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions taking as reference the baseline sum longest diameter.
- 11.3.4 Progressive Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started.
- 11.3.5 Stable Disease: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking the smallest sum longest diameter since the treatment started.²³

11.4 Criteria for Removal from Protocol Treatment

- 11.4.1
 - 1) Disease progression at any time during therapy or the follow-up period. The patient should be re-staged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.
 - 2) The development of unacceptable toxicity defined as unpredictable, irreversible, or grade 4.
 - 3) Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up.
 - 4) The patient may elect to withdraw from study treatment at any time for any reason.
 - 5) All patients will be followed until death.

All reasons for discontinuation of treatment must be documented.

12.0 DATA COLLECTION

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

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of registration
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Study-Specific Flowsheets (SF)	Within 2 weeks of day 8, day 29, and day 43

(must include pretx lab values, ht, wt, calculated BSA, and 1st dose of chemo)

of concurrent chemotherapy; Within 2 weeks of completing each cycle of adjuvant chemotherapy.

Initial Dosimetry Information

Treatment Planning CT Scan (C1)

RT prescription (*Protocol Treatment Form*) (T2)

Initial Large Field Films (*simulation and portal*) (T3)

Calculations (T4)

Within 1 week of start of RT

Final Dosimetry Information:

Treatment Record (T5)

Isodose Distribution (T6)

Boost Films (*simulation and portal*) (T8)

Radiotherapy Form (T1)

Within 1 week of RT end

Initial Follow-up Form (FS) **

At 3 months (90 days) from RT start

Follow-up Form (F1)

At 6 months from start of RT, q 3 months for one year, then q 6 months x 2 years, then annually. Also at progression/relapse, onset of severe or unusual toxicity and at death.

Autopsy Report, final/microscopic (D3)

As applicable.

** This form collects the acute effects following completion of treatment. Submit at 90 days from RT start regardless of duration of RT. The FS is required on all patients at progression/relapse/death if these events occur within 90 days of RT start.

12.2 Timely Data Submission for Toxicity Evaluation

Timely data completion and submission is critical in order to meet the study's objectives for toxicity evaluation and to safely assign treatment levels. For this study, only institutions with a current data score of $\geq 80\%$ will be accepted for study participation.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (2/11/03)

13.1.1 Frequency of patients experiencing a dose limiting toxicity (DLT) to be used for the determination of the maximum tolerated dose (MTD) for each of the two protocol treatment combinations

13.2 Sample Size

13.2.1 Evaluation of Acute and Late Toxicity (2/11/03)

Patients will be followed for a minimum of 90 days from the start of radiation therapy and carefully evaluated with respect to treatment morbidity. A dose limiting toxicity (DLT) is defined as:

- 1) Acute grade 3 or 4 nonhematologic toxicities (*acute nonhematologic toxicity is defined to be a toxicity occurring from day 1 of study entry to day 1 of adjuvant chemotherapy or within 90 days from the start of radiotherapy treatment, which ever occurs first*) or grade 4 hematologic toxicities occurring during concurrent chemoradiation therapy;
- 2) Grade 3 or 4 pneumonitis or grade 3 or 4 delayed onset esophagitis occurring during the consolidation phase.

Asymptomatic grade 4 hematologic toxicities (*e.g. neutropenia, thrombocytopenia*) occurring during the consolidation phase will not be considered as DLTs. The study chairs will be reviewing reported toxicities, and if patients develop symptomatic grade 4 hematologic toxicities during the consolidation phase, the consolidation dose will be modified (*see Section 7.5.2*). Consolidation therapy doses will not be escalated.

The goal of this study is to establish the maximum tolerated dose (MTD) of each of the two versions of protocol treatment at which no patients will develop acute grade 5 toxicity and less than 50% of patients will develop acute dose limiting toxicities. If, at any time, a Grade 5 toxicity is observed, then accrual will be suspended for that treatment sequence, and the Study Chair will review the event. Furthermore, if the combined acute/late DLTs estimates the toxicity rate to be greater than 50% within a treatment

sequence (*obtained by time to event analysis*), at any time, at any dose level, then the Executive Committee will be notified and the committee will determine whether that arm should be closed.

13.2.2 Dose Escalation (9/11/03) Note: Sequence B (Gemcitabine/Paclitaxel) closed 5/22/03

This study consists of two separate sequences of dose escalation. Sequence A involves an escalation of gemcitabine administered concurrently with a constant carboplatin dose. Sequence B involves an escalation of gemcitabine while also escalating paclitaxel in an alternating stepwise fashion, such that only one of the drugs is escalated at a time. Both sequences are contingent on first testing 300g/m²/wk of gemcitabine alone (*Arm 1*). If this dose is considered acceptable (*as defined in the next paragraph*), then the two separate sequences of dose escalation will begin. Since only one arm will be open for accrual at a time, Arm 2 will be the first arm to follow Arm 1. As soon as Arm 2 accrual closes, then Arm 3 accrual may begin. From this point on, a new arm cannot open until dose acceptability has been determined for the preceding arm *within the sequence*. In addition, only one arm of the study will be open for accrual at time.

For each arm, six patients will be accrued. After 90 days of evaluation, the current dose will be considered acceptable if less than three of the six patients experience DLTs. In which case, dose escalation will occur by accruing six new patients to the next arm in the sequence. Otherwise, if three or more patients experience DLTs, the current dose will be considered too toxic and the preceding dose will be declared the MTD. At a given dose level, the probability of halting dose escalation when the true toxicity is 50% or higher is at least 66% (*power*). In addition, if the true DLT rate is instead 20%, there will still be a 10% probability of halting dose escalation at a given dose level (*type I error*). **Maximum size for the phase I portion of the study will be 78 patients.**

13.3 Patient Accrual

The patient accrual is projected to be 6 patients per month. At this rate, it will take one month for each dose escalation. With three months of evaluation required for each arm, the expected time for all arms to be accrued and evaluated is 29 months.

13.4 Inclusion of Women and Minorities

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer. However, the RTOG did not show this to be the case in a recent analysis.⁴⁴ Furthermore, an analysis of race did not indicate an association with outcome.⁴⁵ 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 have also considered the possible interaction between gender/to race and treatments.

The projected gender and minority accruals are shown below:

	White, not of Hispanic Origin	Hispanic	Black, not of Hispanic Origin	Native Hawaiian or other Pacific Islander	Asian	American Indian or Alaskan Native	Other or Unknown	Total
Female:	22	1	3	0	0	0	0	26
Male:	45	2	5	0	0	0	0	52
Unknown:	0	0	0	0	0	0	0	0
Total:	67	3	8	0	0	0	0	78

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APPENDIX I (4/27/04)

RTOG 0017

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE I STUDY OF GEMCITABINE, CARBOPLATIN OR GEMCITABINE, PACLITAXEL, AND RADIATION THERAPY FOLLOWED BY ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have lung cancer.

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.

WHY IS THIS STUDY BEING DONE? (9/11/03)

The purpose of this study is to find out the highest dose of the chemotherapy drugs, gemcitabine and carboplatin or gemcitabine and paclitaxel, that can be given in combination with radiation without causing severe side effects.

Note: Patients enrolling after May 22, 2003 will receive gemcitabine and carboplatin. The gemcitabine and paclitaxel portion of this study has been stopped due to side effects experienced by patients.

This research is being done because, although platinum-based therapy (like carboplatin) in combination with radiation may show some improvement in long-term outcome, currently, there is no truly effective treatment for this type of cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 78 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (9/11/03)

- All patients will receive:

Radiation Therapy:	You will receive radiation therapy once a day, five days a week, Monday-Friday, for seven weeks. All radiation therapy treatments will be given as an outpatient at your institution.
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Chemotherapy: There are two types of chemotherapy treatments that are being given. The first six patients treated on this study will receive gemcitabine alone to evaluate any drug reaction. The rest of the study patients will receive either: gemcitabine and paclitaxel or gemcitabine and carboplatin. Whether you receive carboplatin or paclitaxel with gemcitabine will depend on when you enter the study.

Note: Patients enrolling after May 22, 2003 will receive gemcitabine and carboplatin. The gemcitabine and paclitaxel portion of this study has been stopped due to side effects experienced by patients.

The chemotherapy will be given to you once a week during the first, second, fourth, fifth, and seventh week of radiation therapy. Gemcitabine and carboplatin will be injected into a vein (intravenously). Each treatment infusion will last for about one to one and a half hours. Your chemotherapy treatments will be given as an outpatient at your institution.

These chemotherapy treatments given with radiation will be followed by two other cycles of chemotherapy with gemcitabine (given weekly 2 weeks out of 3) and carboplatin (given once every 3 weeks) given alone. This chemotherapy will be given over a six-week period. It will be injected into a vein (intravenously).

If you take part in this study, you will have the following tests and procedures:

- Procedures that are part of regular cancer care and may be done even if you do not join the study.

<u>Procedure</u>	<u>Schedule</u>
Physical exam, blood counts, liver function test	Prior to study entry, weekly during treatment, and at follow-up visits
Chest CT scan, pulmonary function tests	Prior to study entry, after the radiation and every six months for 2 years, then yearly
Chest x-ray, tumor measurements	Prior to study entry and then at the completion of treatment

- Standard procedures being done because you are in this study.

Neurological exam	Prior to study entry, weekly during treatment, at the end of treatment
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Pregnancy test	Prior to study entry (if applicable)
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Bone scan and CT scan or MRI of the brain	Prior to study entry and then as medically indicated
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EKG	Prior to study entry
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Blood counts, chemistries, and follow-up visits may be more frequent because you are enrolled in a research study.

- Follow-up visits with your physician will be scheduled every three months for one year, then every six months for two years, and then annually for the rest of your life.

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy for seven weeks. During that time, chemotherapy will be given on weeks 1, 2, 4, 5, and 7. This will be followed by chemotherapy given for 2 cycles over 6 weeks. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, 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 early 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? (5/13/03)

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

Risks Associated with Radiation Therapy

Very Likely

- Difficulty, pain, or burning sensation when swallowing, which is temporary
- Tiredness, which is temporary
- Tanning, redness of skin in the treatment area, and hair loss within the treatment area, which is temporary
- Skin in treatment area may remain permanently dry, and chest hair may not grow back
- Decrease in blood counts while undergoing treatment, which may result in bleeding and bruising easily and in some cases, in severe and/or life-threatening infection
- Cough and some difficulty in breathing due to lung damage

Less Likely, But Serious

- Pericarditis - irritation of the heart sac
- Myocarditis - irritation of the heart muscle
- Transverse myelitis - irritation of the spinal cord
- Narrowing of the esophagus (feeding tube)
- Fistula formation between the esophagus and trachea (a hole that leads to an abnormal connection between the swallowing tube and windpipe)

Risks Associated with Paclitaxel (9/11/03) Note: Patients enrolling after May 22, 2003 will receive gemcitabine and carboplatin. The gemcitabine and paclitaxel portion of this study has been stopped due to side effects experienced by patients; however, the risks associated with Paclitaxel remain in the consent for those patients who have received the gemcitabine/paclitaxel treatment.

Very Likely

- Slow pulse
- Loss of hair
- Tingling, numbness, burning pain in hands and feet
- Lower blood counts, which in some cases may lead to severe and/or life-threatening infection
- Gastrointestinal (stomach) discomforts
- Skin redness or rash

Less Likely

- Nausea and/or vomiting
- Diarrhea
- Anemia
- Headaches
- Blurred vision
- Skin or nail darkening
- Aches and pains in muscle joints
- Mouth sores

Less Likely, But Serious

Cardiovascular changes

Seizures

Severe rash called Stevens-Johnson Syndrome, which can cause fever and red sores in your mouth and eyes

Risks Associated with Gemcitabine

Very Likely

Lower blood counts, which in some cases may lead to severe and/or life-threatening infection

Nausea and/or vomiting

Tiredness

Less Likely

Skin rash

Constipation

Diarrhea

Fever

Hair loss

Pain

Shortness of breath

Sores in the mouth

Less Likely, But Serious

Change in liver function

Decrease in kidney function

Pneumonia

Risks Associated with Carboplatin

Very Likely

Tingling, numbness, burning pain
in hands and feet

Lower blood counts, which in some cases may lead to severe and/or life-threatening infection

Nausea and/or vomiting

Tiredness

Less Likely

Pain

Less Likely, But Serious

Allergic reactions

Change in liver function

Blurred vision

Hearing loss

Reproductive risks: Because the drug 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 your doctor 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 lung 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) other chemotherapy; or (3) 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? (9/11/03)

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 Philadelphia office of the American College of Radiology (ACR). 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), the Radiation Therapy Oncology Group (RTOG), and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS? (5/13/03)

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 issues.

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

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

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

A Data Safety and Monitoring Board, 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 (5/13/03)

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 legally authorized 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
ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 5th Edition)

TNM CATEGORIES (Note Definitions)

Primary Tumor (T)

- TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
- T0** No evidence of primary tumor.
- Tis** Carcinoma *in situ*.
- T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (*i.e., not in the main bronchus*).
- T2** Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
- T3** Tumor of any size that directly invades any of the following: chest wall (*including superior sulcus tumors*), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
- T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

***Note:** The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

****Note:** Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathological examination of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed.
- N0** No regional lymph nodes metastasis.
- N1** Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.
- N2** Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).
- N3** Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

APPENDIX III (cont'd)

**ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 5th Edition)**

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present

Note: M1 includes separate tumor nodule(s) in a different lobe (*ipsilateral or contralateral*)

STAGE GROUPING

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

APPENDIX IV (5/13/03)

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

i. Phase I Studies Utilizing Investigational Agents

- | | |
|---|---|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |
| - All life threatening (<i>grade 4</i>) events which may be due to agent. | As above |
| - First occurrence of any toxicity (<i>regardless of grade</i>). | Report by phone within 24 hours to IDB <u>drug</u> monitor and RTOG Headquarters.
**A written report may be required. |

ii. Phase II, III Studies Utilizing Investigational Agents

- | | |
|---|---|
| - All fatal (<i>grade 5</i>) and life threatening (<i>grade 4</i>) <u>known</u> adverse reactions due to investigational agent. | Report by phone to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within 10 working days with a copy to IDB.
(<i>Grade 4 myelosuppression not reported to IDB</i>) |
| - All fatal (<i>grade 5</i>) and life threatening (<i>grade 4</i>) <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent. | Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours .
**A written report to follow within 10 working days. |
| - All grade 2, 3 <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent. | **Report in writing to RTOG Headquarters and IDB within 10 working days. |

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