RADIATION THERAPY ONCOLOGY GROUP

RTOG 0117

A PHASE I/II DOSE INTENSIFICATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY AND CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER

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RTOG 0117 ***(2/2/05)***

A PHASE I/II DOSE INTENSIFICATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY AND CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER

SCHEMA ***(10/28/04) (11/21/05)***

Arm	Radiation Therapy*	Chemotherapy**	Optional Adjuvant Chemotherapy
1	75.25 Gy/35 fx *(2.15 Gy per fraction)* **Arm 1 completed 9-26-02**	Paclitaxel 50 mg/m^2, over 1 hour, days 1, 8, 15, 22, 29, 36, 43 followed by Carboplatin AUC=2, over 30 minutes, days 1, 8, 15, 22, 29, 36, 43	Paclitaxel and carboplatin: two cycles, the first cycle at least 3 weeks after the last day of radiation therapy and the second cycle 3 weeks after the first cycle
2	74 Gy/37 fx *(2.0 Gy per fraction)* **Arm 2 completed 1-13-04** **Phase I MTD**		
3	**Dose De-Escalation from Arm 2 not necessary** If necessary: 70 Gy/35 fx *(2.0 Gy per fraction)*		
4	**Phase II Component** 74 Gy/37 fx *(2.0 Gy per fraction)*		

* All prescription doses are at the ICRU-50 Reference Point
** Chemotherapy: concurrent beginning day 1 with RT

Following completion of the above Phase I portion of the study, we will proceed to a Phase II study testing the efficacy of the tolerated dose derived from Arm 1.
(10/28/04) **The MTD from the Phase I component of this study is 74 Gy/37 fractions *(2.0 Gy per fraction)*. The Phase II component of this study will follow all evaluable patients from Arm 2 and will accrue *(on Arm 4)* and follow an additional 46 patients.**

Eligibility: *(See Section 3.0 for details)* ***[8-15-02]***

- Histologically-proven, unresectable lung cancer of the following types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, non-small cell carcinoma.
- AJCC Stage I-IIIB if all detectable tumor can be encompassed by radiation therapy fields, including both the primary tumor and the involved regional lymph nodes.
- Granulocytes ≥ 1500/µl; platelets ≥ 100,000/µl; bilirubin < 1.5 mg/dl; AST *(SGOT)* < 2 ULN; serum creatinine ≤ 2.0 mg/dl.
- Zubrod Performance Status 0-1.
- Weight loss ≤ 5% in previous six months.
- Measurable disease on the 3D planning CT.
- $FEV_1 \geq 1.0$ L
- Atelectasis, if present, must be less than one lung.
- Evaluation of the total lung must be V20 ≤ 30%; a mean esophageal dose ≤ 34 Gy and the esophageal V55 ≤ 30%.
- No prior or concurrent malignancy except non-melanomatous skin cancer unless disease-free for one year or more; no prior lung cancer within last two years.
- No prior RT to thorax.
- No previous chemotherapy or previous biologic response modifiers for current lung cancer or within the past five *(5)* years.

(Continued on next page)

- No distant metastases or supraclavicular lymph node involvement or significant atelectasis.
- No pleural effusions, pericardial effusions or superior vena cava syndrome.
- No pregnant or lactating females.
- Signed study-specific informed consent prior to study entry.

Required Sample Size: 73 Maximum; 27 Patients for Phase I Component; 46 Patients for Phase II Component

RTOG Institution # _____

RTOG 0117 ***(2/2/05)*** **ELIGIBILITY CHECKLIST** ***(8-15-02)***

Case # _____ ***(page 1 of 2)***

_____(Y/N) 1. Has the histology been confirmed a nonsmall cell type *(squamous cell, adenocarcinoma, large cell, or non-small cell, not otherwise specified)*?

_____(I-IIIB) 2. What is the AJCC tumor stage?

_____(N) 3. Is there evidence of supraclavicular lymph node involvement?

_____(N) 4. Is there evidence of distant metastasis?

_____(Y) 5. Is there measurable disease on the 3D planning CT?

_____(N) 6. Is there significant atelectasis *(obscuring the definition of the GTV)*?

_____(Y) 7. Has the 3D treatment plan been completed **and** has the attending physician approved the dose-volume histograms as follows:

- _____(Y) Is the total lung V20 less than or equal to 30%?
- _____(Y) Is the esophagus V55 less than or equal to 30%?
- _____(Y) Is the esophagus mean dose less than or equal to 34 Gy?

_____(Y) 8. Can all detectable tumor be encompassed by the radiation fields?

_____(N) 9. Is there evidence of pericardial or pleural effusion*(s)*, or superior vena cava syndrome?

_____(N) 10. Has the patient undergone surgical resection or is the patient eligible for definitive surgery?

_____(N) 11. Other than non-melanomatous skin cancer, has the patient had a previous malignancy within the previous year?

_____(N) 12. Has the patient had previous lung cancer within the prior 2 years?

_____(N) 13. Has the patient received prior radiation therapy to the thorax?

_____(N) 14. Has the patient been treated with biologic response modifiers or chemotherapy for the current lung cancer or within the past five years?

_____(0-1) 15. What is the Zubrod Performance Status?

_____(Y) 16. Are all laboratory values within the range specified in Section 3.1.3?

_____(Y) 17. Is the $FEV_1 \geq$ 1.0 L?

_____(N) 18. Does the patient have atelectasis of an entire lung?

_____(N) 19. Has the patient had a weight loss of > 5% in the previous six months?

_____(Y) 20. Have all the required tests been performed and are they within the time frame specified in Section 4.0?

(cont'd on next page)

_____(N/NA) 21. If female, is the patient pregnant or lactating?

_____(Y/NA) 22. If patient has reproductive capability, has the patient agreed to utilize effective contraception?

The following questions will be asked at Study Registration: (1-16-03)

_____ 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. Medical Oncologist's Name

_____ 17. Treatment Start Date

_____ 18. Treatment Assignment

_____ (N) 19. Is this patient going to receive IMRT?

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background Information

The "standard of care" for the dose, volume and beam arrangements for the treatment of non-small cell lung cancer *(NSCLC)* were established by the Radiation Therapy Oncology Group *(RTOG)* dose-escalation trial 7301.[1] In this study, 375 patients were randomly assigned to receive either 40 Gy in 4 weeks with a 2-week break *(split-course)*, 40 Gy in 4 weeks, 50 Gy in 5 weeks, or 60 Gy in 6 weeks. The complete and partial response rates *(as assessed clinically and radiographically)* were 48% in patients treated with 40 Gy, 53% in those treated with 50 Gy, and 56% in those receiving 60 Gy. The incidence of local failure *(also evaluated clinically)* was lower in patients treated with 60 Gy *(33%)* than in those receiving 50 Gy *(39%)* or 40 Gy *(44%-49%)*. Perez and co-workers[2] reported that irradiation technique clearly affected results. Patients with major deviation from protocol compliance had poorer response rates and decreased survival. In this protocol large volumes of the chest and regional lymphatics were included in the treatment volume. The electively irradiated areas included both hila, bilateral regions of the mediastinum, bilateral supraclavicular areas and 5-8 cm below the carina of the inferior mediastinum. Despite a modest improvement at three years, by five years the overall survival was approximately 5%.

In the early 1990's, the results of several large randomized trials reported increased survival with the addition of cisplatin-based chemotherapy.[3,4,5] Each of these trials utilized conventional radiation therapy and delivered 40-50 Gy to the elective nodal regions and 60-65 Gy to the gross disease. Despite the modest improvement demonstrated in these trials, there remains much room for improvement. Long-term survival is still only 8-14%.[3,5] LeChevalier and co-workers[4] reported a decreased metastatic incidence, but both arms had a local control rate of only 15-17% when evaluated by bronchoscopy and biopsy at 3 months and 10% at 2 years after completion of therapy. These results are considerably lower than the local control rates of 40-60% reported by soft clinical evaluation.[1,2] Perhaps contributing to poor local control was the uncertainty of target delineation and localization. Dillman and associates reported that a retrospective quality control review identified 23% of cases in which portal films failed to completely encompass the tumor.[3]

In addition, lung cancers are usually quite large at presentation. It is the norm to have bulky tumors measuring greater than 2-5 cm. From basic principles advocated by Fletcher, it is thought that doses up to 100 Gy may be necessary to sterilize the size of tumors frequently treated in bronchogenic carcinoma.[6] More recent publications suggest that dose escalation of portions of the GTV may be therapeutically advantageous.[7,8]

Further attempts at dose escalation were carried out in the RTOG prospective hyperfractionation trial 8301.[9] Fractions of 1.2 Gy were administered twice daily and patients were dose escalated through 60 Gy, 64.8 Gy, 69.6 Gy, 74.4 Gy and 79.2 Gy. Among the 519 patients, 248 were considered favorable *(absence of weight loss and a Karnofsky performance status of 70-100)*. Although no significant difference in disease-free survival was found in the unfavorable patients among the five arms, among the favorable patients a survival benefit was seen at the 69.6 Gy dose level but not higher. The reasons for this have never been fully elucidated, although a higher incidence of high-grade pneumonitis was seen in the higher dose arms of the study. This suggested that indiscriminate dose escalation, without knowledge of dose and volume effects to the surrounding lungs, may have a deleterious effect on survival. It is well known that the lungs are exquisitely sensitive to the damaging effects of radiation resulting in a significant chance for injury including acute pneumonitis and symptomatic pulmonary fibrosis.[10,11] What is less well understood or quantitated is the impact of radiation lung damage on long-term survival.

1.2 3D Treatment Planning Studies

Assessment of normal tissue toxicity early studies with 3DRTP were computer-simulated studies comparing 3D with conventional 2D treatment plans for lung cancer.[12,13,14,15,16] In each of these studies the authors demonstrated the improvement in treatment planning by either dose escalation, reduction in dose to surrounding organs, or both. The authors concluded that 3D planning potentially improved tumor target delineation and target volume coverage.[12,15] It appeared that traditional beam arrangements were inadequate or potentially harmful *(in terms of normal lung irradiation effects)* in the delivery of target doses of greater than 70 Gy.[14,15]

The development of acute pneumonitis is an undesirable and potentially debilitating or even fatal complication after radiation therapy to the chest. The doses of radiation that cause either acute radiation pneumonitis or chronic radiation fibrosis have only been partially characterized.

Emami and co-workers gathered data of available literature and published initial estimates of partial volume lung tolerance.[13] The data published normal tissue tolerance doses for a 5% *(TD5/5)* and 50 % *(TD50/5)* chance of a complication occurring by five years of uniform irradiation of one-third, two-thirds and whole lung. The TD50/5 for whole lung was 17.5 Gy, for two-thirds of the lung it was 30 Gy and for one-third of the lung it was 45 Gy.

Martel and co-workers retrospectively reviewed the 3D dose volume histograms *(DVH)* for the lungs of 21 patients with Hodgkin's disease and 42 lung cancer patients with the development of acute pneumonitis.[17] The authors reported a reasonable prediction for low versus high risk for the development of pneumonitis by dividing the patients into risk groups based upon the calculation of the effective volume *(Veff)* of the total lung volume *(both lungs together)*. There were differences in the mean lung dose between patients with complications versus no complications for both groups of patients. Patients without the development of acute pneumonitis had mean lung doses of 18-21 Gy *(average doses)*, vs. 24-26.1 Gy *(average doses)* for patients with acute pneumonitis. A study by Oetzel and coworkers showed good correlation for the pneumonitis risk estimations with observed complication rates for ipsilateral lung DVHs, but not paired lungs *(or total lung volume)*.[18] Mean lung dose differed somewhat for patients with and without complications *(23.8 Gy vs. 20.1 Gy)*. Marks and co-workers found the total lung NTCP was the single best predictor for pulmonary symptoms after irradiation.[19] The V30 *(volume receiving > 30 Gy)* was also a strong predictor. Graham et al. reported the single best predictor of acute pneumonitis was the V20 *(volume of total lung receiving > 20 Gy)*, although on univariate analysis both Veff and total lung mean dose were also correlated with acute pneumonitis.[20] Kwa et al. pooled the data from five institutions *(University of Michigan, University of Heidelberg, Washington University, Duke University and Netherlands Cancer Institute)* for a total of 540 patients.[21] Mean lung dose was the only dosimetric parameter collected. Increasing mean lung dose correlated well with the increasing pneumonitis rate.

Graham and co-workers reported the correlation between the V20 and actuarial incidence of $\geq$ Grade 2 pneumonitis to be very strong *($p=0.001$)*.[20] When the V20 was <22% the incidence of pneumonitis was 0. When the V20 was 22-31%, 32-40% and >40% the actuarial incidence of pneumonitis was 7%, 13%, and 36% respectively. Graham reported the severity of pneumonitis to also be related to the V20.[20] *(Table 1)*

Table 1: Acute Pneumonitis and Severity

V20*(%)*	Grade 2*(%)*	Grade 3(%)
< 22	0	0
22-31	7	0
32-40	13	5 *(1 fatal)*
> 40	36	23 *(3 fatal)*

Graham also reported the very close relationship between the V20, Veff and mean lung dose.[16] She reported that from the Washington University data, upon multivariate analysis the V20 was the single best predictor of acute pneumonitis.[20]

1.3 Results of Clinical Trials *(8-15-02)*

The results of single institution 3D clinical trials for NSCLC are shown in Table 2.

Table 2: Results of Clinical Trials for NSCLC using 3D CRT

Institution	Number of Patients	Dose	Median	Survival 1yr*(%)*	Survival 2yr*(%)*	Survival 3yr*(%)*
University of Michigan[22]	88	> 60 Gy	15 mo	-	37	15
University of Chicago[23]	37	60-70 Gy	19.5 mo	75	37	-
Memorial Sloan Kettering[24]	45	64-72 Gy	16 mo	-	33	-
Washington University[25]	126	60-74 Gy	21.5 mo	57	43	29

Because these were early trials before the use of significant dose escalation the doses treated ranged from 60-74 Gy. These reports thus represent the results of more standard doses but with the technical support such as BEV and 3D dose calculation. One can see that the results appear only marginally better than those from the large chemoradiation trials of the early 1990's. Of course, one must be cautious about any significant conclusions because these are single institution trials.

The RTOG has further tested dose escalation in the multi-institutional setting with RTOG 9311. This protocol was the first multi-institutional trial to utilize 3D therapy in lung cancer. To date the trial has successfully *(without acute pneumonitis)* escalated the dose of radiation therapy to 83.8 Gy *(conventional fractionation with once daily treatment given in 2.15 Gy per fraction)* in a selected population of patients. This trial was unique in several aspects from previous radiation therapy trials. Based on data from Washington University and the University of Michigan, it stratified patients for their risk of developing pneumonitis based upon the percent volume of the total lung exceeding 20 Gy. This factor has been shown to be highly correlated with the incidence of acute high-grade pneumonitis[20]. The second unique aspect of the RTOG 9311 trial was that it was the first multi-institutional trial to eliminate elective nodal irradiation, primarily to reduce the amount of lung irradiated and the risk of pneumonitis. Preliminary results of this trial indicate reports of no significant acute lung toxicity but 2/94 patients have developed Grade 3 esophageal late toxicity and 3/93 patients have developed late Grade 3 lung toxicity.

(2/2/05) As per our initial statistical guidelines described in Section 13.1 of this protocol, our primary endpoint for the Phase I portion of the 0117 study was to establish the maximum tolerated dose *(MTD)* of radiotherapy, in terms of Gy per fraction, that can be delivered using three-dimensional conformal radiation treatment *(3D-CRT)* concurrently with Taxol® and carboplatin chemotherapy. We have evaluated seven patients on the initial dose level (Arm 1) of this trial (75.25 Gy/35 fractions). We experienced two dose-limiting toxicities at this dose level, one patient with Grade 3 pneumonitis and one patient with Grade 5 pneumonitis. Per statistical Section 13.2, seven evaluable patients were followed for a minimum of 90 days from the start of RT and were carefully evaluated with respect to treatment morbidity. There was one acute DLT observed in the first 5 patients *(1/5)* and one acute DLT observed in the last two patients *(1/2)*. Therefore, our initial dose level was not acceptable due to pneumonitis toxicity. We propose to de-escalate the radiation dose from the initial dose level of 75.25 Gy in 35 fractions. Our de-escalation scheme will be as follows: 74 Gy in 37 fractions in Arm 2 and 70 Gy in 35 fractions in Arm 3, if necessary. Our primary objective is unchanged, which is to establish the MTD of radiotherapy that can be delivered using 3D-CRT concurrently with Taxol® and carboplatin chemotherapy.

The entry criteria for patients treated on this study are listed in Section 3.0 of this protocol and will remain unchanged for the de-escalation phase of the study. The amendments to the study consist of two changes. 1.) The total dose will be de-escalated from the Arm 1 level of 75.25 Gy and 2.) the fraction size will be decreased from 2.15 Gy to 2 Gy.

There are institutional data to suggest that a dose of 74 Gy is tolerable in the setting of concurrent weekly carboplatin and Taxol® chemotherapy. Rosenman et al. recently reported results from a Phase I/II trial escalating the radiation dose to 74 Gy in patients with Stage IIIA/B non-small cell lung cancer[65]. Patients received two cycles of carboplatin (AUC=6) and Taxol® (225 mg/m^2) on days 1 and 22, followed by concurrent weekly chemotherapy with daily radiation therapy beginning on day 43. Chemotherapy consisted of carboplatin (AUC=2) and Taxol® (45 mg/m^2) delivered weekly during radiation therapy. Radiation therapy was delivered in 2 Gy fractions and was escalated to total doses of 60, 66, 70, and 74 Gy. The authors reported one case of Grade 3 esophagitis at each dose level of 66, 70, and 74 Gy (3 patients with Grade 3 esophagitis out of 29 enrolled on phase I portion of study). Grade 3 and 4 toxicities observed on the phase II portion of the study with patients receiving 74 Gy were limited to one case of Grade 3 esophagitis (1 in 32 patients) and one case of Grade 3 malaise (1 in 32 patients). No cases of radiation pneumonitis were observed.

Based on these data, we have chosen to de-escalate the radiation dose from 75.25 Gy in 35 fractions to 74 Gy in 37 fractions with concurrent chemotherapy. The corresponding biological equivalent dose (BED) calculations comparing conventional radiation doses (63 Gy as in RTOG 9410) to the arms of this trial are as follows:

Table 3:

	Regimen	Total Dose (Gy)	Fraction size	Number of Fractions	Number of Days	Fractions per Day	Gy 10 BED	Gy 3 BED
1.	Standard	63	1.8	35	47	1	74.3	101
2.	93-11 # 1	70.9	2.15	33	47	1	86.1	122
3.	93-11 # 2	77.4	2.15	36	50	1	94	133
4.	93-11 # 3	83.8	2.15	39	53	1	101.8	144
5.	93-11 # 4	90.3	2.15	42	58	1	109.7	155
6.	0117 # 1	75.25	2.15	35	47	1	91.4	129
7.	0117 # 2	74	2	37	51	1	88.9	123
8.	0117 # 3	70	2.0	35	49	1	84	117

1.4 Role of Chemotherapy

It has been clearly shown that systemic chemotherapy improves the outcome of patients with locally advanced non-small cell lung cancer.[3,4,5] Two cycles of induction chemotherapy with cisplatin and vinblastine over 5 weeks followed by radiation therapy *(60Gy)* has been shown to be superior to radiation therapy *(60Gy)* alone. There was a higher response rate *(56% vs. 43%)*, improved median survival *(14 months vs. 10 months)* and better overall 5-year survival *(17% vs. 7%)* with combined modality therapy over radiation alone.[3] These findings have been confirmed by the intergroup study, reported by Sause et al.[4] One year survival was superior in the combined modality arm *(60% vs. 46%)* and the median survival was 13.8 months for those who underwent combined modality therapy as opposed to 11.4 months for those who received only radiation therapy. In a study reported by LeChevalier, patients were randomized to receive induction chemotherapy consisting of lomustine, vindesine and cyclophosphamide followed by radiation therapy or radiation therapy alone.[5] The three-year survival was 12% in the combined modality arm and 4% in the single modality arm *($p<.02$)*. Interestingly, the increased survival rates in the patients receiving combined chemoradiation were attributed to decreased systemic relapse. In addition, meta-analysis published a few years ago revealed that combined modality therapy improved median survival from 10.3 to 12 months with a mean gain in life expectancy of approximately 2 months by the end of three years. [39]

Apart from eradicating micro-metastatic disease, the addition of chemotherapy during radiation therapy appears to enhance local control as well. The majority of drugs used in the treatment of non-small cell lung cancer have been found to be the "good radiosensitizers". It has been postulated that concomitant administration of chemotherapy along with radiation may improve the local control by either eradicating cells that are resistant to radiation therapy *(cells in S phase, hypoxic cells)* or by inhibiting the repair of potentially lethal or sublethal damage. Agents like paclitaxel have been shown to result in accumulation of cells in the G2/M phase, a phase during which cells are very sensitive to radiation induced cell kill.

There is some evidence to suggest that concurrent administration of chemotherapy along with radiation therapy may improve the outcome of patients with locally advanced non-small cell lung cancer compared with sequential administration of chemotherapy followed by radiation therapy. In a randomized trial comparing sequential administration of 2 cycles of mitomycin, vinblastine, cisplatin *(MVP)* followed by split course of radiation therapy versus concomitant administration of the same chemotherapy and split course of radiation therapy, Furuse et al. reported better outcome with concomitant chemo-radiation therapy.[40,54] In a randomized study conducted by the RTOG, *(RTOG 94-10)* 611 patients with newly diagnosed, unresectable stage II-III NSCLC were enrolled in a phase III trial comparing two concurrent chemotherapy and thoracic radiotherapy regimens to a standard sequential chemotherapy followed by radiotherapy. Of the 597 analyzable patients, the rates of Grade 3-4 non-hematologic toxicity rates were higher with concurrent than sequential therapy, but late toxicity rates were similar. Most importantly there were no increased mortality rates in the concurrent chemoradiation arm. With median and minimum potential follow-up times of 40 and 15 months respectively, the median survival for the concurrent chemotherapy and once a day radiation therapy was trending superior *(17.0 months vs. 14.6 months, respectively, $p=.08$)*.

Thus, it is clear that addition of chemotherapy to radiation results in improved survival over radiation therapy alone. The preliminary results suggest that concurrent chemoradiation may result in superior outcome than sequential chemoradiation.

The combination of chemotherapy with paclitaxel and carboplatin has become extremely popular in this country for the treatment of metastatic non-small cell lung cancer.[50] It has been shown that combination chemotherapy regimens consisting of paclitaxel and carboplatin is less toxic when compared with cisplatin containing regimens in two randomized studies in patients with metastatic non-small cell lung cancer.[41,42] The survival rates in the paclitaxel containing arms were identical to those of cisplatin containing arms.[42]

It has been shown that weekly administration of paclitaxel and carboplatin with concurrent radiation followed by two cycles of chemotherapy with paclitaxel, results in a response rate of 75% with a median survival of nearly 20 months in patients with locally advanced non-small cell lung cancer. The two-year survival rate was 38%. This regimen was well tolerated although 48% of the patients developed Grade III or IV esophagitis.[43]

Paclitaxel has also been administered on an every three-week schedule along with radiation therapy, instead of a weekly chemotherapy schedule.[44] It is unclear at the present time as to whether a weekly administration of chemotherapy is superior to an every three-week regimen in the setting of concurrent chemoradiation. It is conceivable that chemotherapy administered once every week may result in decreased toxicity while providing radiosensitization and systemic effect. Weekly chemotherapy administration is a commonly practiced method in the United States as proposed in this trial. ***(8-15-02)***

Given the promising results of paclitaxel containing chemoradiation therapy regimens and the potential of 3D conformal therapy to deliver higher tumoricidal doses with acceptable toxicities, as outlined above, it is justifiable to incorporate paclitaxel based chemotherapy regimens along with dose-intensified 3D conformal radiation therapy. We will evaluate two different schedules of chemotherapy administration.

1.4.1 Rationale for Optional Adjuvant Chemotherapy (11/21/05)

The use of adjuvant chemotherapy after the completion of concurrent chemoradiation therapy for Stage III NSCLC has increased. Its feasibility in a multicenter setting was demonstreated by the LAMP trial[66] as well as RTOG 0324.[67] The addition of full-dose adjuvant chemotherapy offers potentially effective treatment for micrometastatic disease as demonstrated in recent randomized adjuvant postoperative chemotherapy data.[68] This study (0117) is thus being amended to allow adjuvant chemotherapy, using the same agents that were used during concurrent chemotherapy.

2.0 OBJECTIVES

2.1 For the Phase I portion of the study, the primary objective is to establish the maximum tolerated dose *(MTD)* of radiotherapy, in terms of Gy per fraction, that can be delivered using three-dimensional conformal radiation treatment *(3D-CRT)* concurrently with Taxol® and carboplatin chemotherapy.

For the Phase II portion of the study, the primary objective is to estimate the percentage of patients that survive at least 12 months. ***(8-15-02)***

2.2 To evaluate the toxicity of concurrent Taxol® and carboplatin with 3D-CRT.

2.3 To identify partial organ tolerance doses for lung and esophagus when treating with involved field thoracic 3D-CRT combined concurrently with Taxol® and carboplatin.

2.4 To estimate complete response rate as defined by diagnostic CT performed 3 months after completion of all therapy.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically-proven, by biopsy or cytology, unresectable lung cancer of the following histologic types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, non-small cell carcinoma, not otherwise specified.

3.1.2 Patient with AJCC Stage I-IIIB if all detectable tumor can be encompassed by radiation therapy fields, including both the primary tumor and the involved regional lymph nodes.

3.1.3 Patients must have granulocytes $\geq$ 1500/μl; platelets $\geq$ 100,000/μl; bilirubin < 1.5 mg/dl; AST

(SGOT) < 2 ULN; serum creatinine ≤ 2.0 mg/dl.

3.1.4 Zubrod 0-1.

3.1.5 Weight loss ≤ 5% in the previous six months. ***(8-15-02)***

3.1.6 FEV_1 must be ≥ 1.0 L. ***(8-15-02)***

3.1.7 Patients must sign a study-specific informed consent form prior to study entry

3.1.8 Patients must have measurable disease on the 3D planning CT.

3.1.9 Patient must have a completed 3D plan and the attending physician must have reviewed and approved the dose volume histograms as follows: total lung V20 ≤ 30%, mean esophageal dose ≤ 34 Gy, and the esophageal V55 ≤ 30%. ***(8-15-02)***

3.1.10 Patients with reproductive capability must utilize effective contraception.

3.2 Ineligibility Criteria

3.2.1 Undifferentiated small cell *(oat cell or high grade neuroendocrine)* carcinoma, any stage.

3.2.2 Stage IV NSCLC.

3.2.3 Complete tumor resection, recurrent disease, or those patients eligible for definitive surgery.

3.2.4 Concurrent malignancy except non-melanomatous skin cancer or prior cancer unless disease-free for one year or more.

3.2.5 Prior radiation therapy to the thorax.

3.2.6 Eligible for currently open RTOG phase III lung protocols.

3.2.7 Previous chemotherapy or previous biologic response modifiers for current lung cancer or within the past five *(5)* years.

3.2.8 Distant metastases or supraclavicular lymph node involvement, or atelectasis of an entire lung. **(8-15-02)**

3.2.9 Patients who have not had the pre-treatment evaluations in Section 4.0 or evaluations performed > 8 weeks prior to study entry.

3.2.10 Patients with pleural effusions, pericardial effusions or superior vena cava syndrome.

3.2.11 Prior lung cancer within the last two years.

3.2.12 Patients who have significant atelectasis and in whom the CT definition of the gross tumor volume *(GTV)* is difficult to determine.

3.2.13 Pregnant or lactating females. It is not known what effects this treatment may have on the developing fetus.

4.0 PRETREATMENT EVALUATIONS

(All lab tests and radiographic studies should be done within 8 weeks prior to registration)

4.1 Complete history, physical examination, and evaluation of Zubrod Performance Status.

4.2 Pathological *(biopsy)* or cytologically proven non-small cell lung cancer.

4.3 CT with contrast of chest and upper abdomen to include the liver and adrenals; baseline brain MRI or CT scan.

4.4 Chest x-ray.

4.5 Bone scan, only if the patient has bone pain and/or and elevated alkaline phosphatase.

4.6 Pulmonary function tests - including DLCO and FEV_1

4.7 CBC; serum chemistry tests to include alkaline phosphatase, glucose, creatinine, electrolytes, AST *(SGOT*), and total bilirubin.

5.0 REGISTRATION PROCEDURES

5.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Appendix VI may enter patients to this study. The 3D questionnaire is to be sent to the Image-guided Therapy Center (ITC) for review prior to entering any cases. Upon review and successful completion of "DRY RUN" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study**. Institutions that have passed the QA criteria for RTOG 9311 do not need to repeat the credentialing procedure**. After the patient is registered to a treatment arm, the institution will submit the required data *(both hardcopy and digital)* to the ITC *(See Section 12.2)* and to the RTOG *(See Section 12.1)*. ***(1-16-03)***

5.2 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 Dose Specifications

6.1.1 The prescription dose will be specified at the ICRU-50 reference point which is defined in Section 6.4.3. 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 6.4.2.

6.1.2 The daily prescription dose at the ICRU reference point will be determined by the Arm of the protocol that is currently open to accrual and will be at the ICRU reference point.

6.1.3 The prescription dose to PTV *(Section 6.4.2)* shall be according to the following dose escalation schema: ***(1-16-03)***

RT - 3D treatment plan - no elective nodal irradiation

(10/28/04)

Arm 2 --74 Gy/37 fx *(2.0 Gy per fraction)** **Arm 2 completed 1-13-04; Phase I MTD**
Arm 3 – 70 Gy/35 fx *(2.0 Gy per fraction)* Dose De-Escalation from Arm 2 not necessary
Arm 4 – Phase II Component: 74 Gy/37 fx *(2.0 Gy per fraction)*
*All prescription doses are at the ICRU-50 Reference point.
(Only one dose level or Arm open at any one time)

6.1.4 The reported dose shall include the dose to the ICRU-50 Reference Point. The maximum point dose *(within the PTV)*, minimum point dose *(within the PTV)* will be reported.

6.1.5 The method used for tissue heterogeneity calculations shall be reported. Both the uncorrected and corrected dose distributions shall be calculated and submitted to the ITC. Dose escalations to be based on the **heterogeneity uncorrected** dose distribution.

We will continue to require that this trial be based on uncorrected dose distributions for two reasons. The first is that different institutions use different algorithms to calculate for heterogeneity corrections leading to potentially different dose levels that would be used within a given dose level on the protocol. Different dose calculation algorithms used by various radiation therapy institutions may result in significant variations in specific dose parameters such as ICRU point dose, mean dose, and various dose-volume histogram threshold parameters. For this reason, the uncorrected dose calculation algorithm (water density) should be used for this protocol and the stratification criteria thereof. Thus, we will require that each institution submit two plans, one with heterogeneity uncorrected doses *(upon which the dose is prescribed),* and the second with heterogeneity corrections *(for the same monitor units derived from the heterogeneity uncorrected plan)*, for the RTOG database. The heterogeneity corrected plan will usually have a higher reference point dose than the uncorrected *(prescription)* plan. ***(1-16-03)***

6.1.6 The percentage of total lung volume *(the volume of both lungs minus the PTV)* exceeding 20 Gy *(V20)* shall be $\leq$ 30%.

6.1.7 The total volume of the esophagus shall be contoured and the PTV should NOT be subtracted from this volume. The percentage of this esophageal volume exceeding 55 Gy *(V55)* shall be $\leq$ 30% and the mean esophageal dose shall be $\leq$ 34 Gy. ***(8-15-02)***

6.1.8 All radiation fields must be treated EVERY DAY. There are no field reductions, and all fields treat the same volume and must be treated each day. Unless approval has been obtained from the study chair, only one set of fields is to be planned and delivered over the entire course of therapy.

6.2 External Beam Equipment

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

6.2.2 3D conformal radiotherapy capabilities are required as defined and confirmed by the ITC. See Appendix VI for 3D Quality Assurance Guidelines. ***(1-16-03)***

6.3 Treatment Planning Imaging and Localization Requirements

6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volume *(GTV)* and planning target volume *(PTV)*. For this study the clinical target volume *(CTV)* will be considered equivalent to the gross target volume *(GTV)*. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having 3-5 mm thickness through the regions harboring gross tumor and grossly enlarged lymph 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 entire liver volume. The GTV, and PTV and normal organs will be outlined on all appropriate CT slices. Normal tissues to be contoured include both lungs *(as the total lung volume),* skin, heart, spinal cord, esophagus and liver.

6.3.2 I.V. contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT.

6.3.3 Optimal immobilization is critical for this protocol. Immobilization to assure reproducibility of the set up is necessary.

6.4 Volume and ICRU Reference Point Definitions

The definitions of volumes will be in accordance with the 1993 ICRU Report #50:[45]
Prescribing, Recording and Reporting Photon Beam Therapy.

6.4.1 *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).*[46,47,48,49] These volume*(s)* may be disjointed. Note ICRU Report #50 also defines a clinical target volume *(CTV)* which may include the area of subclinical involvement around the GTV. For this protocol, we have chosen to define the GTV=CTV.

6.4.2 *Planning Target Volume (PTV)* will provide margin around the GTV to compensate for variabilities in daily treatment setup and internal CTV motion due to breathing or motion during treatment. The PTV for which dose escalation will be occurring must include the entire GTV plus a minimum 3D margin of 10 mm. More margin may be necessary if the tumor movement is increased because of physiologic movement which should be checked, in most cases by fluoroscopy.

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

6.5 3D Planning

6.5.1 *Planning Volume (PTV)* - The PTV is to be treated with any combination of coplanar or noncoplanar 3-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. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures.

6.6 Normal Tissue Volume and Tolerances

6.6.1 The normal organs, including skin, lungs *(either as total, or contralateral and ipsilateral)*, esophagus, heart, liver, spinal cord, shall be contoured in their entirety.

6.6.2 The tolerance of the lungs are related to the volume of the organ*(s)* irradiated. Data from the Washington University[20] reported that high-grade acute pneumonitis did not occur when the V20 was < approximately 30%. The incidence and the grade or severity of pneumonitis was clearly related to the V20. In the Washington University data, maximum dose *(with conventional fractionation)* was not related to acute pneumonitis. For this protocol all eligible patients must have the V20 $\leq$ 30%. ***(1-16-03)***

6.6.3 The esophagus volume *(outer muscular contour)* must be contoured from the level of just below the larynx to the gastro-esophageal juncture. Oral contrast at the time of scanning is necessary to delineate the esophagus. The percentage of the esophageal volume exceeding 55 Gy shall be $\leq$ 30% and the mean esophageal dose shall be $\leq$ 34 Gy. If the esophageal dose exceeds this with the best plan possible, then the patient should not be treated on this protocol. ***(8-15-02)***

6.6.4 The maximum spinal cord *(point)* dose should not exceed **45 Gy. *(1-16-03)***

6.6.5 Partial volume tolerance data for heart is not available. The heart dose should be kept as low as possible. Whole heart dose should not exceed **40 Gy**.

6.6.6 The liver dose should be kept to a minimum. Half the liver should not exceed 35 Gy. The whole liver should not exceed **30 Gy**.

6.7 Treatment Verification

6.7.1 First day port films or portal images of each field must be obtained and sent to the Quality Assurance Center. Port films of each treated field must be obtained on the first treatment day along with an orthogonal pair *(AP and lateral)*. Subsequent films will be obtained weekly and must include, as a minimum, an orthogonal pair. Individual treatment field port films are at the discretion of the treating physicians after the first full set of films is obtained.

6.8 Quality Assurance of Target Volumes and Critical Structure Volumes

6.8.1 The ITC will perform a review of all designated critical structures and the PTV margin on the GTV. The study chair, or their designee will spot check the ITC reviews and will review all GTV definitions. ***(1-16-03)***

6.8.2 Each treatment shall be judged as documented in the Quality Assurance Guidelines.

6.9 Quality Assurance of Field Placement

The ITC will review the first day port and isocenter placement films. The study chair, or their designee will spot check the ITC reviews. *(1-16-03)*

6.10 Quality Assurance of Dose Distribution *(1-16-03)*

6.10.1 The ITC will display, and compare with hard copies, isodose distributions for the axial, sagittal, and coronal planes through the isocenter.

6.10.2 The ITC will display, compute and evaluate the dose-volume histograms for the PTV, designated critical structures, and unspecified tissues. In those cases where a deviation from protocol requirements is noted as part of this review, the submitted digital DVHs will be evaluated for comparable results.

6.10.3 Each treatment plan shall be scored as documented in the Quality Assurance Guidelines.

6.10.4 *Dose Heterogeneity* The maximum dose to the PTV should not exceed the prescription by >10%. The maximum point dose to critical normal structures outside the PTV including unspecified tissue should not exceed the prescription dose. In addition to the dosimetric normal structure limits noted above, the treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

6.11 RTOG 3D-CRT Summary of 1993 ICRU Report on Recommendations for Prescribing, Recording, and Reporting External Beam Radiation Therapy

6.11.1 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. The next paragraphs summarize the ICRU definitions which are relevant for this protocol.

6.11.2 The gross tumor volume *(GTV)* includes the known disease as determined by physical examination, imaging studies and other diagnostic information, such as mediastinoscopy. More than one GTV can be defined *(i.e. GTV-P or GTV-N)*. Though for purposes of this protocol all gross disease is called GTV. It does not need to be contiguous.

6.11.3 The clinical target volume *(CTV)* includes the area of subclinical involvement around the GTV. The CTV is the GTV plus the margin for micro extensions of the tumor. More than one CTV can be defined. For this protocol CTV=GTV.

6.11.4 The planning target 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 which contain the GTV *(e.g. respiration)* and size variations in the tissue containing the GTV. The PTV is a geometric concept.

6.12 Criteria for Toxicity

6.12.1 Acute and late toxicity related to radiation therapy includes fatigue, nausea and vomiting, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, pericarditis, myelitis, acute radiation pneumonitis, and late pulmonary fibrosis, and esophageal stricture. Grade 3 or 4 non-hematologic *(excluding nausea, vomiting, and alopecia)* and Grade 4 hematologic toxicities will be referred to as dose limiting toxicities *(DLT)*. ***(8-15-02)***

6.12.2 *Acute toxicity monitoring*: Acute *(≤ 90 days from RT start)* side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 2.0.

6.12.3 *Late toxicity monitoring*: Late *(> 90 days from RT start)* side effects will be evaluated and graded according to the RTOG Late Radiation Morbidity Scoring Scale. *(Appendix IV)*

6.12.4 All **fatal** toxicities *(Grade 5)* resulting from 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.

6.12.5 All life-threatening *(Grade 4)* toxicity 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.

6.12.6 Appropriate data forms, and if requested a written report, must be submitted to headquarters within 10 working days of the telephone report.

7.0 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 Chemotherapy for this protocol will be according to the schedule below. ***(8-15-02)***

7.2 Chemotherapy: concurrent beginning day 1 with RT:
Paclitaxel 50 mg/m^2, over 1 hour, days 1, 8, 15, 22, 29, 36, 43
Followed by Carboplatin AUC=2, over 30 minutes, days 1, 8, 15, 22, 29, 36, 43

The formula for the carboplatin dose is:

DOSE = AUC *(Calculated Creatinine Clearance + 25)*

Calculated Creatinine Clearance = $\frac{(140\text{-}age) \times Wt\ in\ Kg}{72 \times serum\ creatinine} \times .85$*(female)* 1.0*(male)*

Premedication Procedures

Prior to receiving paclitaxel all patients will receive the following premedications:

- Dexamethasone 10 mg i.v. prior to paclitaxel infusion
- Diphenhydramine 50 mg i.v. 30 minutes prior to paclitaxel infusion
- Cimetadine 300 mg i.v. *(or Ranitidine 50 mg or famotidine 20 mg)* 30 minutes prior to paclitaxel infusion) [***8-15-02]***

7.3 Paclitaxel

7.3.1 *Chemistry*

Paclitaxel *(5, 20-epoxy-1,2 ,4,7 ,10 ,13 -hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13 ester with (2R,3S)-N-benxoyl-3-phenylisoserine)* is a white to off-white powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly pilophilic, insoluble in water, and melts at around 216-217°C.

7.3.2 *Mechanism of Action*

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

7.3.3 *Known Side Effect and Toxicities*

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

7.3.4 *Pharmaceutical Data*

Prior to infusion, dilute paclitaxel concentrate in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for $\leq$ 27 hours at ambient temperature (~25°C; 77° F) and room lighting conditions. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. In order to minimize patient exposure to the plasticizer DEHP *(di-(2-ethyhexylphthalate)*, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles, *(glass, polyprophylene)* or plastic bags *(polypropylene, polyolefin)* and administered through polyethylene-lined administration sets. During administration, use of gloves in recommended. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

7.3.5 *Supply*

Commercially available.

7.4 Carboplatin *(paraplatin)*

7.4.1 *Chemistry*

The chemical name from carboplatin is platinum, diamine *(1,1-cyclobutane-dicarboxylate(2-)-0,0')-(SP-4-2)*. Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/ml, and the pH of a 1% solution is 5-7.

7.4.2 *Mechanism of Action*

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein crosslinks. This effect is apparently cell-cycle nonspecific.

7.4.3 *Pharmokinetics*

In patients with creatinine clearances of about 60ml/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300-500mg/m^2. The initial plasma

half-life was found to be 1.1-2 hours, and the postdistribution plasma half-life was found to be 2.6-5.9 hours. The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4L/hr, 16L and 3.5 hours, respectively. Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing compounds other than carboplatin are present in plasma. The major route of elimination of carboplatin is renal excretion.

7.4.4 *Known Side Effect and Toxicities*

Thrombocytopenia, neutropenia, leukopenia, anemia, infections, bleeding, requirement for transfusions, nausea and vomiting, peripheral neuropathies, ototoxicity, central neurotoxicity, serum creatinine elevations, blood urea elevations, bilirubin elevations, SGOT elevations, alkaline phosphatase elevations, electrolytes loss, pain, asthenia, cardiovascular, respiratory, genitourinary, alopecia, mucositis.

7.4.5 *Pharmaceutical Data*

When prepared as directed, solutions are stable for 8 hours at room temperature (25°C; 77° F). Because no antibacterial preservative is contained in the formulations, discard solutions 8 hours after dilution. Carboplatin is usually administered by an infusion lasting 15 minutes or longer. No pre-or post-treatment hydration or forced diuresis is required.

7.4.6 *Supply*

Commercially available.

7.5 Dose Modifications

Toxicities that can be directly attributable to chemotherapy will be scored using the NCI Common Toxicity Criteria, Version 2.0.

7.5.1 *Hematologic Toxicity*

7.5.1.1 Concurrent chemoradiotherapy: Dose modifications are based on the counts on the day of the treatment. Dose reductions are made for both carboplatin and paclitaxel.

Platelets	Granulocytes		
	≥ 1500/UL	1000-1499/UL	< 1000/UL
>75,000/UL	100%	50%	0
50,000-74,999/UL	50%	50%	0
<50,000/UL	0	0	0

If a dose is omitted, then counts are repeated weekly. Chemotherapy is resumed when the platelets are > 75,000 and granulocytes are > 1,500. If nadir of granulocytes is < 1,000, further chemotherapy is reduced 50%.

7.5.2 *Renal Toxicity*

The dose of carboplatin will be based on the creatinine clearance as above (Section 7.2).

7.5.3 *Neurotoxicity/CNS Toxicity*

Grade	Carboplatin	Paclitaxel
0-2	100%	100%
3	0	0

For Grade 3, omit until symptoms improve to Grade 1 or better. Subsequent chemotherapy is resumed at 75% dose level for both agents.

7.5.4 *Hypersensitivity Reactions*

Patients who have experienced Grade 4 toxicity will not receive paclitaxel. Patients who experience Grade 3 hypersensitivity will receive twice the dose of steroid premedications. Paclitaxel administration will be slower *(half the usual rate)* for the first hour infusion. The infusion rate will be increased during the latter two hours. The total duration of infusion will be three hours.

7.5.5 *Ototoxicity*

Patients who experience Grade 3 or more ototoxicity will not receive carboplatin any further.

7.5.6 *Cardiotoxicity*

If a patient develops chest pain, cardiac arrhythmia, or hypotension, they will not receive paclitaxel any further.

7.5.7 *Hepatotoxicity*

The dose adjustments needed only for paclitaxel:

AST *(SGOT)*	Bilirubin	Paclitaxel
< 2.0 ULN	≤ 1.5 mg/dl	100%
2.0 – 5.0 ULN	≤ 1.5 mg/dl	50%
> 5.0 ULN	≥ 1.5 mg/dl	0%

7.5.8 *Esophagitis or Mucositis*

For Grade 3 esophagitis or mucositis that is related to radiation therapy, hold paclitaxel, continue carboplatin and radiation. Resume paclitaxel at 50% of the dose when the toxicity has resolved to ≤ Grade 2. For Grade 4, hold all the protocol treatment. Resume therapy with radiation and carboplatin when the toxicity has resolved to ≤ Grade 2. Administer paclitaxel at 50% doses.

7.5.9 Grade 3 or 4 non-hematologic *(excluding nausea, vomiting, and alopecia)* and Grade 4 hematologic toxicities will be referred to as dose limiting toxicities *(DLT).* For all the other toxicities that exceed Grade 2 *(except alopecia, nausea and vomiting, weight loss, fatigue and anorexia)* further drug administration should be discontinued and/or the principal investigator notified**. (8-15-02)**

7.6 Adverse Drug Reaction Reporting Guidelines

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. ***(8-15-02)***

7.6.2 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents.

- Any unexpected (not listed in the package label), life threatening (Grade 4) or unexpected, fatal (Grade 5) adverse event with an attribution of possible, probable or definite should be reported in ten (10) working days. The AE should be reported on the FDA Form 3500 MedWatch (available from the FDA -www.fda.gov/medwatch.)

- The completed form should be forwarded to the FDA:

MedWatch
5600 Fishers Lane
Rockville, Maryland 20852-9787
Fax: *(800)* 332-0178

- A copy should be forwarded to the NCI:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
Fax*: (301)* 402-1584

7.6.3 Within 24 hours of discovery, the AE should be telephoned to RTOG Headquarters Data Management and to the Study Chairman; the report should be sent to RTOG within 10 working days.

7.6.4 Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery. ***(8-15-02)***

7.6.4.1 Special Reporting for this Study *(Fax 215/928-0153)*

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

7.6.4.1.2 All Grade ≥ 4 hematologic toxicities must be reported to RTOG within 24 hours.

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

7.7 Adjuvant Chemotherapy (11/21/05)

7.7.1 Adjuvant chemotherapy with carboplatin and paclitaxel is allowed after the completion of protocol treatment.

7.7.2 *Optional Adjuvant Therapy*

Adjuvant chemotherapy should begin no sooner than 3 weeks after the last day of radiation therapy (corresponding to approximately week #11 of overall therapy, assuming no interruptions). The paclitaxel and carboplatin will be given every 3 weeks for a total of 6 weeks (two cycles). Premedications will be given as per Section 7.2. Colony-stimulating factors (e.g., G-CSF) may be given per physician discretion. Paclitaxel will be administered at 200 mg/m² over 3 hours and carboplatin at AUC=6 IV over 30 minutes.

7.7.3 *Dose Levels for Adjuvant Therapy*

Dose Levels of Paclitaxel and Carboplatin for Adjuvant Therapy

	Starting Dose	Dose Level -1	Dose Level -2
Paclitaxel	200 mg/m²	150 mg/m²	NA
Carboplatin	AUC=6	AUC=4.5	NA

7.7.4 *Dose Modifications During Adjuvant Therapy*

7.7.4.1 *Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity*

Toxicity NCI CTCAE Grade (CTCAE v3.0)	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a, c]	**Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a, c]
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
3 (500-999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
4 (< 500/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Neutropenic fever	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Thrombocytopenia		
1 (≥ 75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000 - 74,999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
3 (25,000- 49,999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
4 (< 25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3
Other Hematologic toxicities Dose modifications for leukopenia are based on CTCAE, v3.0 and are the same as recommended for neutropenia above.		

[a]Dose levels are relative to the worst toxicities in the previous cycle. For adjuvant therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed.
[b]Repeat lab work weekly and resume chemotherapy based on this table.
[c]Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the adjuvant cycles.

7.7.4.2 *Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Adjuvant Therapy*

Worst Toxicity NCI CTCAE Grade (CTCAE v3.0)[a,d]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy**[b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy**[b]
Nail changes (paronychia)		
Grade 2	Maintain dose level	Maintain dose level
Neuropathy		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities[c]		
Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

[a]For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guidelines above.
[b]Dose levels are relative to the worst toxicities in the previous cycle.
[c]With the exception of allergic/hypersensitivity reaction (see Section 7.5.4), anorexia, and viral infections.
[d]Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

When a chemotherapy dose reduction is required during the adjuvant course of therapy, re-escalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

7.7.4.3 *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.

8.0 SURGERY

Does not apply to this study.

9.0 OTHER THERAPY

Does not apply to this study.

10.0 PATHOLOGY

Does not apply to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8-15-02) (11/21/05)

Assessments	Pre-treatment[a]	Weekly during RT	3 wks	6 wks	Before and during optional adjuvant chemotherapy	3 mos.	6 mos.	9 mos.	12 mos.[g]
H&P	X		X	X		X	X	X	X
Zubrod/Weight	X	X	X	X		X	X	X	X
Biopsy/Cytology	X								
PFT's *(including DLCO and FEV_1)*	X						X		X[b]
CXR	X			X					As indicated
CT Scan Chest[e]	X					X[d]	X[d]		X[c,d]
CT/MRI Brain	X								
Bone scan	X[f]	At follow-up as clinically indicated							
CBC	X	X	X	X	X				
Alk Phos, Glucose, Creatinine, Electrolytes, AST *(SGOT)*, Total Bilirubin	X	As indicated			X				
Toxicity Eval.		X	X	X	X	X	X	X	

a. Pretreatment tests and radiographic studies should be done within 8 weeks prior to registration.
b. At 6 and 12 months after treatment.
c. At 3, 6, and 12 months after treatment and annually as indicated.
d. CT scans should have 5 mm contiguous cuts through the region of the tumor and 5-10 mm cuts through upper region of the abdomen.
e. CT scan to include liver and adrenals.
f. If patient is symptomatic, has bone pain, and/or elevated alkaline phosphatase.
g. Evaluations after the first year are every 4 months for year 2; every 6 months for years 3-5; then annually.

11.2 Disease Response

11.2.1 The patient will be considered to be in local control if there is complete radiographic response at 3 months after treatment. If there is no evidence of progression of local tumor after 6 months time, then the patient will be considered to have "Absence of Progression". Length of survival with or without local control and/or "Absence of Progression" or distant metastasis will be recorded.

11.2.2 Patients who fail in the chest will be recorded as "in-field, primary", "in-field, nodal", "out-of-field, nodal", "out-of-field, lung parenchyma", "out-of-field, pleura".

11.3 Evaluation and Follow-up

11.3.1 *Evaluations During Treatment*

11.3.1.1 Patients will be seen and evaluated at least weekly during radiation therapy with documentation of tolerance, including acute reactions and weight.

11.3.2 *Evaluation Following Treatment*

11.3.2.1 At each visit the patient will have an interval history, complete physical examination and assessment of Zubrod performance status.

11.3.2.2 Patients will be evaluated every 3 months for the first year, every 4 months in the second year, every six months for the next 3 years and yearly thereafter.

11.3.2.3 A chest x-ray will be done at 6 weeks and annually as indicated.

11.3.2.4 Pulmonary function tests will be done at 6 and 12 months after treatment.

11.3.2.5 In an attempt to capture follow up radiologic data both for tumor and normal tissue effects, follow up CTs of the chest *(similar to the treatment planning scan)* should be obtained at 3 months and 12 months. In order that these follow up scans be in the ITC database, they will need to be sent either via direct transmission to the ITC, or a hard copy sent to the ITC to be digitized in. **(1-16-03)**

12.0 DATA COLLECTION (11/21/05)

(RTOG, 1818 Market Street, Suite 1600, Philadelphia, PA 19103)

12.1 Summary of Data Submission *(1-16-03) (11/21/05)*

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)**	Within 2 weeks of study entry
Radiotherapy Form **(T1)** (*copy to ITC*) Daily Treatment Record **(T5)**	Within 1 week of RT end
Treatment Form **(TF)**	Within 2 weeks of completion of Day 22 and Day 43 and within 2 weeks of completion of optional adjuvant chemotherapy, to include all pre-treatment and nadir lab values
Initial Followup Form **(FS)**	At Week 13 (*Day 90*) from start of RT
Follow-up Form **(F1)**	Every 3 months for first year; q 4 months for second year, every 6 months for next 3 years and yearly thereafter. Also at progression/relapse and at death.
Autopsy Report **(D3)**	As applicable

12.2 Summary of RT QA Requirements (ITC) *(1-16-03) (2-7-06)*

Preliminary Dosimetry Information:	Within 1 week of start of RT
Digital patient data (CT scans, critical normal structures, all GTV/CTV/PTV contours, doses for all fraction groups, DVHs for total dose plan)	
Simulation and port films	
Hard copy isodoses for total dose plan	
Digital Patient Submission Information Form (**T2**)	
Final Dosimetry Information	Within 1 week of end of RT
Digital patient data for any modified or changed planning data (contours, doses or DVHs)	
Hard copy isodoses for total dose plan if any changes made after initial submission.	
Simulation and port films for boost and/or field changes	
Copy of Daily Treatment Record	
Radiotherapy Form (**T1**) (*copy to RTOG)*	

12.2.1 *For Mail or Federal Express*:

Image-guided Therapy Center (ITC)
4511 Forest Park Avenue, Suite 200
St. Louis, MO 63108
Tel. 314/747-5414 Fax # 314/747-5423

12.2.2 *To send over Internet or using magnetic tape:*

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the ftp account assigned to the submitting institution shall be used and e-mail identifying the data set(s) being submitted shall be sent to :

itc@castor.wustl.edu

For tape submission, please contact the ITC about acceptable tape types and formats.

12.2.3 **(11/21/05)** See the ITC web site, accessible through the ATC web site, http//atc.wustl.edu, for additional helpful information, the current Facility Questionnaire document, Quality Assurance Guidelines and the Dry Run Guidelines as necessary for acquiring institutional credentials.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints *(8-15-02)*

13.1.1 *Primary Endpoint*

For the Phase I portion of the study: to establish the maximum tolerated dose *(MTD)* of radiotherapy, in terms of Gy per fraction, that can be delivered using three-dimensional conformal radiation treatment *(3D-CRT)* concurrently with Taxol® and carboplatin chemotherapy.

For the Phase II portion of the study: to estimate the percentage of patients who survive at least twelve months using three-dimensional conformal radiation treatment *(3D-CRT)* concurrently with Taxol® and carboplatin chemotherapy.

13.1.2 *Secondary Endpoints*

- To evaluate the toxicity of weekly concurrent Taxol® and carboplatin with 3D-CRT
- To identify partial organ tolerance doses for lung and esophagus when treating with involved field thoracic 3D-CRT combined concurrently with Taxol® and carboplatin
- To estimate complete response rate at 3 months after therapy.

13.2 Sample Size and Dose Escalation *(8-15-02, 1-16-03)*

Phase I Sample Size and Dose Escalation (Arm 1 Completed)

In order to establish the maximum tolerated dose *(MTD)* of radiotherapy, in terms of Gy per fraction, that can be delivered using three-dimensional conformal radiation treatment *(3D-CRT)* concurrently with Taxol® and carboplatin chemotherapy, acceptable morbidity criteria must be defined. Based on RTOG 9410, the dose limiting toxicity *(DLT: defined as a Grade 3 or Grade 4 non-hematologic toxicity ([excluding nausea, vomiting, and alopecia] and Grade 4 hematologic toxicities)* rate for this study is determined to be 40%. Each institution must be approved by the QA Center before beginning accrual. A more detailed description of these procedures is provided within the QA Guidelines Section of this protocol. When the QA Center approves an institution, that institution will be able to begin accruing to the highest available dose level.

Because the original Arm 1 dose was determined to be too toxic *(1/5 and 1/2 DLTs in the first seven patients evaluated),* a de-escalation to Arm 2, and if necessary, Arm 3 was implemented. Arm 1 is completed, so nine patients (to insure seven evaluable patients) will be accrued to Arm 2. Acute toxicity information will be collected. If Arm 2 is still too toxic, nine patients (to insure seven evaluable patients) will be accrued to Arm 3. DLTs from the treatment on Arm 2 and Arm 3, if necessary, will be determined as follows. After 7 evaluable patients have been followed for a minimum of 90 days from the start of RT, these patients will be carefully evaluated with respect to treatment morbidity. If there are no acute dose limiting toxicities *(DLTs: defined as a Grade 3 or 4 non-hematologic toxicity [excluding nausea, vomiting, and alopecia] and Grade 4 hematologic toxicities)* in the first 5 patients *(0/5)*, then the Arm 2 dose will be

deemed to be acceptable. If there is one acute DLT observed in the first 5 patients *(1/5)* and no acute DLTs observed in the last two patients *(0/2)*, then the dose will be deemed to be acceptable.

This design gives at least 90% confidence that the true acute DLT rate at a given dose level is less than 40% and for any given dose level, the probability of not escalating when the true toxicity rate is 40% or higher is at least 83%.

If at any time a Grade 5 toxicity *(death*) is observed, the accrual will be suspended and the event will be reviewed by the study chair. If the cumulative incidence (*obtained by time to event analysis*[51]*)* of combined acute/late DLTs estimates the toxicity rate to be greater than 40% at any time, for any dose level, then the Executive Committee will be notified and this committee will determine whether the dose level should be closed. This study is designed with 3 possible RT dose levels. If accrual for the 2nd de-escalated dose level (Arm 3) is necessary**,** then the **sample size required for the Phase I portion of the study is 27 patients *(9 for each dose level).***

Phase II Sample Size

The historical control for this study is the best arm of RTOG 94-10, Arm 2. The comparison of interest is the proportion of patients surviving at least 12 months. In RTOG 94-10, that proportion was 0.6233. Using a one-group χ^2 test with $\alpha = 0.10$ a sample size of 50 gives 87% power to detect a 25% or greater relative increase, or an absolute increase of at least 0.1558, in the proportion of patients surviving at least 12 months *(0.6233 versus 0.7791).* Using the 7 evaluable patients at the MTD from the Phase I portion of this study means that 43 additional evaluable patients will need to be accrued to the Phase II portion. Allowing for 5% of the patients accrued to be ineligible or inevaluable, 46 patients will need to be accrued to the Phase II portion. Combining the Phase I and II sample sizes, **the maximum sample size for this study is 73.**

13.3 Patient Accrual

RTOG 92-04 accrued approximately 8 patients per month and RTOG 93-11 accrued approximately 3 patients per month. Based on these two studies, the projected accrual for the current study is approximately 6 patients per month. If the average monthly accrual is less than 2 patients, the study will be reevaluated with respect to feasibility.

13.4 Analysis Plan *(8-15-02)*

13.4.1 *Interim Reporting of Accrual and Toxicity Data*

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

- the patient accrual rate with a projected completion date for open dose levels
- protocol compliance and the quality of the submitted data;
- distribution of important prognostic baseline variables;
- the frequency and severity of the toxicities.
- the cumulative incidence of acute/late toxicities.

Any problems will be reported to the RTOG Lung Committee and, if necessary, the Executive Committee, so that corrective action can be taken.

13.4.2 *Analysis for Reporting the Initial Treatment Results* *(1-16-03)*

This analysis will be undertaken when the MTD has been established for each sequence and each patient has been potentially followed for a minimum of 3 months following radiotherapy. The usual components of the analysis are:

- tabulation of all cases entered and those excluded from the analysis, with reasons for the exclusion;
- reporting institutional accrual;
- distribution of important prognostic baseline variables; and,
- observed results with respect to the endpoints described in Section 13.1. Further subgroup analyses will not be undertaken due to the small sample sizes.

The null and alternative hypotheses of the study's primary outcome, the overall two-year survival rate, are $H_o : p \le 0.6233$ and $H_a : p \ge 0.7791$. H_o and H_a will be tested with a Fleming single stage

Phase II procedure[64] using a one-sided 90% normal approximation confidence interval on 62.33%, the percentage of patients surviving at least twelve months under the best arm of RTOG 94-10. If the point estimate for twelve-month survival is less than or equal to 0.71113, the upper bound of the one-sided 90% confidence interval on 62.33%, then H_a is rejected and the conclusion is that the twelve-month survival rate did not statistically improve from 62.33% under the new treatment. If the point estimate is greater than 0.71113, then H_o will be rejected and the conclusion is that the twelve-month survival rate did improve from 62.33% to 77.91% under the new treatment.

13.5 Inclusion of Minorities *(8-15-02, 1-16-03)*

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender and treatments and race and treatments. 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.[52] Furthermore, an analysis of race did not indicate an association with outcome.[53] The participation rates of men and women will be examined according to Section 13.4.

The following table gives the projected number of patients in each race and gender group.

Planned Gender and Minority Inclusion

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	30	41	71
Ethnic Category: Total of all subjects*	31	42	**73**
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	1	2
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	0	0
White	28	38	66
More than one race	0	0	0
Racial Category: Total of all subjects*	31	42	**73**

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APPENDIX I

RTOG 0117 *(2/2/05)*

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE I/II DOSE INTENSIFICATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY AND CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH INOPERABLE, NON-SMALL CELL LUNG CANCER

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? (10/28/04)

The purpose of this study is to find out the highest dose of radiation that can be given with the drug combination of paclitaxel and carboplatin without causing severe side effects (Part 1 of the study). The radiation technique that is used in this study increases the radiation to the tumor area while decreasing the amount of radiation to normal tissues.

This research is being done because the addition of chemotherapy to radiation may show some improvement in long-term outcome (Part 2 of the study). There is clearly a probability of long-term survival when chemotherapy is given with radiation particularly in patients that have not experienced weight loss and who are able to carry on with their normal activities.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY (11-16-03)

About 73 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Radiation Therapy:

(8-15-02, 1-16-03)	You will receive radiation therapy once a day, five days a week for seven to eight weeks. The dose of radiation that you receive will depend on how many patients have entered the study before you and what kind of side effects these patients

have had. If you are entering into "Arm 2" of this study, you will get 37 treatments of radiation therapy at 2 Gy per day. If Arm 2 has too many side effects, the dose will be reduced to 35 treatments of radiation therapy at 2 Gy per day. All radiation therapy treatments will be given as an outpatient at your institution.

(10/28/04) Part 1 of this study was completed and found that Arm 2 (37 treatments at2 Gy) was the highest dose of radiation that can be given with the drug combination of paclitaxel and carboplatin without causing severe side effects. Part 2 of the study began on 8/3/04. All patients entered on Part 1 of the study will be followed as described below. Forty-six patients will be entered on Part 2 of the study and will receive 37 treatments at 2 Gy.

Chemotherapy **(11/21/05)**: You will receive paclitaxel and carboplatin once a week for seven weeks. This chemotherapy is delivered through a tube in your vein (intravenously) and will take about two hours.

After you complete treatment, you and your doctor will decide if you should receive two additional treatments with paclitaxel and carboplatin to prevent your cancer from coming back. The first of these additional treatments will be given three weeks or more after you finish radiation/chemotherapy, and the second will be given three weeks after the first. The treatments will be delivered intravenously and will each take about three hours.

You also may be given a medication to decrease the side effects of chemotherapy and radiotherapy. For example, you may be given medication to prevent nausea and vomiting, to stimulate the growth of new blood cells, or to reduce pain on swallowing.

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

Prior to study entry:

- History and physical exam
- Pulmonary function tests
- Blood tests
- Chest X-Ray
- CT Scan of the chest
- CT/MRI of the brain
- Additional X-rays or a bone scan will be done if indicated by your physician

Weekly during chemotherapy and radiation therapy together:

- Physical exam
- Blood tests

During followup:

- Physical exam – at 3 weeks, 6 weeks, 3 months, and then every 3 months for the first year, every 4 months in the second year, every 6 months for the next 3 years and then yearly after that
- Blood tests – at 3 weeks and 6 weeks
- Chest X-ray – at 6 weeks, then annually as indicated
- Pulmonary function tests – at 6 and 12 months after treatment
- CT scan of the chest – at 3, 6 and 12 months after treatment and then annually as indicated by your physician
- Additional X-rays or a bone scan will be done if indicated by your physician

HOW LONG WILL I BE IN THE STUDY? (6/10/04) (11/21/05)

You will receive radiation therapy for seven to eight weeks along with chemotherapy. If you have the two additional chemotherapy treatments, you will receive the first treatment three or more weeks after you finish radiation/chemotherapy and the second treatment three weeks after the first. 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, if your condition worsens, or if 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?

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.

Risks Associated with Radiation Therapy to the Chest

Very Likely

Difficulty, pain, or burning sensation when swallowing, which is temporary

Fatigue, which is temporary

Tanning, redness of skin, 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 that may result in bleeding and bruising easily

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 (requiring feeding tube)

Risks Associated with Paclitaxel

Very Likely

Low pulse
Low blood pressure
Loss of hair
Tingling, numbness, burning pain in hands and feet
Lower blood counts which can lead to a risk of infection and bleeding
Gastrointestinal discomforts
Skin redness or rash
Fatigue

Less Likely

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

Less Likely, But Serious

Cardiovascular changes in EKG
Seizures
Severe allergic reactions
Non-itching lesions in mouth and/or mucous membranes
Fever

Temporary changes in blood tests that measure liver function
Temporary "blind spots" in vision
Severe rash called Steven-Johnson syndrome which can cause fever and red sores in your mouth and eyes

Risks Associated with Carboplatin

Very Likely
Tingling, numbness, burning pain in hands and feet
Lower blood counts which can lead to a risk of infection and bleeding
Nausea and/or vomiting
Fatigue
Loss of hair

Less Likely
Weakness, loss of strength
Pain
Mouth Sores

Less Likely, But Serious
Allergic reactions
Cardiovascular changes
Respiratory changes
Temporary changes in blood tests which measure kidney and liver function
Blurred vision
Hearing loss

Reproductive risks: Because the treatment 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?

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),* 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? (1-16-03)

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

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

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

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name	Telephone Number

For information about this study, you may contact:

Name	Telephone Number

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

Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

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

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

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)*.

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	T*is*	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

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

APPENDIX IV

ORGAN TISSUE	0	*GRADE 1*	*GRADE 2*	*GRADE 3*	*GRADE 4*	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION EFFECTS
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low Grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatitic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bonesclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff *(215/574-3214)* within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to Grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(Grade 4)* events which may be due to agent.	As above

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

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

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

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

APPENDIX VI *(2/2/05)*

Quality Assurance Guidelines

The current version of the Quality Assurance Guidelines for **RTOG protocol 0117** must be obtained from the ITC web site:

http://itc.wustl.edu

The Quality Assurance Guidelines contain the following informational and directive items:

1. Background information to assist participants in meeting protocol specified radiation therapy treatment planning and delivery requirements.

2. Credentialling requirements to be completed for eligibility to enroll patients in the protocol.

    a. Facility Questionnaire assistance. Note : the Facility Questionnaire Form is available only from the ITC web site identified above. Only acquire this form in close time proximity to when it will be completed as it may be updated depending on protocol developments and modifications.
    b. Dry Run test requirements.

3. Patient digital data and hard copy data submission requirements.

4. Evaluation criteria and scoring system applied to submitted radiation therapy patient data.

    a. Scoring system for critical structures and tumor/target volumes.
    b. Scoring system for port and isocenter localization films.
    c. Scoring system for dose delivery analysis.
    d. Methods of obtaining scores assigned.