RADIATION THERAPY ONCOLOGY GROUP

RTOG 0241

PHASE I STUDY OF IRINOTECAN AND CISPLATIN IN COMBINATION WITH TWICE DAILY THORACIC RADIOTHERAPY (45 Gy) OR ONCE DAILY THORACIC RADIOTHERAPY (70 Gy) FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

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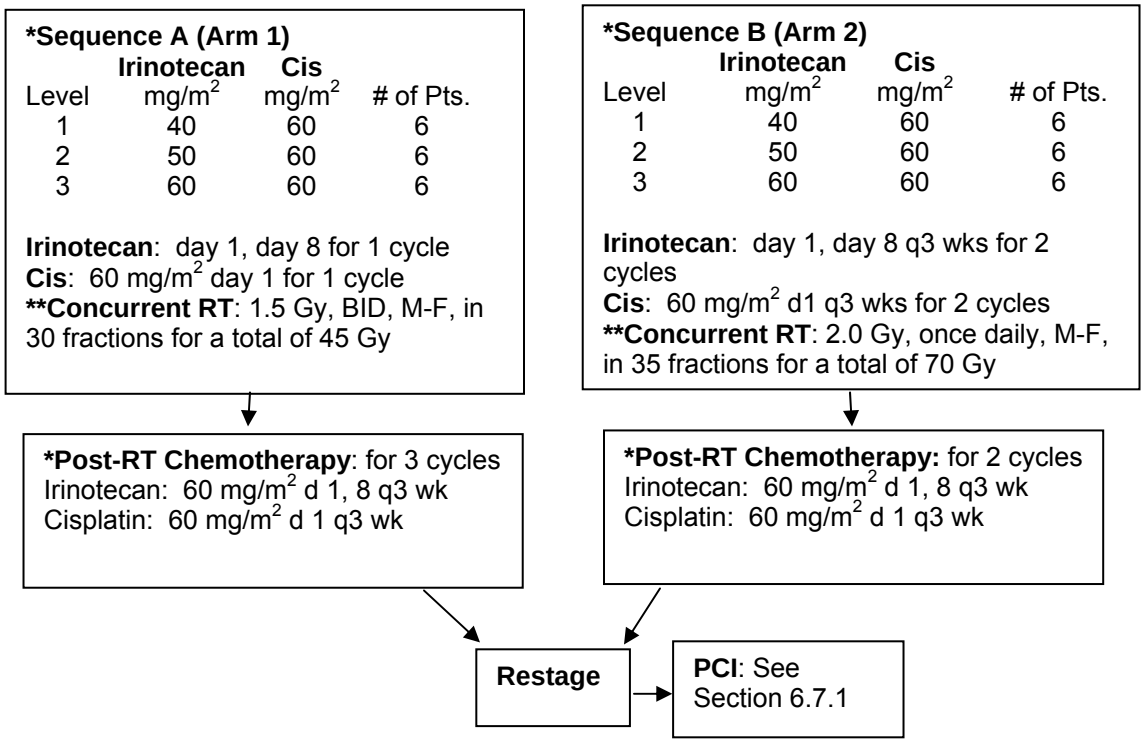
PHASE I STUDY OF IRINOTECAN AND CISPLATIN IN COMBINATION WITH TWICE DAILY THORACIC RADIOTHERAPY (45 Gy) OR ONCE DAILY THORACIC RADIOTHERAPY (70 Gy) FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

SCHEMA (1/12/04)

This is a non-randomized dose escalation study in which patients are assigned in a sequential fashion, alternating between treatment sequences. Treatment assignment will begin with Sequence A, Level 1 and after enrollment of 6 patients, will progress to Sequence B, Level 1. Dose escalation will follow this pattern to the next level until the MTD in both treatment sequences is reached; see Section 13.2.2 for details.



*See Section 7.0 for details

****** Treatment is administered 5 days/week. A minimum of three days concurrent therapy is required, i.e., therapy should begin on Monday, Tuesday, or Wednesday of the first week; see Section 6.0 for details.

Eligibility: (See Section 3.0 for details)

- Histologic or unequivocal cytologic proof (fine needle aspiration biopsy or two positive sputa) of SCLC is required.
- Patients must have limited disease, clinical stage I-IIIB: confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement.
- Patients with minimal pleural effusion too small to tap under CT guidance, and not evident on CXR, are eligible.
- Pretreatment FEV-1 ≥ 1.0 L/sec
- Patients must have measurable or evaluable disease.
- Age ≥ 18
- Zubrod Performance Score 0-1

Continued on the next page

- No prior chemotherapy, radiotherapy, or biotherapy is permitted.
- Absolute granulocytes $\geq$ 1500/μl, platelets $\geq$ 120,000/μl, bilirubin $\leq$ 1.5 mg/dl, creatinine $\leq$ 1.5 mg/dl are required; no minimum HGB level is specified; however, HGB level of ≥ 9.0 gm/100 ml is desirable.
- No pre-existing ≥ grade 2 peripheral neuropathy
- No prior active, invasive malignancy in prior two years
- Pregnant or lactating women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- Patients with known Gilberts disease are excluded.
- Patients who have been receiving phenytoin, phenobarbital, carbamazepine or any other enzyme-inducing anti-convulsant drug (EIACD) on a regular basis for > 2 weeks who are unable or unwilling to discontinue EIACD use or switch to a non-EIACD at least 7 days prior to first treatment dose of irinotecan are ineligible.
- Patients who are unable or unwilling to discontinue St. John's wort (hypericum perforatum) at least 14 days prior to the first treatment dose of irinotecan are ineligible.
- Patients must sign a study-specific consent prior to study entry.

Required Sample Size: Maximum of 36

Institution # _____

RTOG 0241 **ELIGIBILITY CHECKLIST (3/17/03)**

Case # _____

_____(Y)	1.	Does the patient have documented histologic or unequivocal cytologic proof of small cell lung cancer?
_____(I-IIIB)	2.	What is the stage?
_____(Y)	3.	If no TMN staging, is there confirmed limited small cell disease?
_____(N)	4.	Does the patient have N3 disease based on contralateral hilar or contralateral supraclavicular nodal involvement?
_____(Y/N)	5.	Is there evidence of pleural effusion?
		_____(Y) If yes, is the amount of effusion too small to tap under CT guidance and not visible on chest X-ray?
_____(Y)	6.	Does the patient have an FEV-1 ≥ 1 L/sec?
_____(Y)	7.	Does the patient have measurable or evaluable disease?
_____(≥ 18)	8.	What is the patient's age?
_____(Y)	9.	Is the Zubrod 0-1?
_____(N)	10.	Has the patient received any prior chemotherapy, radiotherapy, or biotherapy?
_____(Y)	11.	Is the patient's hematologic, hepatic, and renal function adequate as specified in Section 3.1.6?
_____(Y)	12.	Has the radiation oncologist verified that tumor can be encompassed by radiation fields as defined in Section 6.0 without significantly compromising pulmonary function?
_____(N)	13.	Does the patient have pre-existing ≥ grade 2 peripheral neuropathy?
_____(N)	14.	Does the patient have a pericardial effusion or malignant pleural effusion?
_____(N)	15.	Has the patient had a myocardial infarction within the last 6 months, symptomatic heart disease, uncompensated COPD, or uncontrolled bronchospasms?
_____(N)	16.	Is there history of a prior malignancy from which the patient has not been disease free for a minimum of 2 yrs, other than adequately treated basal/squamous skin cancer or *in situ* cervix cancer or other *in situ* malignancy?
_____(N/NA)	17.	If female, is the patient pregnant or lactating?
_____(Y/NA)	18.	If the patient has reproductive capability, has the patient agreed to utilize effective contraception?
_____(N)	19.	Has the patient had a complete tumor resection?
_____(Y)	20.	Has the patient agreed to be available for follow up?

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_____(N) 20. Has the patient been diagnosed with Gilberts disease?

_____(N) 21. For patients who have been receiving phenytoin, phenobarbital, carbamazepine or any other enzyme-inducing anti-convulsant drug (EIACD) on a regular basis for > 2 weeks, is the patient unable or unwilling to discontinue EIACD use or switch to a non-EIACD at least 7 days prior to first treatment dose of irinotecan?

_____(N) 22. Is the patient unable or unwilling to discontinue St. John's wort (hypericum perforatum) at least 14 days prior to the first treatment dose of irinotecan?

_____(Y) 23. Has the patient signed a study-specific consent form?

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

_____ 5. Patient's Initials (Last, First) [Initials only effective 2/2002]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

(continued on next page)

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

_____ 16. Treatment Start Date

_____ 17. Treatment Assignment

_____ 18. Medical Oncologist

_____(Y/N) 17. Was a PET scan performed on this patient?

_____(NA/Y/N) 18. Was the PET scan used in staging?

_____(NA/Y/N) 19. Was the PET scan used in treatment planning for radiation therapy?

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 Roughly one-fifth of all patients with lung cancer will have small cell lung cancer (SCLC). Although SCLC can be staged by the TNM classification for lung cancer, more typically it is staged as "limited" or "extensive". Limited stage disease shows clinical evidence of involvement not exceeding one hemi-thorax and its regional lymph nodes. Extensive disease denotes spread beyond these regions. At presentation, no more than 30-40% of all small cell patients have limited stage disease.[1]

Milestones in the management of limited stage SCLC have included recognition of the following:[1-13]

- Survival without systemic chemotherapy is severely limited.
- This disease is quite chemoresponsive, and the use of combination chemotherapy increases survival.
- The use of thoracic radiotherapy improves both local/regional disease control and long term survival and this effect appears to be optimized when the thoracic radiotherapy is introduced early in the course of disease management.

Currently, the combination of etoposide (VePesid®; VP-16) with cisplatin is felt to be one of the most active in the management of SCLC.[10-13]

The use of twice daily (BID) radiotherapy (RT) has received substantial attention in the management of both non-small cell and SCLC. In the non-small cell setting Cox, et al. and subsequently, Sause, et al. confirmed that twice daily radiotherapy results in improved results, as compared to once daily fractionation, for favorable Stage III patients.[14,15] Choi described the rationale and the anticipated limitations for accelerated radiation therapy in SCLC.[16] Subsequently, he has reported for the CALGB that 45 Gy in 30 fractions over 19 elapsed days represents the maximum tolerated dose (MTD) of twice daily radiotherapy when administered with PCE chemotherapy (cisplatin 33 mg/m^2 *i.v.* days 1, 2, 3; cyclophosphamide 500 mg/m^{2}day 1; and etoposide 80 mg/m^2 *i.v.* days 1, 2, 3) as judged by a 29% incidence of grade $\geq$3 esophagitis and a 43% incidence of grade 4 leukopenia and granulocytopenia.[17]

Turrisi, et al.[18,19] reported their pilot results at the University of Pennsylvania using limited radiotherapy fields and concurrent VP-16 and cisplatin in doses of 120 mg/m^2 i*.v*. days 4, 6, and 8 and 60 mg/m^2 *i.v.* day 1, respectively. Radiotherapy was given in 1.5 Gy fractions twice daily with an interfraction interval of at least 4 hours. Radiotherapy portals were AP/PA a.m. and p.m. in week 1, AP/PA in the a.m. and off cord obliques in the p.m. during weeks 2 and 3. Radiotherapy volumes included the primary tumor and ipsilateral hilum, involved mediastinal nodes, and inclusion of nodes one level beyond those involved without routine irradiation of contralateral hilum or either supraclavicular region. Their results of 94% complete response (CR), 96% local control in patients with non-variant histology, median survival of 21 months, and actuarial disease-free survival of 45-50% at 2 years represented the best results reported in limited stage disease. Prophylactic cranial irradiation was administered to all complete responders. These results were confirmed by a joint study of the RTOG (RTOG 88-15) and ECOG using the same chemotherapy regimen with randomization to either 45 Gy in 25 fractions (1.8 Gy once daily) or 45 Gy in 30 fractions (1.5 Gy BID). As reported by Wagner,[20] et al., the CR+ partial response (PR) rate was 81% in both groups, median survival time was 18.6 - 20.3 months, and two-year survival rate was 41.7 - 44.3% in a study involving 358 eligible patients. Myelotoxicity in the two groups was the same *(40% grade 3 and 4)*. Grade 3-4 esophageal toxicity was less with once daily radiotherapy (15% vs. 31%). At the time of publication,[26] the combined RTOG/ECOG effort showed superiority of BID RT compared to single daily fractionation, with reduction in intrathoracic failures from 52% to 36% (p=0.06), and statistically significant improvement in five-year survival rate (26% vs 16%, p=0.04).

The intergroup trial employed four cycles of systemic therapy with etoposide/cisplatin (EP): two administered during radiation, and two following RT. To date, in this setting, no other permutation of chemotherapy and radiation, and no other chemotherapy combination have demonstrated superiority to the BID RT concurrent approach.

Pending subsequent long term analysis of the above study, the RTOG has elected to continue studies of concurrent BID radiotherapy/cisplatin/VP-16 with modifications made in the chemotherapy regimen, in an effort to enhance therapeutic effect with acceptable toxicity. RTOG 93-12, modified the chemotherapy regimen by adding ifosfamide + mesna, changing the cisplatin schedule and using an oral 14 day schedule for VP-16. The use of G-CSF was permitted for rescue from febrile neutropenia and to maintain dose intensity in subsequent cycles. In order to avoid recruitment phenomena that might paradoxically enhance myelotoxicity, G-CSF was not initiated until at least 24 hours after the last dose of oral VP-16 or radiation fraction and was stopped 48 hours prior to the initiation of the next cycle of chemotherapy.[22] As of February 2001, the incidence of severe esophagitis was 43%; 55% of patients had grade 4 neutropenia 26% had grade 4 thrombocytopenia. There was one septic death. Two-year survival rate was 50%; three-year survival rate was 39%, and the median survival time was 23.7 months. There were no treatment related deaths.

More recently, RTOG 96-09 grafted paclitaxel onto the "anchor" regimen of BID XRT etoposide and cisplatin. The two-year survival rate was approximately 50%, but long-term survival data are not yet available to determine if this triplet regimen is worth comparing to the standard doublet in conjunction with BID RT[23]. Pending analysis of mature data from RTOG 93-12 and 96-09 for toxicity and therapeutic outcomes, we propose a trial building on the theme of BID fractionation/cisplatin/ VP-16. In this trial, our major modification will be the substitution of the drug irinotecan for etoposide. In addition, we will test this regimen in combination with high dose single daily fraction RT (70 Gy) based on work by Noah Choi et al.,[24] which demonstrated a median survival of 29.8 mos and six-year survival rate of 36% for once daily RT (median dose: 63.0 Gy) in combination with etoposide, cisplatin and ifosfamide:

CALGB 8837: Phase I Study of STD QD or ACCEL HFx BID RT with Concurrent Chemotherapy for LD-SCLC (n=47)

	N	MS (mo)	6-yr OS (%)
STD QD	22	29.8	36
HFx BID	25	24	20
All	47	25.4	28

Even though systemic failure appears the greatest challenge, local control remains a problem in small cell lung cancer. In the Intergroup Phase III trial,[26] the local control rate was 64% in the twice daily arm, and it was reported as 80% at two years in the RTOG 93-12 Phase II study.[22] Out of 37 patients treated in the NCI Phase II study with twice daily RT to 45.0 Gy and concurrent etoposide, cisplatin, followed by cyclophosphamide, doxorubicin and vincristine,[27] 38% experienced local failure, after having an initial partial or complete response to treatment. Local control decreases with the length of follow up, as reported in the analysis of 150 patients enrolled in intramural combined modality studies at NCI.[28] Local control was 81% at one year, 62% at two years, and 55% at three years.

Even though twice daily thoracic RT to 45.0 Gy became a standard approach for patients with a limited stage small cell lung cancer treated off-study, many have pointed out that a once daily arm of that trial (45.0 Gy once daily) was radiobiologically inferior to 45.0 Gy BID. Therefore, higher total doses of standard fractionated RT have to be investigated and compared to the standard 45.0 Gy twice daily. As demonstrated by Choi,[24] no dose-limiting toxicities were reached at a dose of 70.0 Gy when given concurrently with chemotherapy, when target volume included the primary tumor with the margin plus the mediastinum. A recent update of the Choi[24] data indicated similar or improved median and long-term survival results with the QD regimen as compared to the BID regimen, with equivalent or reduced toxicity.

(1/12/04) The current study design is a phase I study by which we will attempt to determine the MTDs of cisplatin and irinotecan in combination with either RT schema. Patients will be accrued to one sequence, then the other; while we suspend accrual in one dose level of a sequence (arm) and evaluate toxicity, accrual to the other sequence (arm) will proceed, then vice versa. Conference calls among the investigators will be held after completion of each cohort to monitor toxicities.

The rationale for the evaluation of irinotecan (CPT-11) follows. In extensive disease, the combination of CPT-11 and cisplatin has proven superior to etoposide and cisplatin (EP).[25] Overall response rate was superior at 83% compared to 67% (p=0.013), and median survival was superior at 14 months, compared to 10 months. With the exception of diarrhea (16% grade $\geq$ 3 or worse vs. 0%), toxicities were less pronounced, with substantially less neutropenia (66% vs 92%, p=0.0002), and substantially less grade $\geq$ 3 thrombocytopenia (5% vs 19%, p=0.01). The treatment death rate was 4% on the experimental arm. The results are shown in greater detail in the table below.[22] The experimental regimen consisted of 60 mg/m^2 of CPT-11 on days 1, 8 and 15, and 60 mg/m^2 of cisplatin on day 1, every 4 weeks for 4 courses. The standard arm consisted of 100 mg/m^2 of etoposide on days 1, 2 and 3, and 80 mg/m^2 of cisplatin on day 1, every 3 weeks for 4 courses. The planned sample size was 230 (115 cases in each arm). Between November 1995 and November 1998, 154 patients were randomized, 77 into each arm. A planned interim analysis showed that the objective response (CR+PR) rates, median survival, and one-year survival rate were significantly better in the CPT-11/cisplatin arm as compared with etoposide/cisplatin arm. The study was closed early based on the advice of the Data Monitoring Committee. Efficacy and toxicity results from the final analysis, as presented at the ASCO 2000 Meeting are summarized in the tables below:

JCOG Phase III Study in ED-SCLC

Efficacy Endpoint[a]	**CPT-11/Cisplatin (N=77)**	**Etoposide/Cisplatin (N=77)**
Objective Response Rate, %:		
PR	80.5	58.4
CR	2.7	9.1
Overall (95% CI)	83.1 (75.3-92.4)	67.5 (55.9-77.8)
Median Survival Time, Days (95% CI)[b]	390 (356-464)	287 (247-330)
One-Year Survival Rate, % (95% CI)	58.4 (47.4-69.4)	37.7 (26.8-48.5)
Two-Year Survival Rate, % (95% CI)	19.5 (10.0-27.8)	5.2 (1.0-12.0)

[a] Updated survival data, 1 January 2002, *NEJM*

[b] Unadjusted one-sided logrank test, p=0.0021

Incidence of JCOG Grade 3/4 Toxicity	**Percent of Patients**	
	CPT-11/Cisplatin (N=77)	**Etoposide/Cisplatin (N=77)**
Leukopenia	26.7	51.9
Neutropenia	66.2	92.2*
Thrombocytopenia	5.3	18.2*
Anemia	26.7	29.9
Diarrhea	16.0*	0
Nausea & Vomiting	13.3	6.5
Fever	1.3	2.6
Infection	5.3	3.9
Treatment-Related Deaths (N)	3	1

* statistically significant difference

Under these circumstances, it seems reasonable to integrate this new and promising combination into the treatment of limited disease, to make certain there are no untoward toxicities, and to gauge potential signals of efficacy. In the interim, two separate phase III trials in extensive disease are underway; one employs an identical schema evaluated in the Japanese trial, the other uses an altered three week irinotecan-cisplatin schedule.

1.2 Feasibility of Irinotecan in Combination with Radiation

The topoisomerase I inhibitor, irinotecan, has established radiosensitizing effects.[29] The radiation (RT) enhancement ratio ranges from 1.4 to 1.46. Kudoh and colleagues from Japan have demonstrated the feasibility of concurrent irinotecan and radical thoracic RT (in locally advanced NSCLC); the maximally tolerated dose for irinotecan was 60 mg/m^2 weekly, and the recommended dose for phase II studies was 45 mg/m^2 weekly without break.[30] Esophagitis, pneumonitis, and diarrhea proved to be dose-limiting toxicities. Median survival was 17.7 mos.[31] A separate phase II study employing irinotecan 60 mg/m^2 weekly in combination with RT (60 Gy)

in 24 patients with locally advanced NSCLC proved feasible; the incidence of grade 3 esophagitis and pneumonitis was 8% and 13%, respectively.[32] In combination with split course RT, Fukuda and colleagues were able to combine full dose cisplatin (80 mg/m^2 q 4 wk) and irinotecan (60 mg/m^2 weekly x 3 every 4 weeks) without untoward toxicity.[33] Finally, Langer and colleagues from Fox Chase Cancer Center conducted a phase I study of irinotecan/cisplatin and radical thoracic RT (63 Gy) in the treatment of locally advanced NSCLC.[34-35] The MTD proved to be irinotecan 30 mg/m^2 weekly x 7 (without interruption) and cisplatin (25 mg/m^2/weekly x 7) in combination with full dose continuous RT (63 Gy). Attempts to escalate the irinotecan dose $\geq$ 40 mg/m^2/wk x 7 resulted in dose-limiting neutropenia and esophagitis. Median survival in this effort, which included patients with up to 10% weight loss and ECOG PS 2, was 27.8 months.

1.3 Integration of Irinotecan into Therapy of LD-SCLC

While the addition of irinotecan to cisplatin/radiation in the treatment of SCLC might result in significant enhancement of therapeutic effect, there also is likely to be significant neutropenia, esophagitis, and some risk of radiation pneumonitis. Furthermore, a triplet combination and mandatory dose attenuation of one or more of the component agents may potentially compromise therapeutic efficacy. In designing this trial we have attempted to deal with these concerns by integrating the new regimen upfront, maintaining a fixed dose of cisplatin and carefully escalating the irinotecan dose in sequential cohorts during radiation. Thus cisplatin during the first two cycles will be 60 mg/m^2 q 3 wk x 2. The irinotecan dose will be escalated from 40 mg/m2 D1, 8 q 3 wk to 60 mg/m^2 d 1, 8 q 3 wk. Each cohort will include 6 patients. After RT is concluded, patients will receive two additional cycles of cisplatin at 60 mg/m^2 q 3 wk and irinotecan 60 mg/m^2 d 1, 8, q 3 wks. We intend to use the "tight" radiation therapy fields implemented in RTOG 88-15 and RTOG 93-12, and omit elective nodal irradiation.

2.0 OBJECTIVES

2.1 To determine the maximum tolerated dose of irinotecan in combination with cisplatin and either twice daily RT (45 Gy) or single daily RT (70 Gy)

2.2 To monitor the qualitative and quantitative toxicity non-dose limiting toxicity and assess the reversibility of all toxicities from this approach

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologic or unequivocal cytologic proof (fine needle aspiration biopsy or two positive sputa) of SCLC is required;

3.1.2 Patients must have limited disease, clinical TNM stages I-IIIB: confined to one hemithorax, but excluding T4 tumor based on malignant pleural or pericardial effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement;

3.1.2.1 Patients with pleural effusion too small to tap under CT guidance and not evident on CXR, are eligible;

3.1.3 Patients must have measurable or evaluable disease. The radiation oncologist must certify that the tumor can be encompassed by radiotherapy fields as defined in Section 6.0 without unacceptable risk of serious pulmonary compromise;

3.1.4 Age $\geq$ 18;

3.1.5 Zubrod Performance Status 0-1 (See Appendix II);

3.1.6 Adequate hematologic, hepatic, and renal function as follows: absolute granulocytes $\geq$ 1500/μl, platelets $\geq$ 120,000/μl, bilirubin $\leq$ 1.5 mg/dl, creatinine $\leq$ 1.5 mg/dl are required. No minimum HGB level is specified; however, HGB level of ≥ 9.0 gm/dl is desirable;

3.1.7 Pretreatment FEV-1 ≥ 1.0 L/sec

3.1.8 Patients must be available for active follow up;

3.1.9 Patients of childbearing potential (male and female) must practice adequate contraception;

3.1.10 Patients must sign a study-specific consent form.

3.2 Conditions for Patient Ineligibility

3.2.1 T4 tumor based on malignant pleural or pericardial effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement;

3.2.2 Patients with complete tumor resection;

3.2.3 Prior chemotherapy, radiotherapy, or biotherapy;

3.2.4 Pre-existing ≥ grade 2 peripheral neuropathy;

3.2.5 Pericardial effusion (regardless of cytology);

3.2.6 Serious intercurrent medical illness including symptomatic heart disease, myocardial infarction within 6 months, uncompensated COPD, or uncontrolled bronchospasm;

3.2.7 Previous or concurrent malignancy other than curatively-treated basal or squamous cell skin cancer or carcinoma *in situ* (e.g., T_{IS} of bladder or cervix); patients managed for a non-pulmonary invasive malignancy more than 2 years previously with no subsequent clinical, laboratory, imaging, or pathologic evidence of recurrence or persistence of the prior malignancy are eligible for this protocol.

3.2.8 Pregnant or lactating women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.

3.2.9 Patients with known Gilberts disease;

3.2.10 Patients who have been receiving phenytoin, phenobarbital, carbamazepine or any other enzyme-inducing anti-convulsant drug (EIACD) on a regular basis for > 2 weeks who are unable or unwilling to discontinue EIACD use or switch to a non-EIACD at least 7 days prior to first treatment dose of irinotecan. Patients who have been receiving EIACDs < 2 weeks must discontinue use prior to first treatment dose on study but do not require a 7-day wash-out period. Concomitant use of gabapentin or other non-EIACDs is permitted.

3.2.11 Patients who are unable or unwilling to discontinue St. John's wort (hypericum perforatum) at least 14 days prior to the first treatment dose of irinotecan.

4.0 PRETREATMENT EVALUATIONS

4.1 A complete history and physical to include performance status, recent weight loss, percent of weight loss, usual weight, and concurrent non-malignant disease and its therapy must be recorded.

4.2 Laboratory studies must be done within 2 weeks prior to study entry and will include: CBC with differential, platelet count, BUN and creatinine, electrolytes, magnesium, LFTs (SGOT, Alk Phos, LDH, Bilirubin), pregnancy test (for females of childbearing potential), and urinalysis.

4.3 Chest X-ray, EKG, CT scans of chest and abdomen, CT scan or MRI of the brain, and radionuclide bone scan are required four weeks prior to study entry. A printed CT simulation film is acceptable as a baseline study. Bone marrow aspirate and/or biopsy should be done on all patients with equivocal bone scan or elevated alk phos or LDH. Bronchoscopy will be performed if clinically indicated.

4.4 Pulmonary function tests within 8 weeks prior to study entry;

4.5 Location and type of all measurable lesions must be recorded.

5.0 REGISTRATION PROCEDURES

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

5.2 CALGB Institutions

Confirm all eligibility criteria listed in Section 3.0. Registration will be accepted through CALGB Main Member/at-large institutions, selected affiliate institutions, and CCOPs. Registrations must occur prior to initiation of therapy. Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 AM-5 PM Eastern Time) with the following information:

Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of responsible CRA
Name of radiation oncologist who gave approval to register patient
CALGB patient ID #, if applicable
Patient's first name, middle initial, and last name
Patient's Social Security #, date of birth, and hospital ID #
Patient's gender
Patient's race
CTC performance status
Type of insurance (method of payment)
Disease, type and stage, if applicable
Patient's Postal Code, if applicable
Treatment start date

Date of signed consent
Patient demographics
Eligibility criteria met (no, yes)
Stratification Factor: Stratum 1 vs. Stratum 2

The CALGB Registrar will then contact the RTOG Randomization Center to randomize the patient. Once the randomization is complete the CALGB registrar will then call the CALGB institution with the randomization assignment. Once the randomization is completed be sure to note the patient's treatment assignment in your records.

The Main Member Institution and registering institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Data Operations, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

6.0 RADIOTHERAPY Note: Intensity Modulated RT (IMRT) is not allowed.

6.1 Thoracic Radiation Dose

6.1.1 Different radiation doses will be used for the two treatment sequences: Each fraction in **Sequence A** will consist of 1.5 Gy to be given twice daily (5-8 hours apart), five days a week for three weeks. Total dose will be 45 Gy in 30 fractions. In **Sequence B**, patients will receive a single daily fraction of 2.0 Gy, five days a week for seven weeks. Total dose will be 70 Gy in 35 fractions.

6.1.2 Patients on Sequence A will be treated two times per day on each treatment day, receiving 1.5 Gy for each treatment fraction, or 3.0 Gy per day. No less than 5 and no more than 8 hours may elapse between each treatment session daily. Treatment times (a.m./p.m.) must be documented in the daily record.

6.1.3 Treatment is administered 5 days/week. A minimum of three days concurrent therapy is required, i.e., therapy should begin on Monday, Tuesday, or Wednesday of the first week.

6.1.4 In Sequence A, week one is given AP/PA in both a.m. and p.m. sessions. The p.m. session of weeks 2 and 3 must be given by oblique or lateral fields (for some treatment situations, all 3 weeks may require more complex field arrangements in order to avoid excess dose to normal tissues or compromised coverage of the target volume). Direct posterior spinal cord blocks are not allowed.

6.1.5 In Sequence B, AP/PA fields are used until cord tolerance is reached (usually at a target dose in the range of 40.0-46.0 Gy). When spinal cord tolerance is reached, off-cord oblique fields will be used for the remainder of therapy. However, any field arrangement is allowed to be used from the beginning of RT, if designed with the purpose of minimizing the doses to the critical organs, particularly healthy lung and esophagus.

6.2 Treatment Techniques

All doses are to be prescribed and calculated assuming homogenous unit-density tissue for the patient, which means there will be no heterogeneity corrections used in the definition of these doses. The doses will be prescribed and calculated according to the following RTOG guidelines for external treatment using photons.

6.2.1 At the center of the target area on a central ray for a single beam

6.2.2 At mid-separation on the central ray for two opposed coaxial equally weighted beams

6.2.3 At the center of the target area on the central ray for two opposed coaxial unequally weighted beams

6.2.4 At the point of intersection of the central rays for two or more intersecting beams which are not coaxial

6.2.5 At the center of the rotation in the plane of rotation containing the central axis for rotation or arc therapy

6.2.6 At the center of the target area for complex treatment arrangements that are not covered above

6.3 Target Volume

There will be one gross target volume (GTV) to be treated by both AP/PA and off-cord fields (or any other field arrangement), which includes the primary tumor plus any enlarged hilar and/or mediastinal lymph nodes, defined as measuring $\geq$1.5 cm in largest dimension on a thoracic CT scan. If lymph nodes measuring $\leq$1.5 cm by the thoracic CT scan are known to contain tumor by means of other diagnostic tests (mediastinoscopy, mediastinotomy, PET scan), then they also should be included in the gross target volume. In a rare patient without obvious lymph node involvement, it is recommended that the ipsilateral hilum/mediastinum be included as part of CTV1 to a dose of at least 36 Gy (Sequence A) or 40-46 Gy (Sequence B), which would

constitute the only departure from the general policy of omitting elective nodal irradiation.

6.3.1 There will be two different clinical target volumes (CTV) required:

6.3.1.1 *CTV1:* In the initial AP/PA fields, the primary tumor and the enlarged lymph nodes will be treated with a 2.0 cm margin (as measured to the edge of the block), constituting CTV1. If multiple field arrangement is used throughout the entire treatment course, the margin should be 2.0 cm until 36.0 Gy is reached (Sequence A) or 40-46.0 Gy (Sequence B), at which point the margin should be 1.5 cm for the remainder of therapy. Planning target volume 1 (PTV1) therefore will be the same as CTV1.

6.3.1.2 *CTV2*: In the off-cord (oblique/other) fields, the primary tumor and the enlarged lymph nodes will be treated with a 1.5 cm margin (as measured to the edge of the block), constituting CTV2. An even smaller margin is allowed in the off-cord fields, if so dictated by the proximity of the spinal cord. Planning target volume 2 (PTV2) therefore will be the same as CTV2.

Note: more margin may be necessary (particularly in the cranio-caudad direction) if the tumor movement is increased because of respiratory movement which should be checked by fluoroscopy.

6.3.1.3 Ipsilateral supraclavicular irradiation is allowed when necessary for primary tumor or nodal coverage only.

6.3.2 It is required that target volume for antero-posterior (AP), postero-anterior (PA) and oblique/lateral ports be simulated before initiation of radiotherapy.

6.3.3 Target volumes for AP/PA treatment also define target volumes to be included in oblique or multi-field volume.

6.4 Technical Factors

6.4.1 *Beam Energy*: Megavoltage accelerators with a minimum source to isocenter distance of 100 cm are required. Electron beams, ^{60}Co beams, 4 MV accelerators and 80 cm SAD units are not acceptable. **Only 6MV-10 MV energy photon beams** are to be used for any field arrangement, including oblique or other fields.

6.4.2 *Beam Shaping*: Custom blocks (5 HVL), individually shaped for each field should be used to protect normal tissues outside the target volume defined in Section 6.3. Oblique or lateral fields should be simulated with a **barium swallow** to document the length of the irradiated esophagus. CT planning may be used to delineate the esophagus.

6.4.3 *Compensating Filters or Wedges*: In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may be used as two-dimensional tissue compensator.

6.4.4 *Fractionation:* Each field is to be treated every session. There should be a minimum of 5 hours and a maximum of 8 hours between each fraction in patients receiving twice daily irradiation (Sequence A).

6.4.5 *Therapy Interruptions:* Efforts should be made to avoid interruptions in therapy. Note: Fevers, cytopenias, or < 3 grade esophagitis, do not in general constitute reasons for interruptions. If ≥ grade 3 esophagitis occurs and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Interruptions longer than 3 treatment days should be discussed with Dr. Langer or Dr. Werner-Wasik. Routine holidays are understood. Document in treatment chart reason for treatment interruption. Also see Section 6.5.2

If interruptions of therapy of up to one week become necessary, irradiation should be completed to the prescribed dose. Total number of fractions and elapsed days are to be carefully reported.

If more than one-week interruption is required, resumption of therapy is at the discretion of the radiation oncologist.

6.4.6 *Simulation*: Simulation is mandatory and **CT-based planning** is strongly encouraged. Any CT for treatment planning should be taken in the treatment position. If feasible, patients should be **immobilized** in a customized foam cast (alpha cradle). In order to avoid a second simulation for the off-cord fields, patients should be simulated from the beginning with arms raised above head and treated in that position starting with the AP-PA fields. If either CT scans in the treatment position or CT simulation is used for planning purposes, the administration of **intravenous contrast** is highly desirable, since it allows a better definition of the involved lymph nodes. Careful attention should be paid to the outlining of the tumor and lymph nodes on axial CT images. The lymph nodes should be outlined using a "**mediastinal window**" setting and any tumor interfacing with lung parenchyma, with the "**lung window**" setting. It is encouraged that a conventional simulation using a **fluoroscopic** image intensifier capability be

performed for each patient, including those planned with a CT scanner, to assess the extent of respiratory movement in craniocaudal direction for the purpose of adjusting treatment margins.

6.4.7 *Dose Calculation*: Doses are to be calculated without heterogeneity correction, i.e., no correction is to be made for density differences between air spaces, lung, water-density or bony tissue. Treatment planning should be performed in accordance with the prescribing doses (Section 6.1) to each target, together with restrictions in dose to normal tissues as given below and in Section 6.8.1.6.

6.4.7.1 In addition to the isodose distribution, the following specific points of dose calculation should be included:

Spinal Cord: If compensating filters are not used, the point at which the spinal cord dose is to be calculated is 2 cm below the superior margin of the posterior fields. If compensating filters or wedges are used then the point of maximum dose to the spinal cord must be determined. Maximal spinal cord dose should not exceed **36.0 Gy at any level for patients in Sequence A** (twice daily RT) and **46.0 Gy in Sequence B** (once daily RT). No posterior spinal cord blocks are allowed other than the most superior laryngeal and spinal cord blocks where the tumor does not exist.

6.4.8 *Isodose Distributions*: Isodose plots will be obtained at: a) the central axis level b) 2.0 cm from the top, and c) 2 cm from the bottom of the field. The isodose plans must reflect utilized blocks and compensators. These must be composite plans accounting for the total dose from each component field. Critical structures (spinal cord) and target volume must be clearly delineated on each plot.

6.4.9 Localization (check or port) films will be done before the start of and weekly for each port treated. Simulation and portal beam verification films for each treatment field will be submitted to RTOG for review per Section 12.0.

6.4.10 *Timing of Radiation Therapy and Concurrent Chemotherapy*:

Sequence A: On days when chemotherapy is given concurrently with RT, it should be administered between the a.m. and p.m. RT fractions.

Sequence B: On days when chemotherapy is given concurrently with RT, chemotherapy should be administered first, to be followed by RT.

6.5 Toxicity from Radiation Therapy

6.5.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving $\geq$ 40 Gy, usually within the first six months after initiation of treatment, so it is essential to spare as much normal lung as possible.

6.5.2 *Esophagitis*

Esophageal complaints are common with combined modality therapy. It does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous xylocaine, carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, notify Dr. Langer or Dr. Werner-Wasik.

6.6 Dosimetry Submission

6.6.1 All initial dosimetry and final dosimetry material specified in Section 12.0 must be submitted (with a dosimetry transmittal sheet) directly to RTOG Headquarters, 1101 Market Street, Philadelphia, PA, 19107.

6.7 Prophylactic Cranial Radiotherapy (PCI) [7/1/04]

6.7.1 We suggest that all patients who achieved a complete tumor response (CR) [and patients with partial response, PR, who desire to receive it] be offered Prophylactic Cranial Irradiation (PCI) using 2.0-2.5 Gy daily fractions or 1.5 Gy twice daily. Acceptable time dose fractions schemes will include the following: 25 Gy in 10 fractions; 26.0-30.0 Gy in 13-15 fractions; 36 Gy in 18-24 fractions. As a reminder, a complete response is defined as absence of the tumor maintained for 4 weeks, which dictates obtaining a chest CT scan 1 month from the initial documentation of a CR.

PCI should be initiated in those patients after hematologic recovery from the last cycle of chemotherapy or within 6 weeks thereof. Repeat brain imaging prior to initiating PCI should be performed.

6.8 Compliance Criteria

6.8.1 *Major Deviations*

6.8.1.1 Dose: Deviation of total dose by more than 10%; deviation in any fractional dose by more than 20%

6.8.1.2 Treatment Time: Interfraction interval on Sequence A of less than 4.5 hours on more than two occasions

6.8.1.3 Fields: Failure to use off cord obliques or laterals in weeks 2 and 3 (Sequence A)

6.8.1.4 Target Volumes: Less than 1.0 cm margin on designated target volume; inclusion of volume specifically indicated to be excluded, e.g., uninvolved supraclavicular area

6.8.1.5 Technical Factors: Failure to comply with any factors mentioned in Section 6.3.1; failure to use custom blocking

6.8.1.6 Dose to Critical Tissues: Spinal cord dose at any point along the length in excess of 36.0 Gy in Sequence A and 46.0 Gy in Sequence B; esophageal dose more than 45.0 Gy in Sequence A and 70.0 Gy in Sequence B; ipsilateral whole lung dose more than 20.0 Gy in Sequence A and 25.0 Gy in Sequence B

6.8.2 *Other Variations*

Any variations not specifically mentioned above will be considered variations, but acceptable. When any of the parameters are scored as deviations, unacceptable, whether the patients should be excluded from analysis will be the joint decision of the Radiation Oncology Chair, the Lung Committee Chair, and the study statistician.

7.0 DRUG THERAPY

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

7.1 Treatment Plan

Each cycle of chemotherapy is 3 weeks long and includes day 1 and day 8 of treatment, followed by an idle day on day 15. Each cycle resumes on day 22.

7.1.1 **[1/12/04]** *Chemotherapy with concurrent RT*: Patients in **Sequence A** (all levels) will receive chemotherapy concurrently with radiotherapy for 1 cycle; patients in **Sequence B** (all levels) will receive chemotherapy with radiotherapy for 2 cycles.

7.1.1.1 Irinotecan: (40-60 mg/m^2) intravenously over 60-90 minutes on day 1, day 8 for 1 cycle in **Sequence A,** for 2 cycles in **Sequence B**; given intravenously, will be diluted with D5W to a total volume of 500 ml and infused over 60-90 minutes.

7.1.1.2 Cisplatin: 60 mg/m^2 intravenously on day 1 following the administration of the irinotecan for 1 cycle in **Sequence A**, for 2 cycles in **Sequence B**; cisplatin will be mixed in 250cc of normal saline and given over 1 hour.

Hydration: Patients should receive prehydration prior to cisplatin with up to 1000cc of intravenous 1/2 normal or 0.9 normal saline over $\leq$ 2 hours prior to cisplatin. This may be given concurrently with irinotecan. Following cisplatin, patients should receive post hydration with up to 1000cc of intravenous 1/2 normal saline over 2 hours. Appropriate electrolytes (KCl, $MgSO_r$) should be added as necessary. Mannitol: 25 gm intravenous push prior to cisplatin.

7.1.2 **[1/12/04]** *Post-RT Chemotherapy:* Irinotecan, 60 mg/m^2, days 1 and 8 q 3 week and cisplatin, 60 mg/m^2 day 1 q 3 week; patients in **Sequence A** (all levels) will receive 3 cycles; patients in **Sequence B** (all levels) will receive 2 cycles; these 2 cycles will be delayed 1 week so that radiation therapy can be completed.

7.2 Chemotherapy Administration (3/31/04)

7.2.1 Patients will receive antiemetics prior to chemotherapy at the discretion of the treating physician. Ondansetron (or granisetron) and dexamethasone are recommended. In **Sequence A**, chemotherapy will be infused between RT fractions; in **Sequence B**, chemotherapy will be given before (not after) each RT fraction. No amifostine is permitted during chemoradiation.

7.3 G-CSF Administration (3/31/04)

7.3.1 G-CSF may be given subcutaneously or *i.v*. at 5 μg/kg/d to protect against new episodes of febrile neutropenia in cycles 2-4 of chemotherapy on **Sequence A** and during cycles 3 and 4 on **Sequence B** in patients who have experienced such a complication. Alternately, a dose reduction can be instituted. The G-CSF must be separated from administration of both thoracic

radiotherapy and chemotherapy, i.e. 24 hours should elapse between either the last day of XRT or the last dose of chemotherapy. It is recommended that G-CSF be discontinued when the absolute granulocyte count recovers to > 10,000/μl and that 48 hours elapses between discontinuing G-CSF and initiating a subsequent cycle of chemotherapy.

7.4 Irinotecan

7.4.1 *Chemistry* Irinotecan hydrochloride trihydrate {CPT-11, (4S)-4, 11-diethyl-4-hydroxy-9-{(4-piperidinopiperidino) carbonyloxy}-IH-pyroano{3',4':6,7}indolzino{1,2-b}quino line-3, 14(4H, 12H)dione hydrochloride trihydrate} is a topoisomerase I inhibitor.

7.4.2 *Formulation* The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

7.4.3 *Administration* Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90 minutes. Nothing else should be added to the bag.

7.4.4 *Storage and Stability* Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. CPT-11 is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D5W.

7.4.5 *Toxicity* Virtually all phase I and II studies of CPT-11 have reported neutropenia and/or late diarrhea (diarrhea occurring more than 8 hours after CPT-11 administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia.

Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after CPT-11 administration; this syndrome is thought to be cholinergically mediated. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

Special Precautions for Diarrhea (6/4/04)

Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials (note: this dosage regimen exceeds the usual dosage recommendations for loperamide) consisted of the following: 4 mg at the first onset of late diarrhea and then 2-4 mg every 1-2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 2-4 hours. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea.

Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed. CPT-11 may cause local irritation at infusion sites. Extravasation necrosis of the skin has not been reported in U.S. studies.

7.4.6 *Supply* Irinotecan is commercially available.

7.5 Cisplatin (Platinol®)

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

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

7.5.3 *Administration*: Cisplatin should be given immediately after preparation as a slow intravenous infusion as per Section 7.1.1.3.

7.5.4 *Storage and Stability*: The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5-1/2NS *(ppt. occurs in D5W)*. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.5.5 *Human Toxicity:* Human toxicity studies includes anorexia, nausea, vomiting, weakness, aesthenia, hypomagnesemia, hypokalemia, hypocalcemia, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient), ototoxicity (with hearing loss which initially is in the high frequency range, as well as tinnitus), and hyperuricemia. Rarely, use of cisplatin can lead to loss of taste, muscle cramps, restlessness, involuntary movements, or liver damage. Much more severe and prolonged toxicity has been observed in patients with an abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy.

7.5.6 *Supply*: Cisplatin is commercially available.

7.6 G-CSF (r-metHuG-CSF)

7.6.1 *Description*: G-CSF is a colony stimulating factor that regulates the production of neutrophils within the bone marrow. Endogenous G-CSF is a glycoprotein produced by monocytes, fibrocytes, fibroblasts, and endothelial cells, which has been shown to have minimal direct in vivo or in vitro effects on the production of other hematopoietic cell types. r-metHuG-CSF is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia coli (E. coli) bacteria into which has been inserted the human granulocyte colony stimulation factor gene and has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E.coli. Because r-metHuG-CSF is produced in E.coli, the product non-glycosylated and thus differs from G-CSF isolated from human cell.

7.6.2 *Pharmacokinetics*: In studies in which circulating levels of r-metHuG-CSF were assessed by radioimmunoassay, the levels of r-metHuG-CSF remained relatively constant and proportional to the administered dose *(i.v.)*. After 40 minutes, the serum levels decayed logarithmically with time with an average elimination life of 5.1 ± 0.5 hours. In another study in which patients received r-metHuG-CSF 10 mg/kg *i.v*. elimination from plasma appeared biphasic with half-lives of 8±5 minutes *(alpha)* and 110±40 minutes *(beta)*.

7.6.3 *Administration:* G-CSF may be given subcutaneously or *i.v*. at 5 μg/kg/d to protect against new episodes of febrile neutropenia in cycles 2-4 of chemotherapy on Sequence A and during cycles 3 and 4 on Sequence B in patients who have experienced such a complication.

7.6.4 *Storage and Stability*: Unopened vials should be stored in a refrigerator at 2-8°C (36-46°F). Avoid shaking. Do not freeze. If accidentally frozen for a short while (< 24 hours), it may still be used. Prior to injection, G-CSF may be allowed to reach room temperature for a maximum of 6 hours. Any vial left at room temperature for greater than 6 hours must be discarded. G-CSF is stable for a least one year when stored at 2-8°C.

7.6.5 *Pharmacologic Effects*: In phase I studies involving 96 patients with various non-myeloid malignancies, r-metHuG-CSF administration resulted in a dose-dependent increase in circulating neutrophils counts over the dose range 1-70 mcg/kg. This increase in neutrophil counts was observed whether G-CSF was administered intravenously (1-70 mcg/kg) [once daily] or by continuous subcutaneous infusion (3-22 mcg/kg/day). With discontinuation of therapy, neutrophil counts returned to baseline in most cases within 4 days. The absolute monocyte count was reported to increase, in a dose-dependent manner in most patients receiving r-metHuG-CSF, however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both esoinophils and basophils did not change and were within the normal range. Increase in lymphocyte counts have been reported. WBC differentials obtained during clinical trials have demonstrated a shift towards granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following chemotherapy induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as

hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

Phase III clinical trials have demonstrated that r-metHuG-CSF significantly reduced the incidence of febrile neutropenic episodes, the need for impatient hospitalization and antibiotic use, and the incidence, severity, and duration of severe neutropenia (ANC < 500) following chemotherapy.

7.6.6 *Toxicity*: In clinical trials, medullary bone pain of mild to moderate severity was the only consistently observed adverse reaction. There are no reports of flu-like symptoms, pleuritis, pericarditis, allergic reactions or anaphylaxis. Excessive leukocytosis (WBC > 100,000) was reported in less than 5% of patients and was not associated with any adverse clinical effects. Acetaminophen or other non-narcotic analgesics should be used.

7.6.7 *Supply*: G-CSF is commercially available.

7.7 Toxicities to be Monitored and Dosage Modifications

7.7.1 *Concomitant Chemoradiotherapy Dose Modifications* (Sequence A: cycle 1; Sequence B: cycles 1 & 2; Days 1 and 8). **[6/4/04]**

Treatment for each successive cycle (Day 1) cannot be resumed until ANC has risen to 1500 or higher and platelets have risen to 100,000 or higher.

Dose Modification →	0	-1	-2
ANC Nadir	≥ 500 or < 500 x < 7 days	< 500 x ≥ 7 days or febrile neutropenia (FN)	2nd episode of FN or ANC nadir < 500 x ≥ 7 days despite prior dose reduction
Platelets Nadir	≥ 50,000 or < 50,000 lasting < 7 days	< 50,000 x ≥ 7 days or thrombocytopenic bleeding	2nd episode of thrombocytopenic bleeding or < 50, 000 ≥ 7 days despite prior dose reduction
*Diarrhea	grade < 3	grade ≥ 3	2nd episode of grade ≥ 3 despite prior dose reduction

*The dose reductions for diarrhea apply to irinotecan only.

7.7.1.1 Cisplatin and Irinotecan dose modifications for hematologic toxicity:

Granulocyte nadir		Platelet nadir	Modification
< 500 < 5 days	and	≥ 50,000	No change
< 500 ≥ 5 days	or	< 50,000	Decrease 25%
Febrile Neutropenia*	or	Bleeding	Decrease 25%

*Febrile neutropenia is defined as temperature increase ≥ 100.6 in face of ANC ≤ 1000/cc^3. If febrile neutropenia occurs during subsequent cycles after RT is completed, G-CSF may be used an alternative to dose reduction in the absence of other dose limiting toxicity.

7.7.1.2 **(8/26/03)** Cisplatin and Irinotecan dose modifications for non-hematologic toxicity: (other than renal; diarrhea)

Grade 0 - 2	No change
Grade 3	Decrease 25%
Grade 4	Hold treatment until toxicity has recovered to grade ≤2

7.7.1.3 Cisplatin dose modifications for renal toxicity:

Serum creatinine mg% within 24 hours of anticipated administration	Modification of cisplatin dose
1.6 - 2.0	Decreased to 40 mg/m^2 until creatinine < 1.6
2.1 to 3.5	Withhold one cycle; cisplatin to be reinstituted at next cycle at 40 mg/m^2 if serum creatinine < 2.0; otherwise stop cisplatin.

7.7.1.4 Irinotecan dose modification for diarrhea:

Grade 0-2	No change in Irinotecan dose
Grade 3	Decrease 25%
Grade 4	Decrease 50%

Treatment cannot be resumed until diarrhea has improved to grades ≤1. Anti-diarrheal medications can be used at the discretion of the treating physician.

7.7.2 *Post-RT Chemotherapy Dosage Modifications for Day 1 and Day 8*

7.7.2.1 Definition of Dose Levels after RT Completed:

Drug	Dose Level: 0	-1	-2
Irinotecan: Day 1,8, cycles 2; 3, 4	60 mg/m^2	45 mg/m^2	30 mg/m^2
Cisplatin: Day 1, cycles 2, 3, 4*	60 mg/m^2	60 mg/m^2	60 mg/m^2

Dose Level 0 is the Dose Level for all patients starting their first post radiotherapy cycle
*Cycle 2 is post-RT only in Sequence A

7.7.2.2 Dose modifications for Day 1 and Day 8 therapy **(6/4/04)**
Treatment for each successive cycle (Day 1) cannot be resumed until ANC has risen to 1500 or higher and platelets have risen to 100,000 or higher.

Dose Modification →	0	-1	-2
ANC Nadir	≥ 500 or < 500 x < 7 days	< 500 x ≥ 7 days or febrile neutropenia (FN)	2nd episode of FN or ANC nadir < 500 x ≥ 7 days despite prior dose reduction
Platelets Nadir	≥ 50,000 or < 50,000 lasting < 7 days	< 50,000 x ≥ 7 days or thrombocytopenic bleeding	2nd episode of thrombocytopenic bleeding or < 50, 000 ≥ 7 days despite prior dose reduction
*Diarrhea	grade < 3	grade ≥ 3	2nd episode of grade ≥ 3 despite prior dose reduction

*The dose reductions for diarrhea apply to irinotecan only.

7.7.2.3 Cisplatin dose modifications for renal toxicity

Serum creatinine mg% within 24 hours of cisplatin administration	Modification of cisplatin dose	Recommendations
1.6-2.0	Decrease to 40 mg/m^2 until creatinine decreases < 1.6	Aggressive hydration with NSS; monitor serum creatinine weekly
2.1-3.5	Withhold 1 cycle; cisplatin will be reinstituted at 40 mg/ m^2 once creatinine decreases to < 2.0; otherwise, stop cisplatin	Aggressive hydration with NSS; monitor serum creatinine weekly

7.8 Definitions for Dose Limiting Toxicity (DLT) [6/4/04]

7.8.1 Acute grade 4 neutropenic fever
7.8.2 Acute thrombocytopenia requiring transfusion
7.8.3 Acute grade 4 esophagitis
7.8.4 Acute grade 4 diarrhea
7.8.5 Acute grade 4 treatment-related pneumonitis
7.8.6 Treatment-related grade 5 toxicity
7.8.7 Any other toxicity attributable to treatment requiring interruption in radiation lasting for > 1 week

7.9 Definition of Maximum Tolerated Dose (MTD)

MTD will be one dose level below DLT.

7.10 Adverse Drug Reaction Reporting (3/24/10)

7.10.1 Beginning April 1, 2010, this study will utilize the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

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

7.10.3 An adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after the final dose, regardless of whether it is considered related to a medication. In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the investigational medication should be considered an adverse event. A preexisting condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

7.10.4 An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Death
- Life-threatening (i.e., at immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

7.10.5 Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Serious also includes any other event that the investigator or company judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred. An unexpected adverse event is one that is not listed as a known toxicity of the investigational drug in the package insert or the investigator's brochure. A related adverse event is one for which the investigator assesses that there is a reasonable possibility that the event is related to the investigational drug.

7.10.6 *Adverse Drug Reaction Reporting – Commercial Agent(s)*

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

7.10.6.1 Any ADR that is both serious (life-threatening [grade 4]) or fatal (grade 5) and unexpected;

7.10.6.2 Any increased incidence of a known ADR that has been reported in the package insert or the literature;

7.10.6.3 Any ADR that results in significant disability or incapacity;

7.10.6.4 Any infant born to a patient that was treated on this protocol and has a congenital anomaly or birth defect;

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

7.10.6.6 The ADR report should be documented on FDA Form 3500 (MedWatch) and mailed or faxed to the address on the form, (MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787, FAX 1-800-FDA-0178), as well as to the RTOG Data Management Department:

RTOG Data Management
1101 Market Street, 14th floor
Philadelphia, PA 19107
Phone: 1-800-227-5463, ext. 4189
Fax: 215-928-0153

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included. RTOG will forward by fax a copy of all serious adverse events, regardless of relationship to protocol treatment, to Pharmacia Corporation within 24 hours of receipt by RTOG.

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

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

Investigational Drug Branch (NCI/CTEP) P.O Box 30012 Bethesda, MD 20824 Fax: 301-230-0159	RTOG Data Management AML/MDS Report 1101 Market Street, 14th floor Philadelphia, PA 19107 Phone: 1-800-227-5463 Ext. 4189 Fax: 215- 928-0153

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

7.10.9 *Exposure In Utero*

If any trial subject becomes or is found to be pregnant while receiving an investigational medication/product or within 4 weeks of discontinuing the investigational medication/product, the investigator is to submit this information to Pharmacia on an Exposure in Utero Form (included in the forms packet). This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination. The investigator will follow the subject until completion of the pregnancy and notify Pharmacia of the outcome within 5 days or as specified below. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. If the outcome of the pregnancy meets the criteria for classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedure for reporting serious adverse events, submitting a serious adverse event report to the FDA and submitting the follow-up Exposure in Utero Form with the outcomes completed to Pharmacia.

7.10.10 *CALGB Investigators*

All CALGB investigators are responsible for reporting adverse events to the RTOG Operations Office according to the NCI guidelines. Use the RTOG reporting guidelines above.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY (3/31/04)

9.1 No amifostine is permitted during chemoradiation.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Pre-Study Entry	Before Each Cycle	At Completion of Treatment	q3 mos. in year 1 then q6 mos. for 4 years
History/Physical[a]	X	X	X	X
Zubrod	X	X	X	X
Tumor Evaluation & Response Designation	X			X
CBC/Platelets/Diff	X[c]	X[b]		X[e]
Na, K, Cl, HCO_3, BUN, Cr, LDH, Alkp, SGOT, Bili, Mg^{++}	X[c]	X		X[e]
Pregnancy test	X[c]			
EKG	X			
Chest x-ray	X[c]		X	
Urinalysis *(including Microscopic)*	X[c]			
Bronchoscopy	X[g]		X[d]	
PFTs	X			X[g]
Toxicity Evaluation		X	X	X
CT Chest	X[c]		X[g]	X[f]
CT Abdomen	X[c]		X[g]	X[g]
CT or MRI Brain	X[c]		X[g]	X[g]
Bone Scan	X[c]		X[g]	X[g]
Bone Marrow Asp and BX	X[g]		X[g]	

a. Should include recent weight loss, percent weight loss, usual weight; record concurrent disease and treatment
b. CBC weekly during treatment
c. Lab tests must be done within 2 weeks prior to study entry; pregnancy test is for females of childbearing potential; imaging tests ≤ 4 weeks prior to study entry; see Sections 4.2 and 4.3.
d. Must be repeated if positive at diagnosis and bronchoscopic biopsy was the only documentation of disease. Also recommended if chest CT is equivocal at re-staging.
e. Lab tests are not required after 1 year.
f. Chest CT should be done every 6 months, each year, 1-5.
g. Only if indicated based on specific clinical concerns or suspicions; repeat brain imaging shortly prior to initiating PCI

11.2 Evaluation During Study

11.2.1 History and physical with performance status and weight will be recorded before each cycle.

11.2.2 SMA-12, electrolytes, magnesium, and urinalysis with microscopic analysis will be performed before each cycle; CBC will be done weekly during treatment.

11.2.3 All relevant information regarding drug dosage, tumor response, laboratory data and treatment-related toxicity must be recorded before treatment is given.

11.3 Criteria for Going Off Protocol Therapy

11.3.1 Increasing disease at any time during therapy

11.3.2 The development of unacceptable toxicity, defined as unpredictable, irreversible, or persistent, grade 4 (excluding myelosuppression)

11.3.3 Non compliance with protocol requirements

11.3.4 Patient refusal

12.0 DATA COLLECTION

12.1 Summary of Data Submission

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

Item	Due
Demographic Form **(A5)**	Within 1 week of study entry
Initial Evaluation Form **(11)** Pathology Report **(P1)**	Within 2 weeks of study entry
Preliminary Dosimetry Information RT Prescription (Protocol Treatment Form) **(T2)** Films (simulation and portal) **(T3)** Calculations **(T4)** Pre-treatment/Treatment Planning CT Scan **(C1)**	Within 1 week of start of RT
Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Record **(T5)** *Isodose Distributions **(T6)** Off-Cord Films (simulation and portal) **(T8)**	Within 1 week of RT end
Treatment Summary Form **(TF)**	At 3, 6, 9, 12 weeks and within 2 weeks of early termination of chemotherapy or onset of grade $\geq$ 3 non-hematologic toxicity.
Initial Follow-up Form **(FS)**	At week 13 (day 90) from treatment start
Follow-Up Form **(F1)**	At 6, 9, and 12 mos. from treatment start, then every 6 mos. for 4 years; Also at progression/relapse and at death
Autopsy Report **(D3)**	As applicable

*****3 levels of isodose distributions (see Section 6.4.8)

12.2 CALGB Institutions

CALGB institutions will submit data forms directly to the RTOG Operations Office.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (6/4/04)

13.1.1 To assess the frequency of patients experiencing dose limiting toxicities (as defined in Section 7.8) as well as non-dose limiting toxicities, and to assess the reversibility of all toxicities from this approach.

13.2 Sample Size

13.2.1 *Evaluation of Acute and Late Toxicity* **(6/4/04)**

Patients will be followed for a minimum of 90 days from the start of radiation therapy and carefully evaluated with respect to treatment morbidity. As defined in Section 7.8, a dose limiting toxicity (DLT) is defined as acute grade 4 neutropenic fever, acute thrombocytopenia requiring transfusion, acute grade 4 esophagitis, acute grade 4 diarrhea, acute grade 4 treatment-related pneumonitis, treatment-related grade 5 toxicity, and any other toxicity attributable to treatment requiring interruption in radiation lasting for > 1 week. Acute toxicity is defined to be a toxicity occurring within 90 days from the start of radiotherapy treatment.

The goal of this study is to establish the maximum tolerated dose (MTD) of each of the two sequences of protocol treatment at which no patients will develop acute grade 5 toxicity and

less than 50% of patients will develop acute dose limiting toxicities. If, at any time, a grade 5 toxicity is observed, then accrual will be suspended for that treatment sequence, and the study chairs will review the event. **If the study chairs determine that the grade 5 toxicity is treatment-related, the Executive Steering Committee will be notified; this committee will determine whether the dose level should be closed.** Furthermore, if the combined acute/late DLTs estimate the toxicity rate to be greater than 50% within a treatment sequence (obtained by time to event analysis), at any time, at any dose level, then the Executive Committee will be notified, and the committee will determine whether that sequence (arm) should be closed or reopened at the last dose level.

13.2.2 *Dose Escalation* **(1/12/04)**

This study consists of two separate sequences of dose escalation. Sequence A (Arm 1) involves an escalation of irinotecan administered concurrently with a constant cisplatin dose and thoracic RT at total dose of 45 Gy BID. Sequence B (Arm 2) involves an escalation of irinotecan concurrently with a constant cisplatin dose and thoracic RT (70 Gy) once daily.

Dose escalation will take place in an alternating stepwise fashion, such that only one dose level within a sequence (arm) is escalated at a time. Sequence A (Arm 1), Level 1 will be followed by Sequence B (Arm 2), Level 1. As soon as Sequence B (Arm 2) Level 1, accrual is achieved, then Sequence A (Arm 1), Level 2 accrual may begin (if dose level 1 of Sequence A [Arm 1] has been found acceptable). It is the intent of this "ping-pong" approach, for example, to accrue patients to Sequence B (Arm 2), Level 1 while toxicity is being assessed for Sequence A (Arm 1), Level 1. A new dose level cannot open until dose acceptability has been determined for the preceding dose level *within the sequence (or arm)*. In addition, only one sequence (arm) of the study will be open for accrual at a time. Frequent conference calls will be conducted amongst the principal investigators and RTOG Headquarters staff.

For each dose level, six patients will be accrued. After 90 days of evaluation, the current dose will be considered acceptable if no DLTs are observed in the first three patients (0/3), or if one patient in the first three patients (1/3) and none of the last three patients (0/3) experience a DLT. If the current level is considered acceptable, then dose escalation will occur by accruing up to six new patients to the next level *in the sequence*. Otherwise, the preceding dose level within that sequence (arm) will be declared the MTD. If the MTD is established in Sequence A (Arm 1), Level 2, this will not preclude further dose escalation in Sequence B (Arm 2) to Level 3 or beyond. At a given dose level, the probability of halting dose escalation when the true toxicity is 50% or higher is 83%. In addition, if the true DLT rate is instead 20%, there will still be a 29% probability of halting dose escalation at a given dose level. **Maximum size for the study will be 36 patients.**

13.3 Patient Accrual (1/12/04)

The patient accrual is projected to be 6 patients per month. At this rate, it will take one month for each dose escalation. With three months of evaluation required for each level, the expected time for all levels of a sequence to be accrued and evaluated is 18 months.

13.4 Inclusion of Women and Minorities

Ciampi et al.[36] performed a recursive partitioning analysis on small cell lung cancer dataset and found that gender does influence overall survival in limited stage patients. This has not been shown to be consistent by all authors. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender and treatments and race/ethnicity and treatments. The projected gender and minority accruals are shown below:

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	16	18	34
Ethnic Category: Total*	17	19	**36***
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	2	3	5
Native Hawaiian or other Pacific Islander	0	0	0
White	15	15	30
Racial Category: Total*	17	19	**36***

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APPENDIX I

RTOG 0241

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

PHASE I STUDY OF IRINOTECAN AND CISPLATININ COMBINATION WITH TWICE DAILY THORACIC RADIOTHERAPY (45 Gy) OR ONCE DAILY THORACIC RADIOTHERAPY (70 Gy) FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

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

You are being asked to take part in this study because you have a type of lung cancer called limited small cell lung cancer (SCLC).

WHY IS THIS STUDY BEING DONE?

The standard treatment for limited SCLC is a combination of chemotherapy and radiation. The purpose of this study is to find out what effects (good and bad) the drug, irinotecan, given in combination with chemotherapy (cisplatin) and radiation, has on patients with limited SCLC. While irinotecan is one type of standard therapy for lung cancer, it is considered by most experts to be investigational when given during radiation.

This study will find out the highest dose of irinotecan that can be safely given with chemotherapy and radiation. Groups of patients will receive irinotecan in increasing doses between 40-60 mg until at least some of the patients experience severe side effects.

This research is being done because irinotecan plus cisplatin has been shown to be more effective than other chemotherapy in a type of cancer called extensive small cell lung cancer. However, the safety of irinotecan has not yet been studied in treatment of limited SCLC. Adding irinotecan to chemotherapy and radiation might make these treatments more effective. However, adding irinotecan also could result in a serious increase in side effects.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 36 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

All patients will receive one of the two treatments described below. Which treatment you receive will depend on when you enter the study. The dose of irinotecan will be increased from a starting dose of 40 mg only after the safety at the previous level has been confirmed in several people. The dose of cisplatin will be kept the same for all patients.

Patients will be assigned to one of these treatments in groups of six. The first 6 patients who agree to participate in this study will receive Treatment A. The next 6 patients who agree to participate in this study will receive Treatment B. Patients will continue to be assigned to treatment in groups of six, as they agree to participate, alternating between Treatments A and B. The dose of irinotecan will continue to increase from 40 to 50 to 60 mg until at least some patients experience severe side effects.

Treatment A

You will receive 4 cycles of chemotherapy. In each cycle of chemotherapy, you will receive irinotecan and cisplatin through your vein on the first day and then receive irinotecan alone through your vein seven days later. When you receive irinotecan and cisplatin on the first day of treatment, you also will begin receiving radiotherapy to the chest two times per day (5-8 hours apart). You will receive radiotherapy Monday through Friday for 3 weeks.

You will receive radiotherapy to the chest only with the first cycle of irinotecan and cisplatin. You will receive the other 3 cycles of irinotecan and cisplatin after your radiotherapy is finished (for a total of 4 cycles of chemotherapy).

Treatment will be given on an outpatient or inpatient basis. You also may be given a growth factor for the bone marrow, G-CSF, by injection under the skin, to help decrease the side effects of the chemotherapy and radiotherapy.

Treatment B

You will receive 4 cycles of chemotherapy. In each cycle of chemotherapy, you will receive irinotecan and cisplatin through your vein on the first day and then receive irinotecan alone through your vein seven days later. When you receive irinotecan and cisplatin on the first day of treatment, you also will begin receiving radiotherapy to the chest one time per day. You will receive radiotherapy Monday through Friday for 7 weeks.

You will receive radiotherapy to the chest only with the first 2 cycles of irinotecan and cisplatin. You will receive the other 2 cycles of irinotecan and cisplatin after your radiotherapy is finished (for a total of 4 cycles of chemotherapy).

Treatment will be given on an outpatient or inpatient basis. You also may be given a growth factor for the bone marrow, G-CSF by injection under the skin, to help decrease the side effects of the chemotherapy and radiotherapy.

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

- A physical exam before beginning treatment, before each cycle of chemotherapy, every 3 months for a year, and then every 6 months for 4 years

- Blood tests before beginning treatment, on days 8 and 15 of treatment and before each cycle of chemotherapy, every 3 months for a year, and then as advised by your doctor
- For women who are able to have children, a test prior to study entry to see if you are pregnant
- A urinalysis before beginning treatment
- An EKG before beginning treatment
- Tests of your lung function before beginning treatment and then as advised by your doctor
- A chest x-ray, bone scan, and a CT scan of your chest, stomach, and head before beginning treatment then as advised by your doctor
- A biopsy of your bone marrow, if advised by your doctor

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for a minimum of 12 weeks. You will be seen in follow-up visits every three months for 1 year, then every six months for 4 years.

The researcher may decide to take you off this study if your condition worsens, tumor appears elsewhere in your body, side effects become too severe, or new information becomes available that indicates this treatment is no longer in your best interest.

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. Sudden withdrawal could lead to your tumor growing and/or spreading.

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 and chemotherapy are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks and side effects related to the treatment we are studying include:

Risks from Chemotherapy

Irinotecan

Very Likely

- Diarrhea
- Abdominal cramping
- Nausea and/or vomiting
- Decreased appetite
- Hair loss
- Weakness
- Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily; This lowering of blood counts can lead to need for treatment with antibiotics, transfusions, or hospitalization if severe.
- Skin irritation, if irinotecan leaks from the vein

Less Likely

- Cough

Less Likely, But Serious

- Shortness of breath
- Inflammation of the lining of the digestive system, with possible bleeding from the bowel

Adding irinotecan to chemotherapy and radiation might make these treatments more effective. However, adding irinotecan also could result in a serious increase in some side effects, such as:

- Difficulty, pain, or burning sensation when swallowing
- Decrease in blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Inflammation of the lungs

Cisplatin

Very Likely

- Nausea and/or vomiting
- Hearing loss, ringing in the ears
- Numbness of the fingers and toes
- Lower blood counts with risk of infection or bleeding
- Anemia
- Loss of appetite

Less Likely

- Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
- Loss of taste
- Muscle cramps
- Involuntary movement
- Restlessness

Less Likely, But Serious

- Kidney damage
- Liver damage
- Acute leukemia

Risks from Radiation Therapy

Radiation therapy to the chest

Very Likely

- Difficulty, pain, or burning sensation when swallowing, which is temporary; the use of chemotherapy with radiation may increase this risk. You should avoid acidic or spicy foods and alcoholic beverages.
- Fatigue (tiredness) for no apparent reason, which is temporary
- The skin in the treatment area may become reddened and/or dry, and chest hair may not grow back
- Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Cough
- Some difficulty breathing, due to lung damage, as described below

Less Likely, But Serious

- Irritation of the lining around the heart, which can cause chest pain, shortness of

breath, and irregular or rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Narrowing of the esophagus (tube to the stomach)

The side effects of radiation therapy to the chest twice a day for 3 weeks (Treatment A) are the same as for radiation therapy to the chest once a day for 7 weeks (Treatment B). However, there may be a higher risk of developing painful swallowing or lung damage for patients receiving radiation therapy for a longer period (7 weeks, Treatment B).

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life-threatening. The combined use of chemotherapy and radiotherapy, as in this study, may increase the risk of developing symptoms due to lung damage.

Reproductive Risks

For Women
This clinical treatment would definitely involve risks to both you as a patient and your nursing infant, or an unborn child if you were to be or become pregnant during treatment. To help prevent injury to unborn children, upon recommendation by the attending physician, the participants should practice adequate methods of birth control throughout the period of their involvement in this clinical research study. If you should become pregnant while on the study, you must tell your doctor immediately. If you are able to have children, this treatment may make you sterile or unable to have children.

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

It is not possible to predict whether or not any personal benefit will result from the use of the study treatment program. The information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of your tumor and prolongation of your life than would be obtained with non-research treatment, but these benefits are not guaranteed.

You have been told that should your disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest, or should your doctor feel that this treatment is no longer in your best interest, the treatment would be stopped. Further treatment

would be discussed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Alternatives which could be considered in your case include: 1) radiation therapy once or twice a day with chemotherapy, 2) chemotherapy alone, 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.

Your doctor can provide detailed information about your disease and the benefits of the various treatments available. You have been told that you should feel free to discuss your disease and your prognosis with your doctors. The physicians involved in your care will be available to answer any questions you have concerning this program. In addition, you are free to ask your physician(s) any questions concerning this program that arise in the future.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, Cancer and Leukemia Group B, 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. Medicare should be considered a health insurance provider.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A group of experts in lung cancer from the RTOG Lung Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study. **We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.**

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name	Telephone Number

For information about this study, you may contact:

Name	Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) 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 at **http://cancertrials.nci.nih.gov** or for accurate cancer information including PDQ (Physician Data Query) visit **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's Name	Signature	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature	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)*.

APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER
(IUCC-AJCC, 1997)
Chest 111; 1710-17
Mountain CF

TNM CATEGORIES

DEFINITIONS
Primary Tumor (T)

Tx Primary tumor cannot be assessed, or tumor proven by 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 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 of 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 tumor), 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; separate tumor nodule(s) in the same lobe; or tumor with a malignant pleural effusion**

*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.
***Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgement 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 node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

MX Distant metastasis cannot be assessed

MO No distant metastasis

M1 Distant metastasis present (includes synchronous separate nodule(s) in a different lobe)

Stage Grouping

Occult	**TX**	**N0**	**M0**
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stave 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	
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	DEATH
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	DIRECT
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	RELATED
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	TO
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	RADIATIO
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%	A. EFFE
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	CTS
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	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

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as "known or expected" or "unknown or unexpected".

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

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite:	The adverse event is *clearly related* to the treatment/procedure.
Probable:	The adverse event is *likely related* to the treatment/procedure.
Possible:	The adverse event *may be related* to the treatment/procedure.
Unlikely:	The adverse event is *doubtfully related* to the treatment/procedure.
Unrelated:	The adverse event is *clearly NOT related* to the treatment/procedure.

B. Grading of Adverse Events (3/24/10)

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

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.

3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working

days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

a. The Group Chair in consultation with the Study Chair 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.

b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All "expedited" adverse event reports should be sent to the local Institutional Review Board (IRB).

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

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity (≥ grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. <u>Adverse Event Reporting Related to Radiation Therapy</u> (3/24/10)

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTEP Active Version CTCAE and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.

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

E. Adverse Event Reporting Related to Systemic Anticancer Agents (3/24/10)

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	**Increased Incidence of an Expected AE[1]**	**Hospitalization During Treatment[2]**	**Secondary AML/MDS[3]**
FDA Form 3500[4,5] within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis [4,5]				X
Call RTOG within 24 hrs of event[7]	X[6]			

1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTEP Active Version CTCAE Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
5. Copy to RTOG Data Management labeled: Attention: Adverse Event Report.
6. All grade 5 known toxicity.
7. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, http://ctep.info.nih.gov for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators' reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.
Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**
Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. Expedited Reporting for Phase 1 Studies

Unexpected Event		**Expected Event**	
Grades 2-3 Attribution: Possible, Probable or Definite	**Grades 4 & 5 Regardless of Attribution**	**Grades 1 - 3**	**Grades 4 & 5 Regardless of Attribution**
Grade 2: Expedited report within 10 working days. Grade 3: Report by phone to IDB[1,2] within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting **NOT** required.	Report by phone to IDB[1,2] within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting **NOT** required.	Report by phone to IDB[1,2] within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	**Grades 4 & 5 Regardless of Attribution**	**Grades 1 - 3**	**Grades 4 & 5 Regardless of Attribution**
Expedited report within 10 working days. Grade 1: Adverse Event Expedited Reporting **NOT** required.	Report by phone to IDB[1,2] within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting **NOT** required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).