RADIATION THERAPY ONCOLOGY GROUP
RTOG 0239

A PHASE II STUDY OF ACCELERATED HIGH DOSE THORACIC IRRADIATION WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED SMALL CELL LUNG CANCER

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Activation Date: June 20, 2003
Closure Date: May 23, 2006
Update Date: November 12, 2003
Termination Date: November 5, 2013
Version Date: March 24, 2010
Includes Amendments 1-5
(Broadcast: 4/6/10)

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INDEX

Schema
Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I  -Sample Consent Form
Appendix II  - Performance Status Scoring
Appendix III - Staging System
Appendix IV  - Toxicity Criteria
Appendix V   - Adverse Reaction Reporting Guidelines
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WITH CONC RURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED SMALL CELL LUNG CANCER

SCHEMA (10/29/03)

Radiation Therapy
Large field 28.8 Gy: 1.8 Gy per fraction, 5 days per week for 16 fractions;
On days 23-26, BID: use AP/PA fields in a.m. @ 1.8 Gy per fraction; boost
with 2nd treatment in p.m. @ 1.8 Gy per fraction;
Then off-cord boost, 1.8 Gy, BID, x last 5 days for a total dose of 61.2 Gy
in 5 wks

Concurrent Chemotherapy
Chemotherapy will be started on day 1 of thoracic radiotherapy (+/-24
hours)
Cisplatin, 60 mg/m² i.v. day 1; Etoposide, 120 mg/m² i.v. day 1;
Etoposide, 240 mg/m² p.o. per day on days 2 and 3 or Etoposide 120
mg/m² i.v. per day on days 2 or 3 (see Section 7.1.4);
Repeat cycle every 3 weeks x 2 cycles, followed by adjuvant
chemotherapy alone x 2 cycles

Adjuvant Chemotherapy
Cycle 3: Day 43 (Cisplatin; Etoposide) and days 44 and 45 (Etoposide,
p.o. or i.v.)
Cycle 4: Day 64 (Cisplatin; Etoposide) and days 65 and 66 (Etoposide,
p.o. or i.v.)

DOSE SCHEDULE

<table>
<thead>
<tr>
<th>Large Field (1.8 Gy/fx)</th>
<th>Boost (1.8 Gy BID) x (off cord)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
<td><strong>Day</strong></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>XRT a.m.</td>
<td>L</td>
</tr>
<tr>
<td>XRT p.m.</td>
<td></td>
</tr>
<tr>
<td>Cycles 1-2</td>
<td>CE</td>
</tr>
</tbody>
</table>

KEY: L = Large Field; B = Boost Field; C = Cisplatin; E = Etoposide
Total Dose = 61.2 Gy

ELIGIBILITY: (See Section 3.0 for details)
- Histologic or unequivocal cytologic proof of SCLC with measurable or evaluable disease
- Clinically limited disease, clinical stages I-IIIB
- Age ≥ 18
- Zubrod 0-1

(Continued on next page)
- Absolute granulocytes ≥ 1500; platelets ≥ 150,000; bilirubin ≤ 1.5 mg/dl; creatinine ≤ 1.5 mg/dl
- No prior chemotherapy; no radiotherapy to the chest or other area with large amount of bone marrow, such as ≥ 75% pelvic bone
- No pericardial or pleural effusion on CXR regardless of cytology
- No previous (within 2 years) or concurrent malignancy other than curatively treated basal or squamous cell skin cancer or non-invasive in situ malignancies
- Patients with serious intercurrent medical illness, e.g., symptomatic heart disease, an MI six months prior to study entry, COPD with FEV-1 ≤ 0.8 L, or uncontrolled bronchospasm are not eligible.
- Patients of childbearing potential must practice adequate contraception.
- Patients must be available for active follow up.
- Patients must sign a study-specific consent form prior to study entry.

**Required Sample Size: 71**
1. Does the patient have documented histologic or unequivocal cytologic proof of small cell lung cancer?

2. What is the stage?

3. Does the patient have N3 disease based on contralateral hilar or contralateral supraclavicular nodal involvement?

4. Is there evidence of pleural or pericardial effusion?

5. Does the patient have measurable or evaluable disease?

6. Is the Zubrod 0-1?

7. Has the patient received any prior chemotherapy or radiotherapy to the chest or other area containing a large amount of bone marrow, such as ≥ 75% pelvic bone?

8. At least 18 years of age?

9. Is the patient's hematologic, hepatic, and renal function adequate, as specified in Section 3.1.6?

10. Has the radiation oncologist verified that the tumor can be encompassed by radiation fields as defined in Section 6.0 without significantly compromising pulmonary function?

11. Has the patient had myocardial infarction within the last 6 months, symptomatic heart disease, COPD with FEV-1 ≤ 0.8 liter, or uncontrolled bronchospasms?

12. Is there history of a prior malignancy from which patient has not been disease free for a minimum of 2 years other than adequately treated basal/squamous skin cancer or in situ cervix cancer?

13. Does the patient demonstrate uncontrolled psychiatric illness or chronic alcohol or drug abuse?

14. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?

15. Has the patient had a complete tumor resection?

(Continued on next page)
The following questions will be asked at Study Registration:

1. Has the Eligibility Checklist (above) been completed? (Y)
2. Is the patient eligible for this study? (Y)
3. Date the study-specific Consent Form was signed? (must be prior to study entry)
4. Patient’s Initials (First Middle Last) [Initials only effective 2/2002]
5. Verifying Physician
6. Patient’s ID Number
7. Date of Birth
8. Race
9. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
10. Gender
11. Patient’s Country of Residence
12. Zip Code
13. Patient’s Insurance Status
14. Will any component of the patient’s care be given at a military or VA facility?
15. Treatment Start Date
16. Medical Oncologist
17. Was a PET scan performed on this patient? (Y/N)
18. Was a PET scan used in staging? (Y/N/NA)
19. Was a PET scan used in treatment planning for radiation therapy? (Y/N/NA)

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 (11/12/03)

In the U.S., there will be approximately 169,400 patients with lung cancer diagnosed in 2002, of which 20% will have small cell carcinoma.1 One-quarter to one-third of these patients will be expected to have limited disease in the thorax. Although early development of distant metastasis is a critical problem for patients with clinically limited small cell lung cancer, intrathoracic failure becomes more important once distant metastasis is controlled. Two meta-analyses, using different methods, confirmed the value of thoracic irradiation to decrease local recurrence and to improve survival. The study by Warde and Payne2 based on results from 11 trials showed an increased absolute survival of 5.4% at two years. Pignon and his colleagues3 collected data on 2140 patients from 16 randomized trials comparing chemotherapy alone versus chemotherapy plus thoracic irradiation, and found an improvement in absolute survival of 5.4% at three years. It is obvious that the effectiveness of both thoracic irradiation and systemic chemotherapy needs to be improved. One approach to improve local and distant controls is to apply systemic chemotherapy as a radiosensitizer.

Turrisi et al.4 and Johnson et al.5 reported small series of patients treated with concurrent cisplatin and etoposide with accelerated fractionation: 1.5 Gy bid, 5 days per week was given for 3 weeks for a total dose of 45 Gy. Two-year survival rates were 57% and 65% for the Turrisi6 and Johnson7 studies, respectively; 4-year survival was 36%.6

The question of standard once-a-day fractionation (1.8 Gy per fraction) versus accelerated fractionation (1.5 Gy bid) with a total dose of 45 Gy was investigated in a cooperative randomized trial.8 Radiotherapy was given with concurrent chemotherapy consisting of cisplatin, 60 mg/m² i.v., day 1, and etoposide, 120 mg/m² i.v., days 1-3, for 4 cycles. Four hundred and nineteen patients were enrolled in this randomized trial between 1988 and 1992 with 383 eligible and evaluable.

This intergroup study (ECOG 3588/RTOG 8815) randomly assigned 417 patients with limited small cell lung cancer to receive a total of 45 Gy thoracic radiation therapy (TRT), given either once daily over a period of 5 weeks (Arm 1) or twice-daily over a 3-week period (accelerated hyperfractionation, Arm 2). The hyperfractionated and accelerated TRT group (Arm 2) significantly improved the five-year survival by 26% compared to 16% among patients treated by daily fractionated prolonged TRT (Arm 1) [p=0.04]. Their median survivals were 19 months in Arm 1 and 23 months in Arm 2. Their 2-year survival rates were 26% in Arm 1 and 46% in Arm 2, although acute grade 3 esophagitis was significantly more frequent in Arm 2 (27%) compared with 11% in Arm 1 (p < 0.001) Turrisi.8

Table 1 shows the results of the intergroup study comparing our proposed RTOG phase II study of limited small cell lung cancer.

<table>
<thead>
<tr>
<th>Table 1.0</th>
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<tr>
<td>Intergroup 0096 Turrisi8</td>
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<tr>
<td>TRT</td>
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<td>Duration</td>
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<tr>
<td>MS</td>
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<tr>
<td>1-Yr Surv</td>
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The sequencing and timing of chemotherapy and thoracic radiotherapy also are controversial. The NCI of Canada Clinical Trial Group studied early versus late thoracic radiation therapy in a randomized comparative fashion. Their trial enrolled 308 patients and showed that the early thoracic irradiation group had a significantly better survival and fewer brain metastases compared to the late thoracic irradiation group.9

The radiation dose to the thorax is another controversial area.10 The National Cancer Institute of Canada developed an important study to show dose-response to the thorax.11 They have shown a clear dose response with increased thoracic progression-free survival by giving 37.5 Gy in 15 fractions in 3 weeks compared to 25 Gy in 10 fractions in 2 weeks as a consolidation after completion of cisplatin-etoposide and cyclophosphamide-doxorubicin-vincristin alternating or sequential chemotherapy. Arriagada et al.12 published a report of 173 patients with limited small cell lung cancer treated in 3 consecutive trials at the Institute of Gustave-Roussy, France. The total dose of thoracic radiotherapy increased from 45 Gy (15-15-15), 55 Gy (20-20-15) to 65 Gy (20-20-20), which was given by split courses interdigitating with chemotherapy. Their three-year local control rates were 66%, 70%, and 70%, respectively and five-year survival rates were 16% 16%, and 20%, respectively. There was a 10% rate of lethal toxicity without significant difference depending on the doses. They concluded there were no significant differences in the local control and survival with treatment between 45 Gy and 65 Gy when effective chemotherapy was given in this interdigitating manner.12

Choi et al.13 presented a phase I study to determine the maximum tolerated dose (MTD) of radiation in daily and twice-daily fractionation with concurrent chemotherapy. MTD for hyperfractionated radiotherapy was reached at 45Gy/30fractions/19 days. However, MTD for daily fractionation was not reached at 66Gy/33fractions/ 45 days. Therefore, patients have been accrued to 70 Gy/35 fractions/47 days, which might be too long to treat rapidly proliferating tumors, such as small cell lung cancer. The tumor response rates varied from 78% to 100% without significant difference among the different dose levels. Grade 3 or more esophagitis and granulocytopenia were more marked among the patients who were treated by hyperfractionated and accelerated fractionation.

A Phase I study, RTOG 97-12, was initiated to improve locoregional control by escalating the total dose of radiation therapy using daily fractionation to larger fields and then boost field and bid radiation therapy toward the end of the thoracic radiation therapy with concurrent etoposide and cisplatin. In this way accelerated radiation therapy could be given toward the end, when residual tumors are thought to be more resistant and proliferating rapidly. This boost field, which was much smaller compared to the original AP/PA field, would reduce toxicity to the esophagus. We have learned that Intergroup study 0096 showed significantly better tolerance by daily fractionation with acute grade 3 esophagitis, 11% by using 1.8 GY daily fractionation, compared to 45 Gy in 30 fractions within 3 weeks, which was accelerated, that caused grade 3 acute esophagitis, 26%. Therefore, if we can start daily fractionation to the larger field and boost toward the end with the smaller field to the residual tumor, dose escalation can be achieved without extending the duration of the thoracic radiation therapy, which would be detrimental due to rapid proliferating tumor cells.

RTOG 97-12 sought dose escalation with radiation therapy of concomitant boost irradiation at the end of the course of treatment. Whereas the phase III trial, RTOG 88-15, which tested a five-week course of daily irradiation with a total dose of 45 Gy at 1.8 GY/fraction with concurrent cisplatin/etoposide, had quite acceptable toxicity, the local failure rate (50%) was considered far too high. Accelerating the total dose of irradiation by giving twice-daily treatment to a reduced field encompassing only the tumor (concomitant boost) during the last days of irradiation would permit the total dose be increased within the same five-week period. Chemotherapy given concurrently with irradiation would achieve maximum but acceptable hematologic toxicity, permitting the total dose of thoracic radiation therapy to be escalated based on non-hematologic toxicity.

The first arm of RTOG 97-12 included large field irradiation to 36 Gy at 1.8 Gy/fraction followed by a reduced (boost) field of 1.8 Gy/fraction with twice-daily treatments given during the last three days to achieve a total dose of 50.4 Gy. This was combined with cisplatin, 60 mg/m² iv day 1 and etoposide 120 mg/m² iv day 1 followed by etoposide 120 mg/m² po on days 2 and 3 of each cycle. Eight patients were
treated with this regimen. It was then considered appropriate by the participating medical oncologist to increase the dose of oral etoposide so a cohort of ten patients received the same regimen, increasing the dose of oral etoposide on days 2 and 3 of each cycle to 240 mg/m². Thus, cisplatin 60 mg/m² iv day 1, etoposide 120 mg/m² iv day 1, and etoposide 240 mg/m² po days 2 and 3 became the chemotherapy regimen against which to escalate the thoracic radiation dose. The thoracic irradiation dose would be escalated until such time as 40% or more patients would develop nonhematologic toxicity. Escalations from 50.4 Gy total dose (bid last 3 days) to 54 Gy (bid last 5 days), to 57.6 Gy (bid last 7 days), 61.2 Gy (bid last 9 days) and eventually 64.8 Gy (bid last 11 days) were planned. Only in the last arm (64.8 Gy) did the nonhematologic toxicity exceed 40%. Five of the eleven patients treated on the highest dose arm developed nonhematologic toxicity; three of them had grade 3 esophagitis and five had grade 3 nausea and vomiting. After careful review, the participating investigators concluded that the toxicity in the 64.8 Gy arm was not tolerable, and the decision was made to pursue a phase II trial using the 61.2 Gy arm.

In the current study, we do not start hyperfractionated radiation therapy with concurrent etoposide and cisplatin for limited small cell lung cancer because at the beginning, the volume of the disease is unacceptably large in the mediastinum; using this regimen would cause unacceptable toxicity to the esophagus. As Turrisi found, bid radiation therapy starting day one with concurrent PE showed unacceptable grade 3 acute esophagitis (26%) compared to daily fractionation (11%). SCLC is very sensitive to chemotherapy and radiation therapy; therefore, when the volume of the tumor reduces after receiving 36 Gy in four weeks, then the field can be reduced as a boost by bid radiation therapy. Usually at the beginning of any treatment of cancer, we are dealing with more sensitive tumor; however, after four or five weeks of treatment, whatever tumor is left is fairly resistant and starts to proliferate fairly quickly (clonogens), which was documented by Withers. Starting once-daily radiation therapy does not increase acute severe esophagitis compared to bid radiation therapy with concurrent chemotherapy, based on the previous randomized limited small cell lung cancer trial, but we should be able to give bid radiation therapy when radiation therapy fields are reduced (boost fields).

Since retrospective analysis has shown high incidence of CNS metastasis for small cell lung cancer patients, especially complete responders (CR), and prophylactic cranial irradiation (PCI) can be given safely without causing cognitive deficiency, CR patients will be offered PCI on RTOG 0212 or off study as described in Section 6.6.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the response rate and progression-free and overall survival in patients with limited small cell lung cancer treated with cisplatin and oral etoposide and combined with concurrent higher dose of thoracic radiotherapy (TRT) followed by etoposide and cisplatin.

2.1.2 To determine the qualitative and quantitative toxicity and reversibility of toxicity of daily TRT followed by hyperfractionated TRT as a boost.

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 small cell carcinoma of the lung is required.

3.1.2 Patients must have limited disease (clinical stages I-IIIb, i.e., confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion or N3 disease based on contralateral hilar or contralateral supraclavicular involvement).

3.1.3 Patients must have measurable or evaluable disease.

3.1.4 Age ≥ 18

3.1.5 Zubrod Performance Scale 0-1 (Appendix II)

3.1.6 Adequate hematologic, hepatic, and renal function as follows: absolute granulocytes ≥ 1500; platelets ≥ 150,000; bilirubin ≤ 1.5 mg/dl; and serum creatinine ≤ 1.5 mg/dl are required.

3.1.7 Radiation oncologist must certify that tumor can be encompassed by limited radiotherapy fields without significantly compromising pulmonary function

3.1.8 Patients of childbearing potential (male and female) must practice adequate contraception.

3.1.9 Patients must be available for active follow up.

3.1.10 Patients must sign a study-specific consent form prior to study entry.
3.2 **Conditions for Patient Ineligibility (10/10/05)**

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

3.2.2 Patients with complete tumor resection

3.2.3 Prior radiotherapy to the chest or other area containing a large amount of bone marrow, such as ≥ 75% of pelvic bone; prior chemotherapy

3.2.4 Pericardial or pleural effusions on CXR regardless of cytology

3.2.5 Serious intercurrent medical illness including symptomatic heart disease or myocardial infarction within 6 months, COPD with FEV-1 ≤ 0.8 liter, or uncontrolled bronchospasm in the unaffected lung

3.2.6 Previous (within the past 2 years) or concurrent malignancy other than curatively treated basal or squamous cell skin cancer or non-invasive in situ malignancies

3.2.7 Patients with uncontrolled psychiatric illness or chronic alcohol or drug abuse

4.0 **PRETREATMENT EVALUATIONS**

4.1 A complete history and physical to include performance status, recent weight loss, psychiatric history, head injury, drug or alcohol abuse, central nervous system disease, or previous treatment with cranial irradiation or intrathecal chemotherapy, previous and concurrent non-malignant disease;

4.2 Laboratory studies including: a CBC with differential, platelet count, electrolytes, magnesium, and urinalysis with microscopy done within 2 weeks before study entry;

4.3 Chest X-ray, EKG, MRI or CT of brain, CT of chest/upper abdomen with contrast, radionuclide bone scan, done within four weeks before study entry;

4.4 Bronchoscopy is recommended but not required;

4.5 PFTs (FEV, DLCO, TVC) within 4 weeks before study entry;

4.6 Bone marrow aspiration and biopsy if LDH is elevated > 1.5 x normal value or for abnormal CBC;

4.7 Location, type, and size of all measurable lesions prior to treatment 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.

6.0 **RADIATION THERAPY** Note: Intensity Modulated RT (IMRT) is not allowed.

6.1 **Thoracic Radiotherapy Dose and Fraction Scheme**

6.1.1 Daily large field radiation therapy of 1.8 Gy per fraction will be given through the end of the 3rd week, 1.8 Gy per fraction, 5 days per week, 16 fractions for a total of 28.8 Gy. This will be followed during the 4th week (on days 23-26) by AP/PA fields in the morning, 1.8 Gy per fraction, and boost field using oblique (preferable) or lateral field in the p.m., 1.8 Gy per fraction, for 4 days with a minimum six-hour interfractional interval. Boost field using oblique or lateral field will be continued during the 5th week, 1.8 Gy per fraction, BID, with a minimum six-hour interfractional interval. The total dose is 61.2 Gy in 5 weeks.

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

6.2.1 Complete descriptions of volumes to be treated have been included in the 3D-CRT protocols in order to minimize the institutional variation of tumor and target volume delineation for protocol cases. Please consult the ICRU 1993 document for complete descriptions of the various target volumes defined. The following paragraphs summarize the ICRU definitions which are relevant for this protocol.

6.2.2 The gross tumor volume (GTV) includes the known disease as determined by physical examination, imaging studies and other diagnostic information. More than one GTV can be defined (i.e. GTV-P or GTV-N).
6.2.3 The clinical target volume (CTV) includes the area of subclinical involvement around the GTV. The CTV is the GTV plus the margin for micro extensions of the tumor, which is 1.0 cm. More than one CTV can be defined. For this protocol CTV = GTV + 1.0 cm. Ipsilateral supraclavicular irradiation is allowed when necessary for primary tumor coverage. Contralateral hilar or supraclavicular treatment is not allowed. The lower field border will be 3.0 cm below the carina for upper and middle lobe tumors for the large fields and 1.0 cm as CTV beyond GTV for the boost fields. If there is a gross subcarinal node, the margin needs to be 1.0 cm beyond the nodal involvement (GTV) for both the large and boost fields. Any mediastinal node detected by CT scan > 1.5 cm should be included with at least a 1 cm margin as CTV. Simulation is mandatory.

6.2.4 The planning target volume (PTV) is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the GTV. This margin accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues which contain the GTV (e.g. respiration), and size variations in the tissue containing the GTV. The PTV is a geometric concept, which is 0.5 cm (e.g., upper lobe or proximal lesion) – 1.5 cm (e.g., lower lobe lesion) depending on the motion of the tumor detected by the fluoroscope. PTV = CTV + 0.5-1.5 cm.

6.3 Technical Factors

6.3.1 Radiotherapy Equipment: Megavoltage photon beam required, with minimum peak energy of 6 MeV. 6MV-18MV is an acceptable range of photon beam.

Minimum source to isocenter distance of 100 cm. Electron beams, $^{60}$Co, 4 MeV accelerators, and 80 cm SSD are not acceptable.

6.3.2 Beam Shaping: Custom blocks (5 HVL), or multileaf collimator (MLCs) individually shaped for each field, should be used to protect normal tissues outside the target volume.

6.3.3 Compensators: Due to the sloping of the chest and the resultant variation in patient thickness from the cephalad to the caudal portion of the anterior/posterior thoracic fields, compensators and possibly wedges will be required when the dose variation from the cephalad to the caudal portion of the field exceeds 10%. Dose variations through the target volume, as defined in 6.2, which are greater than 10%, are NOT permitted. Compensation is not required for angled fields.

6.3.4 Doses are to be calculated without correction, i.e., no correction is to be made for density differences between air spaces, lung, water-density or bony tissue.

6.3.5 Dose Heterogeneity

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

6.3.6 Localization Films

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

6.3.7 Maximum Dose to Critical Normal Tissues: (5/20/04)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dose Limit</th>
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<tbody>
<tr>
<td>Contralateral whole lung (nonparamediastinal)</td>
<td>15 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>*36 Gy to 100%; 40 Gy to 50% (10 cm of the spinal cord can receive up to 45 Gy and 5 cm can receive up to 50 Gy). The spinal cord should not be irradiated BID.</td>
</tr>
<tr>
<td>Esophagus</td>
<td>45 Gy (10 cm of the esophagus can receive up to 60 Gy and 5 cm can receive up to 65 Gy within the boost field)</td>
</tr>
<tr>
<td>Heart</td>
<td>36 Gy to 100% of the heart</td>
</tr>
</tbody>
</table>

*40 Gy to 50% of the spinal cord given in daily doses of 1.8 Gy/Fx up to 28.8 Gy; to minimize the risk of radiation myelopathy, the spinal cord should be spared from the 1.8 Gy/Fx, BID radiation.
6.4 Treatment Techniques

6.4.1 All doses are to be prescribed and calculated assuming a homogeneous patient. There will be no heterogeneity corrections used in the definition of these doses.

6.4.2 The doses shall be prescribed and calculated according to the following ICRU recommendation for external treatments using photons and electrons.

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

6.4.2.2 At the center of the target volume on the central rays for two opposed coaxial unequally weighted beams

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

6.4.2.4 At the center of the target volume for complex treatment arrangements which are not covered above

6.5 Radiation Toxicity (3/24/10)

All grade 4 or grade 5 toxicities that are attributable to radiation therapy will be telephoned to RTOG Headquarters within 24 hours of discovery. Please refer to Section D of the Adverse Event Reporting Guidelines (Appendix V) for the appropriate reporting procedures for radiation therapy related toxicity.

6.5.1 Acute Radiation Toxicity Monitoring: Acute (< 90 days from RT start) side effects of radiation therapy were documented using the NCI Common Toxicity Criteria version 2.0.

6.5.2 Late Radiation Toxicity Monitoring: Late (> 90 days from RT start) side effects will be documented using the RTOG Late Radiation Morbidity Scoring Scheme (Appendix IV).

6.5.3 Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management Department within ten days of discovery.

6.6 Prophylactic Cranial Radiotherapy (PCI)

6.6.1 We recommend that patients achieving a complete response (CR) as determined at re-evaluation after completion of 4 cycles of chemotherapy and XRT be offered prophylactic cranial irradiation (PCI). We encourage patients to enroll in the randomized trial RTOG 0212; however, patients not enrolled in RTOG 0212 still should be considered for PCI at 250 cGy once daily x 10 fractions or 2 Gy once daily x 15-18 fractions.

6.6.1.1 Dose: Those patients randomized to Arm 1 of RTOG 0212, standard dose (SD) PCI, will receive 2.5 Gy once daily, Monday through Friday, in 10 fractions for a total of 25 Gy. Those patients randomized to Arm 2, high dose (HD) PCI, will receive once-daily HD PCI, 2.0 Gy, Monday through Friday, in 18 fractions for a total dose of 36 Gy. Those patients randomized to Arm 3 will receive twice-daily HD PCI, 1.5 Gy, Monday through Friday, in 24 fractions for a total dose of 36 Gy.

6.6.1.2 Technical factors: Any megavoltage, photon equipment is acceptable. Simulation is suggested, but not required.

6.6.1.3 Target volume: Entire intracranial content. Eyes should be excluded or protected. Middle cranial fossa, as defined by bony landmarks of sphenoid sinus and temporal lobe, as well as posterior and anterior cranial fossa meninges, are to be included.

7.0 DRUG THERAPY

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

7.1 Concurrent Chemotherapy

7.1.1 Chemotherapy will be started on day 1 of thoracic radiotherapy (+/- 24 hours). All chemotherapy doses will be calculated on the basis of body surface area using a nomogram deriving surface area from height and actual body weight.

7.1.2 (10/29/03) Prehydrate with 500 ml to one liter D5 1/2 NS with 10 mEq KCl and 8 mEq MgSO4 over 1-2 hours. Post-chemotherapy, hydrate with at least one liter 1/2 NS with 10 mEq KCl over 1-2 hours.

7.1.3 (11/12/03) Day 1: Cisplatin, 60 mg/m2 i.v. given in 500 ml of NS with 12.5 gm of mannitol i.v. over two hours; Etoposide 120 mg/m2 i.v. over 1 hour.

7.1.4 (11/12/03) Days 2 and 3: Etoposide 240 mg/m2 p.o. as a single daily dose per day, taken in the morning, one hour before eating. Because etoposide is available in 50 mg capsules, the dose will be calculated for the two-day period, e.g., a patient whose Body Surface Area (BSA)
is 1.7 m² will take a total of 16 tablets (total 800 mg) over the two-day period. Calculated doses should be rounded down.

If the patient is unable to take etoposide by mouth, or gastrointestinal absorption is not predictable due to nausea, vomiting, or diarrhea, or if oral etoposide is not available or affordable, it can be given i.v. Give one-half oral dose. Etoposide i.v. must be given a half hour before radiotherapy.

7.1.5 Repeat cycle every 3 weeks x 4 cycles of therapy. The first two cycles of chemotherapy will be given concurrently with radiation therapy, followed by 2 more cycles of chemotherapy alone.

7.1.6 Patients will receive antiemetics prior to chemotherapy at the discretion of the treating physician. A 5 HT₃ receptor antagonist and dexamethasone ± lorazepam are recommended.

7.1.7 (10/29/03) G-CSF may be given subcutaneously or i.v. at 5 mcg/kg/d to protect against new episodes of febrile neutropenia in cycles 3-4 of chemotherapy in patients who have experienced such a complication. Alternately, a dose reduction can be instituted (See Section 7.5). The G-CSF must be given separately 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 etoposide. It is recommended that G-CSF be discontinued when the absolute granulocyte count recovers to > 10,000/ml and that 48 hours elapses between discontinuing G-CSF and initiating a subsequent cycle of chemotherapy.

7.1.8 (11/12/03) Amifostine (Ethyol) should not be administered prior to cisplatin.

7.2 Cisplatin (DDP)

7.2.1 **Formulation:** Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 10 mg of mannitol and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5.

7.2.2 **Storage:** The dry unopened vials should be stored at refrigeration temperature (4 to 8°C). Reconstitution results in a solution which is stable for not more than one hour at room temperature (22° C) when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

7.2.3 **Administration:** Intravenous

7.2.4 **Availability:** Commercially available

7.2.5 **Mechanism of Action:** The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of anti-tumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces interstrand cross-links. Also, DDP is not phase sensitive, and its cytotoxicity is similar in all phases of the cell cycle.

7.2.6 **Pharmacology:** The pharmacologic disposition of DDP has been studied in experimental animals and man; however, the methodologies are not specific for absorption spectrometry or by -counting of DDP labeled with 193 Pt-DDP or 195 Pt. After intravenous administration of 193 Pt-DDP in the rabbit or the mouse, most of the radioactivity is found in the kidneys and liver. Very little radioactivity, if any, is found in the brain. Excretion of the isotope by the mouse is rapid, 70% in 24 hours. In tumor bearing mice, the tumor/blood isotope ratio varies from 0.3 to 2 at 4 hours and 5 days after drug injection. In the dog, the disappearance of platinum from plasma after a single intravenous dose of DDP is biphasic with an initial half life of less than 1 hour, and a terminal half life of 5 days. The cumulative urinary excretion of platinum is 60-70%. Initial concentrations of platinum are in the liver, ovary, and uterus where a tissue/plasma concentration ratio of 3:4 is maintained for at least 6 days after the IV injection. In man, the plasma disappearance of platinum is similarly biphasic, with an initial half life of 25-49 minutes and a terminal half life of 2.5 - 3 days. Sixty-five to 97% of the plasma platinum is protein-bound. However, excretion of platinum in man is much slower than in experimental animals, 30 to 40% in 2 days and 30 to 45% in 5 days.

7.2.7 **Animal Tumor Data:** In animal systems, DDP is active in the following tumors: Sarcoma 180, Walker 256 carcinosarcoma, mouse reticular cell sarcoma, DNBA-induced rat mammary carcinoma, B16 melanoma, L1210 ascitic leukemia, Ehrlich ascites tumor, and Lewis lung tumor.

7.2.8 **Animal Toxicology:** The principal targets for the toxic actions of DDP in animals are: the gastrointestinal tract, kidneys, bone marrow, and lymphatic system. The major pathology was in the kidneys. This histological change in the kidneys varied depending on the animal species.
and the dose of DDP; however, tubular injury was the predominant findings. Studies of the pathogenesis of platinum nephrotoxicity indicated that as few as 2 doses of platinum resulted in deranged tubular function and decreased excretion of both potassium and sodium which, in turn, caused swelling of the tubular epithelium and a leak of LDH. This swelling, in turn, increased intra-abdominal pressure impairing glomerular filtration of BUN and creatinine. In both, dogs and monkeys, DDP destroyed circulatory lymphocytes and produced lymphoid atrophy. Pancreatitis and myocar ditis were also occasionally observed. No CNS toxicity was described and this is consistent with the low CNS drug concentration.

7.2.9 Human Tumor Data: Clinical responses have been reported in patients with the following diseases: Non-Hodgkin's lymphoma, breast, sarcoma, Hodgkin's disease, testis, ovary, parotid, lung, prostate, thyroid, bladder, head and neck, and multiple myeloma.

7.2.10 Human Toxicology: The major toxic effects have been the following:
Renal: Renal toxicity was manifested by BUN and serum creatinine elevation and was observed within 10 days from the start of therapy; hyperuricemia.
Ototoxicity: Tinnitus and audiologic impairment in the high frequency range (4000-8000 Hz) were usually encountered with high doses (50 mg/m²). Irreversible high frequency loss was occasionally observed.
Nausea and vomiting: Starting 1 to 50 hours after drug administration and lasting from a few minutes to 8 hours
Hematologic: Mild to moderate myelosuppression

7.3 Etoposide (VP-16-213)

7.3.1 Formulation: For i.v. use, VP-16 is supplied in 100-1000 mg vials at a concentration of 20 mg/ml. Each 100 mg vial also contains anhydrous citric acid 10 mg, benzyl alcohol 150 mg polysorbate 80 purified 400 mg, polyethylene glycol, and absolute alcohol. The manufacturer recommends etoposide dilution to a concentration of 0.2 or 0.4 mg/ml with either 0.9% Normal Saline, USP or 5% Dextrose Injection, USP. Diluted to these concentrations, it yields a product that is stable for 96 and 48 hours respectively, at room temperature (25°C), and under normal room fluorescent light in both glass and plastic containers. For oral use, etoposide is available in a blisterpack of twenty 50 mg capsules. Each liquid-filled soft gelatin capsule contains 50 mg of etoposide in a vehicle consisting of citric acid, glycerin, purified water, and a polyethylene glycol 400.

7.3.2 Storage: Refrigeration; the capsules are stable for 24 months. Do not freeze.

7.3.3 Administration: Intravenous on day 1, orally on days 2 and 3; see Section 7.1.4 if oral administration is not possible.

7.3.4 Availability: Commercially available

7.3.5 Pharmacology: After oral capsule administration, the Cmax and AUC values exhibit marked intra- and inter-subject variability. This results in variability in the estimates of the absolute oral bioavailability of etoposide oral capsules. Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%). Dose proportionality in absorption following oral capsule administration has not been established. There is no evidence of a first-pass effect of etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and nonrenal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

The total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and non-renal clearance.

7.3.6 Toxicity: Hematologic Toxicity: Myelosuppression is dose related and dose limiting with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20. Acute myeloid leukemia has been reported in rare instances.
Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. Nausea and vomiting can usually be controlled with standard antiemetic therapy.
Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted.
Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension have been reported to occur in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the drug and to the administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. One fatal acute reaction associated with bronchospasm has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, hypertension, rash, fever, pigmentation, pruritus, abdominal pain, constipation, dysphagia, transient cortical blindness, and a single report of radiation recall dermatitis.

7.4 Drug Modification
7.4.1 Definition of Dose Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level/m²</th>
<th>0</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>i.v.</td>
<td>Day 1</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Etoposide</td>
<td>i.v.*</td>
<td>Day 1</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>Etoposide</td>
<td>p.o.*</td>
<td>Days 2-3</td>
<td>240</td>
<td>160</td>
</tr>
</tbody>
</table>

*On Days 2-3, the patient may receive i.v. etoposide as an alternative, but the i.v. dose must be ½ of the p.o. dose; See Section 7.1.4

7.4.2 For Hematologic Toxicity

<table>
<thead>
<tr>
<th>Granulocyte nadir</th>
<th>Platelet nadir</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 ≤ 5 days</td>
<td>≥ 50,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 &gt; 5 days</td>
<td>&lt; 50,000</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>Infection</td>
<td>Bleeding</td>
<td>Decrease 1 level</td>
</tr>
</tbody>
</table>

In the case of febrile neutropenia or prolonged grade 4 neutropenia, G-CSF may be used prophylactically as an alternative to dose reduction (in the absence of other dose-limiting toxicity). See Section 7.1.7 regarding G-CSF.

7.4.3 For Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>No change</td>
</tr>
<tr>
<td>3</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>4</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

7.4.4 For Renal Toxicity

<table>
<thead>
<tr>
<th>Serum creatinine mg% (immediately pre-tx)</th>
<th>Modification Cisplatin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 - 2.0</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>2.1 - 3.5</td>
<td>Hold one cycle. Cisplatin to be reinstituted at next cycle at 1 level decrease if serum creatinine &lt; 2.0; otherwise, stop cisplatin.</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>Hold cisplatin for all remaining cycles.</td>
</tr>
</tbody>
</table>

7.4.5 All courses will be held pending hematologic recovery to AGC ≥ 1,500 and platelets ≥ 100,000. For AGC ≤ 1,000 or platelets ≤ 50,000, etoposide will be discontinued during the oral therapy for that cycle only.

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

7.5.1 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.

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

7.5.3 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:

7.5.3.1 Any ADR that is both serious (life-threatening [grade 4] or fatal [grade 5]) and unexpected;
7.5.3.2 Any increased incidence of a known ADR that has been reported in the package insert or the literature;
7.5.3.3 Any ADR that results in significant disability or incapacity;
7.5.3.4 Any infant born to a patient that was treated on this protocol and has a congenital anomaly or birth defect;
7.5.3.5 (3/7/05) The ADR report should be documented on FDA Form 3500 (MedWatch) and mailed or faxed to the address on the form, as well as to the RTOG Data Management Department:

RTOG Data Management
1818 Market Street, Suite 1600
Philadelphia, PA 19103
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.

7.5.4 Symptomatic grade 4 hematologic and nonhematologic toxicities that are probably/definitely related to study chemoradiotherapy must be reported to RTOG within 24 hours. Death from any cause while the patient is receiving protocol treatment or up to 90 days after the last protocol treatment must be telephoned to the RTOG Headquarters Data Management department within 24 hours of discovery.

7.5.5 (3/7/05) 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
1818 Market Street, Suite 1600
Philadelphia, PA 19103
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.
8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY
Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (5/20/04)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study</th>
<th>Weekly During XRT</th>
<th>Before Each Course of Chemotherapy</th>
<th>End of Treatment</th>
<th>Follow up^n</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/Physical</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Zubrod, Weight loss</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Tumor measurements</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC/platelets/diff</td>
<td>X^b</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes, magnesium</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SMA-12</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (microscopy)</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>X^c</td>
<td></td>
<td>X</td>
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<td>X</td>
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<tr>
<td>PFTs (FEV, DECO, TVC)</td>
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<td></td>
<td>X</td>
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<tr>
<td>Toxicity Evaluation</td>
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<td></td>
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<td>X</td>
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<tr>
<td>Response</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
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<td>CT chest/upper abdomen</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
</tr>
<tr>
<td>EKG</td>
<td>X^c</td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
</tr>
<tr>
<td>MRI or CT of Brain</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
</tr>
<tr>
<td>Bone scan</td>
<td>X^b</td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
</tr>
<tr>
<td>Bone marrow asp and biopsy</td>
<td>X^c</td>
<td></td>
<td>X</td>
<td></td>
<td>X^n</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. 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
b. Lab tests must be done ≤ 2 weeks prior to study entry; imaging, and EKG must be done ≤ 4 weeks prior to study entry; see Sections 4.2 and 4.3; pretreatment CT of chest/upper abdomen should be done with contrast; PFT must be done within 4 weeks.
c. Recommended if elevated LDH > 1.5 x normal value or abnormal CBC
d. At 6 and 12 months from start of treatment, then annually
e. Only if clinically indicated
f. CT of chest every 6 months for three years
g. Recommended, but not required
h. Every 3 months from treatment start for one year, every 6 months for two years, then annually, as per Section 12.1
i. SMA-12: Total protein, albumin, calcium, phosphorus, glucose (fasting), BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, and SGPT.

11.2 Evaluation During Study

11.2.1 Urinalysis with microscopy will be done prior to starting the first cycle of chemotherapy. Patients will be monitored weekly for CBC, differential and platelet count.

11.2.2 History and physical with performance status and weight will be recorded before each course of chemotherapy.
11.2.3 SMA-12, electrolytes, magnesium, and urinalysis with microscopic analysis will be performed before each course of chemotherapy.

11.2.4 Chest X-ray will be performed before each course of chemotherapy.

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

11.3 Response Assessment

11.3.1 Measurement of Response

Response will be evaluated in this study using both the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

11.3.1.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Response to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination.

11.3.2 Response Criteria

Response and progression to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination.

11.3.2.1 Evaluation of target lesions - RECIST criteria

• Complete Response (CR): Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement.

• Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination.

• Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination.
• **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

**11.4 Criteria for Discontinuing Therapy**

11.4.1 Increasing disease at any time during therapy
11.4.2 The development of unacceptable toxicity, which is defined as unpredictable, irreversible, or prolonged (> 2 weeks) grade 4.
11.4.3 Noncompliance with protocol requirements.
11.4.4 Patient refusal.

**12.0 DATA COLLECTION (3/7/05)**

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA  19103

**12.1 Summary of Data Submission**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
</tbody>
</table>

**Preliminary Dosimetry Information:**
- Pretreatment CT with contrast (C1)
- RT Prescription (Protocol Treatment Form) (T2)
- Films (simulation and portal) (T3)
- Calculations (T4)

**Final Dosimetry Information:**
- Within 1 week of start of RT end
- Daily Treatment Record (T5)
- Isodose Distributions (T6)
- Off-Cord Films (simulation and portal) (T8)
- Radiotherapy Form (T1)

**Treatment Form (TF)**
- Within 1 week of end of concurrent chemo and within 1 week of end of adjuvant chemo

**Initial Follow-up Form (FS)**
- Week 13 (Day 90 from start of RT); RECIST response must be assessed by CT/MRI between 90 and 120 days from start of RT

**Follow-up Form (F1)**
- Every 3 months from treatment start for 1 year; q 6 mos x 2 years, then annually. Also at progression/relapse and at death.

**Autopsy Report (D3)**
- As applicable
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is to estimate overall survival at two years.

13.1.2 To estimate the progression-free and overall survival rates at one year, and to estimate the median survival time.

13.1.3 To estimate the rate of acute treatment-related Grade 3 or 4 esophagitis and the rate of treatment-related fatalities in this patient population with this treatment regimen.

13.1.4 To estimate response rates (complete response, partial response, progressive disease, or stable disease). Response will be recorded as the best response observed two months after the completion of chemoradiation therapy.

13.2 Sample Size

This phase II study aims to improve the two-year survival rate from 47%, achieved in Arm 2 of RTOG-8815, to 60%. Using a one-group \( \chi^2 \) test with a one-sided significance level of 0.10, a sample size of 67 will detect the difference between \( H_0 : p \leq 0.47 \) and \( H_a : p \geq 0.60 \) with 80% power. Assuming that 5% of the patients will be ineligible or inevaluable, a total of 71 patients will be required for this trial.

13.3 Interim Treatment Analyses for Early Stopping Due to Severe Esophagitis and Fatalities

13.3.1 Severe esophagitis is defined as grade 3 or 4 esophagitis due to chemoradiotherapy. The RTOG 97-12 phase I trial did not rule out a grade 3 or 4 esophagitis rate greater than 30%, or a fatality rate greater than 5%. Accrual to this trial will be suspended if the expected grade 3 or 4 esophagitis toxicity rate is greater than 30%, or the expected fatality rate is greater than 5%. Three interim analyses of toxicity due to severe esophagitis and fatalities are planned at 25%, 50%, and 75% of the total number of evaluable patients to be accrued.

13.3.2 The following early stopping rules reject the null hypothesis that the proportion of severe esophagitis is less than or equal to 30% with an overall significance level 0.05:

- 12 or more cases of severe esophagitis out of the first 17 evaluable patients, or
- 17 or more cases of severe esophagitis out of the first 34 evaluable patients, or
- 22 or more cases of severe esophagitis out of the first 51 evaluable patients.

13.3.3 The final analysis will test the same null hypothesis using the rejection rule of 27 or more cases of severe esophagitis out of the total sample of 67 evaluable patients. This will insure an overall significance level of 0.05 for the final conclusion.

13.3.4 If the number of severe esophagitis toxicities observed falls in the rejection region then the conclusion is that the toxicity rate for severe esophagitis is greater than 30% on this treatment regimen. In this case, the study chair(s), lung cancer committee chair, and statistician will review the toxicity data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study. The results of this review will determine whether or not to lower the radiation therapy dose.

13.3.5 We are more concerned with Type II error (i.e., failing to detect a high fatality rate, if it exists) than we are with Type 1 error (i.e., deciding that the treatment has an unacceptable fatality rate, when in fact it does not). The following early stopping rules reject the null hypothesis that the proportion of treatment fatalities is less than or equal to 5% with an overall significance level 0.20:

- 3 or more fatalities out of the first 17 or fewer evaluable patients, or
- 4 or more fatalities out of the first 34 evaluable patients, or
- 5 or more fatalities out of the first 51 evaluable patients.

13.3.6 The final analysis will test the same null hypothesis using the rejection rule of 6 or more fatalities out of the total sample of 67 evaluable patients. This will insure an overall significance level of 0.20 for the final conclusion. Fatalities will be closely monitored; for each block of patients, if the limit specified in Section 13.3.5 is reached, the null hypothesis that the proportion of treatment fatalities is less than or equal to 5% will be rejected immediately, even if the maximum number of patients for that block has not yet been accrued.

13.3.7 If the number of fatalities observed falls in the rejection region then the conclusion is that the treatment fatality rate is greater than 5% on this treatment regimen. In this case, the study chair(s), lung cancer committee chair, and statistician will review the toxicity data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study. The results of this review will determine whether or not to lower the radiation therapy dose.
13.4 **Patient Accrual**  
Patient accrual is projected to be four cases per month. At that rate, it will take 18 months to reach the required 71 cases. If the average monthly accrual rate is less than 1 patient the study will be re-evaluated for feasibility.

13.5 **Analysis Plans**

13.5.1 *Interim Reporting of Accrual and Toxicity Data*
Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The usual components of this report are:

a) the patient accrual rate with a projected completion date for the accrual phase;
b) accrual by institution;
c) the distribution of pretreatment characteristics;
d) the quality of submitted data with respect to timeliness, completeness, and accuracy;
e) the frequency and severity of the toxicities.

The statistician will report any problems identified to the RTOG lung cancer committee, and if appropriate, to the RTOG Executive Committee.

13.5.2 *Analysis for Reporting Treatment Results*
This analysis will be done when each patient has been potentially followed for a minimum of 12 months. It will include:

a) tabulation of all cases entered into the trial; exclusions with reasons;
b) institutional accrual;
c) distribution of important prognostic baseline variables;
d) observed results for the endpoints listed in Section 13.1.

13.5.3 The null and alternative hypotheses of the study’s primary outcome, the overall two-year survival rate, are $H_o : p \leq 0.47$ and $H_a : p \geq 0.60$. $H_o$ and $H_a$ will be tested with a Fleming single stage Phase II procedure using a one-sided 90% normal approximation confidence interval on 47%, the percentage of patients surviving at least two years under the best arm of RTOG 88-15. If the point estimate for two-year survival is less than or equal to 0.54815, the upper bound of the one-sided 90% confidence interval on 47%, then $H_o$ is rejected and the conclusion is that the two-year survival rate did not statistically improve from 47% under the new treatment. If the point estimate is greater than 0.54815, then $H_o$ will be rejected and the conclusion is that the two-year survival rate did improve from 47% to 60% under the new treatment.

13.5.4 Estimates of overall and progression-free survival at one-year (calculated using the Kaplan-Meier method), the median survival time (assuming an exponential distribution of time with constant hazard from 24 months), the rate of combined acute and late severe esophagitis, response rates (complete, partial, progressive disease, or stable disease) as determined at two months post-treatment, and the treatment-related fatality rate for this treatment will be calculated along with their associated 95% confidence intervals.

13.5.5 Further subgroup analyses will be undertaken if the sample sizes involved in each subgroup are adequate to support such analyses.

13.6 **Inclusion of Women and Minorities**
Ciampi et al. 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 regarding inclusion of women and minorities in clinical research, we have considered the possible interaction between gender and treatments and race and treatments. The participation rates of men and women will be examined according to Section 13.4.1. The projected gender and minority accruals are:
## Planned Gender and Minority Inclusion

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<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
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<tr>
<td><strong>Ethnic Category: Total of all subjects</strong>*</td>
<td>30</td>
<td>41</td>
<td>0</td>
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<table>
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</thead>
<tbody>
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<td>0</td>
<td>2</td>
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<tr>
<td><strong>Racial Category: Total of all subjects</strong>*</td>
<td>30</td>
<td>41</td>
<td>0</td>
<td>71</td>
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</tbody>
</table>
REFERENCES


APPENDIX I

RTOG 0239

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II STUDY OF ACCELERATED HIGH DOSE OF THORACIC IRRADIATION WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED 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 limited small cell lung cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) a combination of higher dose radiation to the chest and chemotherapy (cisplatin and etoposide) has on you and your cancer.

Standard doses of radiation to the chest and chemotherapy fail to control this type of lung cancer in most people. This research is being done to find out if higher dose radiation plus chemotherapy may better control your cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 71 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will receive one radiation treatment to the chest per day, 5 days per week, for 16 treatment days (approximately 3 weeks). Then you will receive two radiation treatments to the chest per day, 5 days per week, for 9 treatment days (approximately 2 weeks). The two treatments will be given approximately 6 hours apart. This schedule of radiation is considered a research schedule and differs from standard radiation schedules that you would follow if you did not participate in this study.
You also will receive chemotherapy, beginning on the first day of radiotherapy. You will receive 4 cycles of chemotherapy. Each cycle lasts 3 days and will be repeated every 3 weeks. In each cycle, you will receive two drugs, cisplatin and etoposide. On the first day of each cycle of chemotherapy, you will receive cisplatin through your vein for two hours. You also will be given etoposide on the first day, through your vein for over one hour. Then on days 2 and 3 of each cycle, you will take etoposide by mouth once a day, one hour before breakfast. If oral etoposide causes side effects or if oral etoposide is not available, you will receive etoposide through your vein on days 2 and 3. Your doctor will discuss this with you. This type and schedule of chemotherapy is standard for people with this disease, and you probably would receive this chemotherapy if you did not participate in this study.

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

After you complete treatment, you and your doctor will decide if you should receive radiation to your brain, to try to decrease the chance of your cancer spreading to your brain.

(5/20/04) If you take part in this study, you also will have the following tests and procedures. These tests and procedures are standard for people with this disease and probably would be done if you did not participate in this study.

- A physical exam before beginning treatment, before each cycle of chemotherapy, at the end of treatment, then every 3 months for one year, every 6 months for years 2 & 3, then annually
- Blood tests before beginning treatment, once a week during treatment, before each cycle of chemotherapy, at the end of treatment, then every 3 months for one year, every 6 months for years 2 & 3, then annually; in addition, your blood counts will be checked once a week during treatment.
- A bone scan and an MRI or CT scan of your brain before beginning treatment; the MRI or CT scan will be repeated at the end of treatment. After treatment ends, the bone scan and MRI/CT scan will be done in follow-up visits, if advised by your doctor.
- A CT scan of your chest and upper abdomen before beginning treatment, at the end of treatment, then every six months for 3 years
- A chest x-ray before beginning treatment, at the end of treatment, then every 3 months for one year, every 6 months for years 2 & 3, then annually
- A urinalysis before beginning treatment and before each chemotherapy cycle
- An EKG before beginning treatment, then in follow up as advised by your doctor
- Tests of your lung function before beginning treatment, at the end of treatment, at 6 and 12 months from the start of treatment and then annually
- A biopsy of your bone marrow, if advised by your doctor
- For women who are able to have children, a test prior to study entry to see if you are pregnant
HOW LONG WILL I BE IN THE STUDY?

You will receive treatment for your lung cancer for 12 weeks. You will be seen in follow-up visits every 3 months from the start of your treatment for one year, then every 6 months for years 2 & 3, then annually.

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.

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 radiotherapy 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 Radiation**

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
- Skin in 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 of 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)

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.

When possible, medications will be provided to control nausea and to minimize the side effects associated with radiation therapy, such as problems with swallowing.

**Risks from Chemotherapy**

**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

**Etoposide**

*Very Likely*
- Lower blood counts, which could lead to an increased risk of infection, weakness, or bleeding complications.
- Nausea and vomiting
- Diarrhea
- Hair loss
- Chest pain
- Blood in the urine
- A skin rash.

*Less likely*
- Changes in blood pressure
- Liver damage
- Fever
- Chills
- Muscle cramps
- Leukemia

**Reproductive Risks**

**For Women**
This clinical treatment would definitely involve risks to both you as a patient and your embryo or fetus 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 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.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: 1) radiation therapy (similar to what is being given in this study but at a lower dose); 2) chemotherapy; 3) a combination of radiation therapy and chemotherapy but not as a part of this study, or 4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.
WHAT ABOUT CONFIDENTIALITY?

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

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, 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 obtain follow-up data related 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:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

**WHERE CAN I GET MORE INFORMATION?**

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


**SIGNATURE**

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan).*

<table>
<thead>
<tr>
<th>Patient’s Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
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</table>
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

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

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<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction <em>(Karnofsky 90-100)</em></td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; For example, light housework, office work <em>(Karnofsky 70-80)</em></td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours <em>(Karnofsky 50-60)</em></td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours <em>(Karnofsky 30-40)</em></td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair <em>(Karnofsky 10-20)</em>.</td>
</tr>
<tr>
<td>5</td>
<td>Death <em>(Karnofsky 0)</em>.</td>
</tr>
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</table>
APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 1997)

TNM CATEGORIES (Note Definitions)

**Primary Tumor (T)**

TX  Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0  No evidence of primary tumor.

Tis  Carcinoma in situ.

T1  Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus).

T2  Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3  Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4  Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

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

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

**Regional Lymph Nodes (N)**

NX  Regional lymph nodes cannot be assessed.

N0  No regional lymph nodes metastasis.

N1  Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.

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

N3  Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
APPENDIX III (cont’d)

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 1997)

Distant Metastasis  \((M)\)

- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis present

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

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>Stage 0</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
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<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
</tbody>
</table>

**Stage IV**

- Any T  
- Any N  
- M1
<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>GRADE 0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change;</td>
<td>Patch atrophy; Moderate telangiectasia;</td>
<td>Marked atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some hair loss</td>
<td>Total hair loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBCUTANEOUS</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of</td>
<td>Moderate fibrosis but asymptomatic; Slight</td>
<td>Severe induration and loss of subcutaneous</td>
<td>Necrosis</td>
</tr>
<tr>
<td>TISSUE</td>
<td></td>
<td>subcutaneous fat</td>
<td>field contracture; &lt;10% linear reduction</td>
<td>tissue; Field contracture &gt; 10% linear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>measurement</td>
<td></td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little</td>
<td>Marked atrophy with complete dryness; Severe</td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mucous telangiectasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on</td>
<td>Moderate dryness of mouth; Poor response on</td>
<td>Complete dryness of mouth; No response on</td>
<td>Fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stimulation</td>
<td>stimulation</td>
<td>stimulation</td>
<td></td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cord level treated</td>
<td></td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction</td>
<td>Seizures or paralysis; Coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(partial loss of power or dyskinesia)</td>
<td></td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal</td>
<td>Symptomatic cataract; Moderate corneal</td>
<td>Severe keratitis; Severe retinopathy or</td>
<td>Panophthalmitis/Blindness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ulceration or keratitis</td>
<td>ulceration; Minor retinopathy or glaucoma</td>
<td>detachment Severe glaucoma</td>
<td></td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough);</td>
<td>Moderate symptomatic fibrosis or pneumonitis;</td>
<td>Severe symptomatic fibrosis or pneumonitis;</td>
<td>Severe respiratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight radiographic appearances</td>
<td>severe cough; Low grade fever; Patchy</td>
<td>pneumonitis; Dense radiographic changes</td>
<td>insufficiency/continuous O2/Assisted ventilation</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms;</td>
<td>Moderate angina on effort; Mild pericarditis;</td>
<td>Severe angina; Pericardial effusion;</td>
<td>Tamponade/Severe heart failure/Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transient T wave inversion &amp; ST Changes;</td>
<td>Normal heart size; Persistent abnormal T</td>
<td>Constrictive pericarditis; Moderate heart</td>
<td>constrictive pericarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinus tachycardia &gt;110 (at rest)</td>
<td>wave and ST changes; Low ORS</td>
<td>failure; Cardiac enlargement; EKG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>abnormalities</td>
<td></td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in</td>
<td>Unable to take solid food normally;</td>
<td>Severe fibrosis; Able to swallow only liquids;</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>swallowing solids; No pain on swallowing</td>
<td>Swallowing semi-solid food; Dilation may be</td>
<td>May have pain on swallowing Dilatation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>indicated</td>
<td>required</td>
<td></td>
</tr>
<tr>
<td>SMALL/LARGE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel</td>
<td>Moderate diarrhea and colic; Bowel</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>INTESTINE</td>
<td></td>
<td>movement 5 times daily Slight rectal</td>
<td>movement &gt;5 times daily; Excessive rectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>discharge or bleeding</td>
<td>mucus or intermittent bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild tassitude; Nausea, dyspepsia;</td>
<td>Moderate symptoms; Some abnormal liver;</td>
<td>Disabling hepatic insufficiency; Liver function</td>
<td>Necrosis/Hepatic coma or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slightly abnormal liver function</td>
<td>function tests; Serum albumin normal</td>
<td>tests grossly abnormal; Low albumin; Edema</td>
<td>encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or asctes</td>
<td></td>
</tr>
</tbody>
</table>
| KIDNEY            | None    | Transient albuminuria; No hypertension; Mild | Persistent moderate albuminuria (2+); Mild   | Severe albuminuria; Severe hypertension      | Malignant hypotension; Uremic coma/Urea > 100%
|                   |         | impairment of renal function; Urea 25-35 mg%| hypertension; No related anemia; Moderate    |                                              | %                                                                                           |
|                   |         | Creatinine 1.5-2.0 mg%; Creatinine clearance | impairment of renal function; Urea > 36-60 mg%| improper renal function; Urea > 60 mg%       |                                              |
|                   |         | > 75%                                        | Creatinine clearance > 50%                   | Creatinine clearance > 50%                   |                                              |
|                   |         |                                              |                                              |                                              |                                              |
| 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 | Necrosis/Spontaneous fracture                |
| BONE              | None    | Asymptomatic; No growth retardation;         | Moderate pain or tenderness; Growth          | Severe pain or tenderness; Complete arrest of | Necrosis/Spontaneous                        |
|                   |         | Reduced bone Density                         | retardation; Irregular bonesclerosis         | bone growth; Dense bone sclerosis            | fracture                                      |
| JOINT             | None    | Mild joint stiffness; Slight limitation of     | Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement | Severe joint stiffness; Pain with severe     | Necrosis/Complete fixation                   |
|                   |         | movement                                     |                                              | limitation of movement                       |                                              |

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

APPENDIX IV

GRADE 0
- None
GRADE 1
- Slight
GRADE 2
- Moderate
GRADE 3
- Severe
GRADE 4
- Marked

DEATH
- None

DIRECTIONS
- Directly related

RELATION
- Related

REFERENCES
- Radiation Effects

RTOG 0239
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 used to grade severity of adverse events.

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.
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. **Adverse Event Reporting Related to Radiation Therapy (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**

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 (3/24/10)**

<table>
<thead>
<tr>
<th>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</th>
<th>Increased Incidence of an Expected AE</th>
<th>Hospitalization During Treatment</th>
<th>Secondary AML/MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Form 3500 within 10 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Call RTOG within 24 hrs of event</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong></td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td>Attribution: Possible, Probable or Definite</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td>Grade 2: Expedited report within 10 working days.</td>
<td>Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td>Grade 3: Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>This includes deaths within 30 days of last dose of treatment with an investigational agent.</td>
</tr>
<tr>
<td>Grade 1: Adverse Event Expedited Reporting NOT required.</td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades 1 - 3</th>
<th>Grades 4 &amp; 5 Regardless of Attribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td>This includes deaths within 30 days of the last dose of treatment with an investigational agent.</td>
<td>This includes deaths within 30 days of the last dose of treatment with an investigational agent.</td>
</tr>
</tbody>
</table>

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).
3. Expedited Reporting for Phase 2 and Phase 3 Studies
<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
</table>
| **Grades 2-3**  
Attribution: Possible, Probable or Definite | **Grades 4 & 5**  
Regardless of Attribution |
| **Grades 4 & 5**  
Regardless of Attribution | **Grades 1 - 3** |
| 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).