RADIATION THERAPY ONCOLOGY GROUP
RTOG 97-12

A PHASE I DOSE ESCALATION STUDY OF THORACIC IRRADIATION WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED SMALL CELL LUNG CANCER

Study Chairs

Radiation Oncology Ritsuko Komaki, M.D.
M.D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
(713) 792-3420
FAX (713) 794-5573
rkomaki@notes.mdacc.tmc.edu

Medical Oncology David Ettinger, M.D.
(410) 955-8847
FAX (410) 614-9424
ettinger@welchlink.welch.jhu.edu

Activation Date: February 1, 1998
Closure Date: October 28, 2002
Termination Date: June 30, 2010
Version Date: September 21, 2001
Includes Revisions 1-5

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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 - Karnofsky Performance Status
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting Guidelines
Appendix VI - Protocol Dose Schedule
A PHASE I DOSE ESCALATION STUDY OF THORACIC IRRADIATION WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED SMALL CELL LUNG CANCER

SCHEMA

Radiation Therapy  (only one arm will be open at any given time – see Section 6.1)):

R  Arm 1:  Large field 36 Gy, 1.8 Gy/fx/D/5 days/4 weeks, boost 1.8 Gy/D x 2 days, then BID x last 3 days.
    (closed 6/23/98)  Total dose: 50.4 Gy

E  Arm 5:  Large field 36 Gy, 1.8Gy/fx/D 5 days/4 weeks, boost 1.8 Gy/D x 2 days, then BID x last 3 days.
    (closed 3/19/99)  Total dose 50.4 Gy.

G  Arm 2:  Large field 36 Gy, 1.8 Gy/fx/D/5 days/4 weeks, boost 1.8 Gy BID x last 5 days.
    (closed 9/24/99)  Total dose: 54.0 Gy

I  Arm 3:  Large field 32.4 Gy, 1.8 Gy/fx/D/5 days x 18 fx, boost just in pm @ 1.8 Gy/fx on days 19 & 20 (use ap/pa fields in am @ 1.8 Gy/fx), then boost 1.8 Gy BID x last 5 days.
    (closed 5/5/00)  Total dose: 57.6 Gy

T  Arm 4:  Large field 28.8 Gy; 1.8 Gy/fx/5 days x 16 fx, boost just in pm @ 1.8 Gy/fx on days 17-20 (use ap/pa fields in am @ 1.8 Gy/fx), then boost 1.8 Gy BID x last 5 days.
    (closed 5/4/01)  Total dose: 61.2 Gy

S  Arm 6:  Large field 25.2 Gy; 1.8 Gy/fx/D/5 days x 14 fx, boost just in pm @ 1.8 Gy/fx on days 15-20 (use ap/pa fields in am @ 1.8 Gy/fx), then boost @ 1.8 Gy BID x last 5 days.
    (opened 9/21/01)  Total dose: 64.8 Gy

Chemotherapy  Chemotherapy will be started on day 1 of thoracic radiotherapy (+/-24 hours)
Cisplatin (DDP), 60 mg/M² i.v. day 1.
Etoposide (VP-16), 120 mg/M² i.v. day 1
Etoposide (VP-16), 240 mg/ M² p.o. per day on days 2 and 3
Repeat cycle every 3 weeks x 4 cycles.

G-CSF to be administered as needed (see Section 7.1.7); no amifostine should be given prior to CDDP.

Eligibility:  (See Section 3.0 for details)
- Histologic or unequivocal cytologic proof of SCLC with measurable or evaluable disease.
- Clinically limited disease with no prior chemotherapy or radiotherapy.
- Absolute granulocytes ≥ 1500, platelets ≥ 150,000, bilirubin ≤ 1.5 mg/d., creatinine ≤ 1.5 mg/d.
- KPS ≥ 70; age ≥ 18.
- No pericardial or pleural effusion on CXR regardless of cytology.
- No previous (within 2 years) or concurrent malignancy except for non-melanotic skin cancer or carcinoma in situ of cervix.
- Signed study-specific consent form.
Required Sample Size: 20-66

9/8/98
7/1/99
2/14/00
12/13/00
9/21/01
<table>
<thead>
<tr>
<th>Case #</th>
<th>1. Does the patient have documented histologic or unequivocal cytologic proof of small cell lung cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>______(Y)</td>
<td>2. What is the stage?</td>
</tr>
<tr>
<td>______(I-IIIB)</td>
<td>3. Does the patient have N3 disease based on contralateral hilar or contralateral supravacicular nodal involvement?</td>
</tr>
<tr>
<td>______(N)</td>
<td>4. Is there evidence of pleural or pericardial effusion?</td>
</tr>
<tr>
<td>______(Y)</td>
<td>5. Does the patient have measurable or evaluable disease?</td>
</tr>
<tr>
<td>______(≥ 70)</td>
<td>6. What is the Karnofsky?</td>
</tr>
<tr>
<td>______(N)</td>
<td>7. Has the patient received any prior chemotherapy or radiotherapy to the chest or other area containing a large amount of bone marrow?</td>
</tr>
<tr>
<td>______(≥ 18)</td>
<td>8. What is the patient’s age?</td>
</tr>
<tr>
<td>______(≥ 1500)</td>
<td>9. What is the absolute neutrophil count ( (ANC) )?</td>
</tr>
<tr>
<td>______(≥ 150)</td>
<td>10. What is the platelet count ( (x \ 1000) )?</td>
</tr>
<tr>
<td>______(≤ 1.5)</td>
<td>11. Report the bilirubin results.</td>
</tr>
<tr>
<td>______(≤ 1.5)</td>
<td>12. Report the serum creatinine.</td>
</tr>
<tr>
<td>______(Y)</td>
<td>13. 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?</td>
</tr>
<tr>
<td>______(N)</td>
<td>14. Has the patient had myocardial infarction within the last 6 months, symptomatic heart disease, COPD with FEV-1 ≤ 0.8 liter or uncontrolled bronchospasms in the unaffected lung?</td>
</tr>
<tr>
<td>______(N)</td>
<td>15. 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 \textit{in situ} cervix cancer?</td>
</tr>
<tr>
<td>______(N)</td>
<td>16. Is there history of a prior uncontrolled psychiatric illness, severe head injury, chronic alcohol or drug abuse, or central nervous system disease?</td>
</tr>
<tr>
<td>______(Y/NA)</td>
<td>17. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?</td>
</tr>
<tr>
<td>______(N)</td>
<td>18. Has the patient had a complete tumor resection?</td>
</tr>
</tbody>
</table>

\textit{(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)  

Patient's Name  
Verifying Physician  
Patient ID #  
Referring Institution # (if different)  
Birthdate  
Sex  
Race  
Social Security Number  
Zip Code (9 digit if available)  
Method of Payment  
Will any component of the patient’s care be given at a military or VA facility?  
Treatment Start Date  
Treatment Assignment

Completed by ____________________________  
Date ____________________________
1.0 INTRODUCTION

In the US, there will be approximately 178,000 patients with lung cancer diagnosed in 1997, of which 20% will have small cell carcinoma. 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 Payne based on results from 11 trials showed an increased absolute survival of 5.4% at two years. Pignon and his colleagues collected data on 2140 patients from 16 randomized trials comparing chemotherapy alone vs. 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., and Johnson et al. reported a 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 Turrisi and Johnson studies, respectively; 4-year survival was 36%.

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. Radiotherapy was given with concurrent chemotherapy consisting of cisplatin 60 mg/M² IV day 1 and etoposide 120 mg/M² IV 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. Overall median survival for the entire group was 20 months, with two year progression-free survival of 40%. Trends favored the bid and accelerated regimen for longer duration of response, time to failure, and survival, but none of these reached statistical significance. Acute toxicities in the two arms were identical with the exception of grade 3 esophagitis, seen in 26% of the patients treated by accelerated radiation therapy and 11% of those with daily fractionation. There was no difference in late toxicity between two arms. The treatment related death rate was 2%. Concurrent chemotherapy and radiotherapy proved to be tolerated and efficacious with 5-year survival rates of 21% among the daily fraction group and 28% among the bid/accelerated group: this represents more than a doubling of survival compared with results a decade ago with survival advantage with bid irradiation (p = 0.04, Turrisi, personal communication).

The sequencing and timing of chemotherapy and thoracic radiotherapy are also 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.

The radiation dose to the thorax is another controversial area. The National Cancer Institute of Canada developed an important study to show dose-response to the thorax. 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. 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 45Gy (15-15-15), 55Gy (20-20-15) to 65 Gy (20-20-20) which was given by split courses interdigitating with chemotherapy. Their 3-year local control rates were 66%, 70%, and 70%, respectively and 5-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.

Choi et al. 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.

In selecting a strategy to both improve local control and decrease the rate of distant failure, we attempted to design a treatment that meets the following criteria:

1. Intensified the dose-effectiveness of the RT without increasing the rate and severity of acute and late toxicity.
   a. To increase the likelihood of local control
   b. On the assumption that this may decrease the rate of distant metastases from viable clonogens in the primary/nodal tumor
2. Gives the RT component as early as possible in the course of chemotherapy to avoid development of accelerated repopulation stimulated by the chemotherapy.
3. Shortens the overall treatment time to abrogate any negative impact on local control due to accelerated repopulation stimulated by the early qd portion of the RT.
4. Combines RT and CT concurrently to take advantage of radiosensitization by the chemotherapy.

The proposed strategy accomplishes all four objectives. It accomplishes #1 (and #2 and #4) by giving the first 36 Gy at 1.8 Gy/fraction concurrent with chemotherapy to permit some tumor shrinkage so that reduced volumes can be treated for the bid boost portion of the RT. The reduced volumes during the boost should reduce the risk of toxicity. The bid RT used in the boost portion helps overcome any accelerated repopulation induced by the qd portion (#3) and it shortens the overall treatment time, with the same benefit (#3), from 28 to 25 days for arm 1, from 30 to 25 days for arm 2, from 32 to 25 days for arm 3, and from 34 to 25 days for arm 4.

To improve local control in the thorax without increasing toxicity, this dose escalation of irradiation to the thorax with concurrent chemotherapy is proposed.

Treatment fields are usually larger early in the course of thoracic irradiation before chemotherapy and radiotherapy reduce the tumor volume. This could contribute to acute esophagitis and occasionally pneumonitis, especially with concurrent chemotherapy. To reduce these acute toxicities, daily fraction will be applied during the first three weeks followed by accelerated boost radiotherapy to smaller fields to determine MTD.

The hypothesis for this study is that timing, duration and intensity of treatment will overcome proliferation of clonogens of SCLC, will reduce local failure and consequently will improve survival with tolerable toxicities.

The role of prophylactic cranial irradiation (PCI) has been controversial because of the lack of definitive evidence for improvement of overall survival and reports of late neurotoxicities. However, the risk of brain metastasis from small cell lung cancer is correlated to the length of survival and as more effective treatment extends the patients life longer, higher rates of brain metastasis have been observed. One autopsy series showed 80% of patients who died 2 years after completion of treatment had metastases in the central nervous system (CNS) including the brain parenchyma, leptomeninges and spinal cord. Therapeutic brain irradiation has not been effective for clinical metastases. CR rates range from 25% to 64% with median remission duration of a few months. More efficacious and less toxic treatment has been sought, which revealed that PCI could be given with lower total doses (24 Gy-25 Gy), smaller fraction sizes (2.5 Gy-1.25 Gy), earlier in the course of treatment and less neurotoxic chemotherapy were important factors to reduce late neurotoxicity. Base line and follow-up neuropsychological tests revealed that 83% (25/30) of patients with limited small cell lung cancer had evidence of cognitive dysfunction prior to PCI and no significant differences were found from pretreatment tests after PCI. PCI has significantly reduced brain recurrence among the long-term survivors without obvious neurotoxicities, although the majority of studies have been done retrospectively. In this study, patients who achieve complete response will receive PCI with a total dose of 25 Gy in 10 fractions.

2.0 OBJECTIVES
2.1 Primary Objectives
2.1.1 To find the maximum tolerated dose of thoracic radiation using an accelerated boost with concurrent chemotherapy.
2.1.2 To increase local control by increased radiation dose in thorax to improve survival.
2.1.3 To reduce toxicity to the esophagus and/or the lung.

2.2 Secondary Objective
2.2.1 To monitor baseline and followup neuropsychological function.

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 Karnofsky Performance Status ≥ 70 *(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 must practice adequate contraception *(male and female).*
3.1.9 Patients must sign a study-specific consent form prior to study entry.

3.2 Conditions for Patient Ineligibility *(9-21-01)*
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; 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 and COPD with FEV-1 ≤ 0.8 liter or uncontrolled bronchospasm in the unaffected lung.
3.2.6 Previous *(unless disease free ≥ two years)* or concurrent malignancy other than curatively treated basal or squamous cell skin cancer or carcinoma *in situ* of cervix.
3.2.7 Patients with history of uncontrolled psychiatric illness, severe head injury, chronic alcohol or drug abuse, central nervous system disease.

4.0 PRETREATMENT EVALUATION *(7/1/99)*
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 will include a CBC with differential, platelet count, SMA-12, electrolytes, magnesium, and urinalysis *(including microscopic)* done within 2 weeks before study entry.
4.3 Chest X-ray, EKG, MRI or CT of brain, CT of chest, upper abdomen, radionuclide bone scan, within four weeks before study entry.
4.4 Bronchoscopy is recommended but not required.
4.5 PFTs; bone marrow aspiration and biopsy if LDH is elevated > 1.5 x normal value or for abnormal CBC.
4.6 Location, type, and size of all measurable lesions prior to treatment must be reported.
4.7 Mini-mental status evaluation will be done prior to any protocol treatment.

5.0 REGISTRATION PROCEDURES *(12/13/00)*
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

6.1 Thoracic Radiotherapy Dose and Fraction Scheme (See Appendix VI) (9/8/98, 7/1/99, 2/14/00, 9/21/01)

- **Arm 1**: Total dose: 50.4 Gy (**closed 6/23/98**)
  After 36 Gy, 1.8 Gy/fx/D/5 days/4 weeks, boost 1.8 Gy/D x 2 days, then BID x last 3 days.

- **Arm 5**: Total dose: 50.4 Gy (**closed 3/19/99**)
  After 36 Gy, 1.8 Gy/fx/D/5 days/4 weeks, boost 1.8 Gy/D x 2 days, then BID x last 3 days.

- **Arm 2**: Total dose: 54.0 Gy (**closed 9/24/99**)
  After 36 Gy, 1.8 Gy/fx/D/5 days/4 weeks, boost 1.8 Gy BID x last 5 days.

- **Arm 3**: Total dose: 57.6 Gy (**closed 5/5/00**)
  After 32.4 Gy, 1.8 Gy/fx/D/5 days x 18 fx, boost just in pm @ 1.8 Gy/fx on days 19 & 20 *(use ap/pa fields in am @ 1.8 Gy/fx)*, then boost 1.8 Gy BID x last 5 days.

- **Arm 4**: Total dose 61.2 Gy (**closed 5/4/01**)
  After 28.8 Gy, 1.8 Gy/fx/D/5 days x 16 fx, boost just in pm @ 1.8 Gy/fx on days 17-20 *(use ap/pa fields in am @ 1.8 Gy/fx)*, then boost 1.8 Gy BID x last 5 days.

- **Arm 6**: Total dose: 64.8 Gy (**opened 9/21/01**)
  After 25.2 Gy, 1.8 Gy/fx/D/5 days per week x 14 fx, boost just in pm @ 1.8 Gy/fx on days 15-20 *(use ap/pa fields in am @ 1.8 Gy/fx)*, then boost 1.8 Gy BID x last 5 days.

The radiation therapy will be initiated with concurrent chemotherapy on day 1, 1.8 Gy/day will be given to the original target volume including primary and regional lymph nodes as described in Section 6.2.

In Arm 5, *(formerly Arm 1)*, five fractions per week will be continued up to the end of the fourth week *(36 Gy in 20 fx)*, followed by a boost field using oblique *(preferable)* or lateral fields giving 1.8 Gy twice daily with minimum 6 hours interfractional interval. In Arm 1, the boost field will be given once a day for 2 days and then BID for the last 3 days, giving a total dose of 50.4 Gy.

In Arm 2, daily radiation therapy will be given up to the end of the 4th week followed by boost field giving 1.8 Gy/fx BID with minimum 6 hours interfractional interval, x 5 days, which will give a total dose of 54.0 Gy.

In Arm 3, 1.8 Gy per fraction daily radiation therapy will be given up to 18 treatment days. Starting on day 19, the original AP/PA radiation field with 1.8 Gy per fx will be given in the morning and at least 6 hours after, the boost field will be added with oblique *(preferable)* or lateral field given 1.8 Gy/fx which will be repeated on day 20. During the 5th week of radiation therapy BID radiation therapy with 1.8 Gy/fx will be given for 5 days with minimum 6 hours interfractional interval giving a total dose of 57.6 Gy.

In Arm 4, 1.8 Gy per fraction daily radiation therapy will be given up to the end of the 3rd week followed by AP/PA fields in the morning, during the 4th week and boost field using oblique *(preferable)* or lateral field, 1.8 Gy/fx for 4 days with minimum 6 hours interfractional interval. 1.8 Gy/fx BID boost field using oblique or lateral field will be continued during the 5th week with minimum 6 hours interfractional interval to a total dose of 61.2 Gy.

In Arm 6, 1.8 Gy per fraction daily radiation therapy will be given up to 14 treatment days. Starting on day 15 and continuing through day 20, the original ap/pa radiation field will be given in the morning and at least 6 hours after, a boost field to be off spinal cord will be added with oblique *(preferable)* or lateral field giving 1.8 Gy/fx. During the 5th week of radiation therapy, BID radiation
therapy will be continued using only the boost volume with 1.8 Gy per fx for 5 days with minimum 6 hours interfractional interval to a total dose of 64.8 Gy.

6.2 **Target Volume:**
The target volume that will be treated by AP/PA fields includes the primary tumor plus regional hilar and mediastinal lymph nodes, and as required the ipsilateral supraclavicular lymph nodes (see below). The target volume must have a minimum of 1 cm margin and no more than a 1.5 cm margin. Inclusion of mediastinum requires extending field margins 1.5 to 2.0 cm beyond the border of the contralateral vertebral bodies. Ipsilateral supraclavicular irradiation is allowed when necessary for primary tumor coverage or when there is bulky (>5 cm) pre- or paratracheal adenopathy detected on CT scan of the chest (with contrast). Contralateral hilar or supraclavicular treatment is not allowed. The lower field border will be two vertebral bodies or 5 cm below the carina for upper and middle lobe tumors. For lower lobe lesions a 2 cm margin below the lowest margin of the tumor will define the inferior extent of the field. Any mediastinal node detected by CT scan >1.5 cm should be included with at least a 2 cm cephalad or caudad margin. Simulation is mandatory.

6.2.1 Target volume for antero-posterior and postero-anterior ports must be simulated before initiation of radiotherapy. The second simulation needs to be done 3 days before boost fields which will be given preferably by oblique fields; lateral fields may be used if necessary.

6.2.2 No posterior spinal cord blocks are allowed.

6.2.3 Volume for boost will encompass grossly visible tumor, around both primary and nodes with a 1.0 cm margin.

6.3 **Technical Factors**

6.3.1 **Radiotherapy Equipment:** Megavoltage photon beam required, with minimum peak energy of 6 MeV.
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), 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 chests and the attendant variation in patient thickness from top to bottom of thoracic fields, compensators are required for AP/PA fields when dose inhomogeneity exceeds 10% (+ 5%) from top to bottom of field. Compensators are 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 In order to insure homogeneity of dose between ± 5%, contours and isodose plots at: a) central axis, b) 2.0 cm from the top, and c) 2 cm from the bottom of the field. The isodose plans must account for shaped fields and compensators. These must be composite plans accounting for the total dose from each component field. Critical structures (spinal cord) and target volume must be clearly delineated on each plot.

6.3.6 Localization (check or port) films are required before the start of and weekly for each port treated. Films will be submitted for review.

6.3.7 **Dose Maximum to Critical Normal Tissues:** (9/8/98)

   a) Ipsilateral whole lung 10 Gy
   b) Contralateral portion of lung (nonparamediastinal) 15 Gy
   c) Spinal Cord 36 Gy
   d) Esophagus 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)
   e) Heart 36 Gy

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 Prophylactic Cranial Radiotherapy (PCI)

6.5.1 Patients achieving a complete response as determined at reevaluation after completion of 4 cycles of chemotherapy and XRT should be considered for prophylactic cranial irradiation.

6.5.2 Dose: 25 Gy (2.5 Gy/fx), 10 fractions, 2 weeks. Dose prescribed to midplane.

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

6.5.4 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.

7.1Chemotherapy Schedule (9/8/98, 7/1/99, 2/14/00)

7.1.1 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 Prehydrate with 500 ml to one liter D5 1/2 NS with 10 Meq KCl and 8 Meq MgSO4 over 1-2 hours followed by Cisplatin.

7.1.3 Cisplatin (DDP), 60 mg/M2 IV day 1, given in 500 ml of NS with 12.5 gm of mannitol IV over two hours on day 1 of thoracic radiotherapy (+/-24 hours). Post chemotherapy, hydrate with at least one liter 1/2 NS with 10 Meq KCl over 1-2 hours.

7.1.4 Day 1: Etoposide 120 mg/M2 i.v. over 1 hour.

Days 2 and 3: Etoposide 240 mg/M2 p.o. per day taken orally in the morning and one hour before eating as a single daily dose. Because etoposide is available in 50 mg capsules, the dose will be calculated for the 2 day period, e.g., a patient who 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, intravenous route can be used. Give one half oral dose; i.v. etoposide must be given half hour before radiotherapy.

7.1.5 Repeat cycle every 3 weeks x 4 cycles of therapy.

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 G-CSF may be given S.C. or I.V. at 5 µg/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. 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/µl and that 48 hours elapses between discontinuing G-CSF and initiating a subsequent cycle of chemotherapy.

7.1.8 Amifostine (Ethyol) should not be administered prior to CDDP.

7.2 Cisplatin

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: Commercial

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 antitumor 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 myocarditis 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.
- **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.
- **Hyperuricemia**: Mild to moderate myelosuppression.

7.3 **Etoposide (VP-16-213) (9/8/98)**

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, benzy 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 pink 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**: i.v. 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 administer 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 (9/8/98)

7.4.1 Definition of Dose Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level/M^2</th>
<th>0</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>i.v.</td>
<td>D1</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Etoposide</td>
<td>i.v.</td>
<td>D1</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>Etoposide</td>
<td>p.o.</td>
<td>D2-3</td>
<td>240</td>
<td>160</td>
</tr>
</tbody>
</table>

7.4.2 For Hematologic Toxicity

**Granulocyte nadir**

<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>or 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

**Serum creatinine mg%**

<table>
<thead>
<tr>
<th>Modification Cisplatin dose (inmed. pre-tx)</th>
</tr>
</thead>
</table>
1.6 - 2.0 Decrease 1 level

2.1 - 3.5 Hold one cycle. Cisplatin to be reinstituted at next cycle at 1 level decrease if serum creatinine < 2.0, otherwise stop cisplatin.

> 3.5 Hold cisplatin for all remaining cycles.

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. (9-21-01)

7.5 Toxicity Reporting

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

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

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

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

7.5.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.5.2 The ADR report should be documented on Form FDA 3500 (Appendix V) and mailed to:

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

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

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

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

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

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (7/1/99, 9/21/01)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study</th>
<th>Day 6,10,14 18 of each cycle</th>
<th>Before each course</th>
<th>End of Treatment q 3 mos. x 1 yr then per Section 12.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/Physical</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Karnofsky, Weight loss</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurements</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC/platelets/diff</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SMA-12, electrolytes,magnesium</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Xc</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis <em>(including micro)</em></td>
<td>Xc</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFTs</td>
<td>X</td>
<td></td>
<td></td>
<td>Xb</td>
</tr>
<tr>
<td>Toxicity Evaluation, Response</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CT chest/upper abdomen</td>
<td>Xc</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>Xc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI or CT of Brain</td>
<td>Xc</td>
<td></td>
<td></td>
<td>Xb</td>
</tr>
<tr>
<td>Bone scan</td>
<td>Xc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow asp and bx</td>
<td>Xd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini Mental Status Exam</td>
<td>X</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 restaging.
b. Only if clinically indicated.
c. Lab tests must be done < 2 weeks prior to study entry; imaging must be done < 4 weeks prior to study entry. See Sections 4.2 and 4.3.
d. Only if elevated LDH > 1.5 x normal value or abnormal CBC.
e. At 6 and 12 months from start of treatment, then annually.

11.2 Evaluation During Study

11.2.1 Urinalysis with microscopy will be done prior to starting chemotherapy for each cycle. Patients will be monitored on days 6, 10, 14, 18 and before each cycle for CBC, differential and platelet count. *(9/21/01)*

11.2.2 History and physical with performance status and weight will be recorded before each course.

11.2.3 SMA-12, electrolytes, magnesium, and urinalysis with microscopic analysis will be performed before each course.

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

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 Definitions

11.3.1 **Complete Response:** Complete disappearance of all clinically detectable malignant disease lasting at least 4 weeks at the time of restaging.

11.3.2 **Partial Response:** Greater than or equal to 50% decrease in tumor size lasting for at least 4 weeks without increase of 25% of the product of perpendicular diameters of any lesion, and no new areas of documented disease. No significant deterioration in symptoms or performance status *(more than 1 score level).*

11.3.2.1 **Measurable, bidimensional:** Greater than or equal to 50% decrease in tumor size *(multiplication of longest diameter by the greatest perpendicular diameter)* for at least 4 weeks.

11.3.2.2 **Measurable, unidimensional:** Greater than or equal to 30% decrease in linear tumor measurement lasting for at least 4 weeks.

11.3.2.1 Mediastinal and hilar width response may be determined by the formula:

\[
PR = \frac{(A-B)-(C-B)}{(A-B)} \geq 0.3
\]

11.3.2.2 Palpable masses that can be measured in only one dimension may be evaluated for response by using the formula:

\[
PR = \frac{A-B}{A} \geq 0.3
\]
11.3.2.3 **Non-measurable, evaluable:** Definite improvement in evaluable malignant disease estimated to be in excess of 50% and agreed upon by two independent investigators, lasting for at least 4 weeks.

11.3.3 **Stable:** No significant change in measurable or evaluable disease for at least 4 weeks. No increase in size of any known disease and no new disease. This designation includes decrease in bidimensional, measurable, or evaluable, non-measurable disease of < 30% or increase in malignant disease of < 25% in any site *(or an increase of < 50% if only 1 lesion was available and was < 2 cm² at initiation of therapy).*

11.3.4 **Progression:** Any increase > 25% in the sum of products of diameters of any measurable lesion or in estimated size of non-measurable lesions or appearance of an unequivocal new lesion.

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.

11.5 **Data and Protocol Management**

11.5.1 The attending physician and oncology research nurse must see each patient prior to drug administration. All required interim and pre-treatment data should be available and the physician must have made a designation as to tumor response and toxicity grade.

11.5.2 A brief explanation for required but missing data should be recorded as a comment.

11.5.3 The study chairman will be the final arbiter of responses or toxicity should a difference of opinion exist.

11.5.4 Patients who refuse all radiotherapy or chemotherapy will be considered canceled. No follow-up need be submitted.

11.5.5 Patients who start radiotherapy and chemotherapy will be evaluable regardless of when therapy is discontinued. All data will be required.

11.5.6 Patients who are found to be ineligible after enrolling onto the trial will be removed from the study. No further data beyond confirmation of ineligibility will be required. A letter will be sent to the institution by RTOG Headquarters to acknowledge the ineligible status.
12.0 DATA COLLECTION

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

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>
<tr>
<td>Baseline Mini Mental Status (MS)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td></td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 wk of RT end</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Off-Cord Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Study Specific Flowsheet (SF)</td>
<td>At 2, 5, 8, 11 wks and within 2 weeks of early termination of chemotherapy or onset of grade ≥ 3 toxicity.</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from treatment start for 1 year; q 6 mos x 2 years, then annually. Also at progression/relapse and at death.</td>
</tr>
<tr>
<td>Mini Mental Status (MS)</td>
<td>At 6 and 12 months from start of treatment, then annually.</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoint.

13.1.1 The primary endpoint is the frequency of patients developing unacceptable (Grade 3 or higher) acute toxicities attributable to thoracic irradiation with concurrent chemotherapy. Acute toxicities are defined as those toxicities that occur within 90 days from the start of treatment.

13.1.2 The second endpoint is to compare baseline and followup mini mental status examinations regardless of PCI.

13.2 Sample Size (9/8/98)

In order to establish the maximum tolerated dose (MTD) for external irradiation combined with chemotherapy, acceptable morbidity criteria must be defined. A 50% acute Grade 3 or Grade 4 esophagitis toxicity rate is determined to be dose limiting. The dose escalation will be determined as follows. Initially, 5 evaluable patients will be accrued to the current dose level. If no Grade 3 or Grade 4 esophagitis toxicities are reported within 90 days from the start of radiotherapy, then the dose will be escalated to the next dose level. This will provide at least a 97% confidence (0/5) that the true toxicity rate is less than 50%. However, if one Grade 3 or Grade 4 non-hematologic toxicity is observed, then an additional 5 patients will be accrued at this dose level. If less than two additional Grade 3 or Grade 4 esophagitis toxicities are observed, then the dose will be escalated to the next dose level. This will provide a 95% confidence (2/10) that the true morbidity rate is less than 50%. If three or more Grade 3 or Grade 4 esophagitis toxicities are observed in the first 10 patients, then this dose will be deemed too toxic. This design has 83% power if the true toxicity rate is ≤ 40%. If at any time a Grade 5 toxicity is observed, then accrual will be suspended and the event will be reviewed by the Study Chair.
13.3 Patient Accrual

The patient accrual is projected to be 4 cases per month. At this rate, it will take a minimum of 5 months and a maximum of 10 months to accrue enough patients to determine the maximum tolerated dose level. If the average monthly accrual rate is less than four cases a month, the study will be re-evaluated with respect to feasibility.

13.4 Dose Escalation (9/8/98)

After 5 evaluable patients (based on QA review of the treatment plan and treatment delivery) have been followed for a minimum of 90 days from the start of radiotherapy, the current dose arm will be carefully evaluated with respect to treatment morbidity. If no Grade 3 or Grade 4 esophagitis toxicities were observed, then the radiotherapy dose will be escalated. If one Grade 3 or Grade 4 esophagitis toxicity is observed, then an additional 5 evaluable patients will be accrued. A total of 10 evaluable cases will then be analyzed for toxicity, and if there are less than three Grade 3 or Grade 4 esophagitis toxicities observed, then the dose will be escalated to the next level. If at any time a Grade 5 toxicity is observed, then accrual will be suspended and the Study Chair will review the event.

While the phase I portion of this study is the determination of dose-limiting acute toxicities, combined acute/late toxicities will also be monitored. If the cumulative incidence (obtained by time to event analysis), at any time, of combined acute/late toxicity estimates the rate to be greater than 40% of any level, then the Executive Committee will be notified and the committee will determine whether that arm should be closed.

13.5 Analysis Plans

13.5.1 Interim Analyses

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

- the patient accrual rate with a projected completion date for accruals phase;
- compliance rate of treatment delivery with respect to protocol prescription;
- the frequency and severity of the toxicities;
- the cumulative incidence of acute/late toxicities.

Any problems will be reported to the RTOG committee responsible for this study and, if necessary, the Executive committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

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

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

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 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The participation rates of men and women will be examined according to Section 13.5.1.
REFERENCES


APPENDIX I

RTOG 97-12

A PHASE I DOSE ESCALATION STUDY OF THORACIC IRRADIATION WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH LIMITED SMALL CELL LUNG CANCER

SAMPLE PATIENT CONSENT FORM

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

This is a clinical research study is to evaluate the effectiveness of combination chemotherapy (cisplatin and etoposide) and concurrent radiotherapy (given with the chemotherapy) to the chest in the treatment of patients with limited small cell lung cancer. This research will also study whether a higher dose of radiation to the chest better controls or eliminates the tumor. A growth factor for the bone marrow, G-CSF, may be given to help decrease the side effects of treatment.

DESCRIPTION OF PROCEDURES (9/8/98, 2/14/00)

The treatment to be given to me is as follows:

Chemotherapy will consist of two drugs, cisplatin and etoposide. Cisplatin will be given intravenously (i.v.) for two hours on the first day. Etoposide will also be given by i.v. on the first day over one hour. The next two days, I will take the etoposide orally once a day, one hour before breakfast. If because of side effects or etoposide availability, oral etoposide cannot be given, i.v. etoposide may be used instead of oral etoposide. My doctor will discuss this with me. This chemotherapy will be repeated approximately every three weeks for a total of four times. Radiation treatments will be given once per day, five days per week for approximately five weeks. The last week of radiation will be given twice a day six hours apart.

I will be asked to complete a form about my mental status before I start treatment then again six months later. A third form will be completed six months later, then once a year after that.

G-CSF may be used during the treatment period to help manage and prevent infection related to low blood cell counts. Before each treatment cycle, appropriate tests will be done to evaluate the response of the cancer. Treatment will be discontinued if at any time the cancer has progressed in size or at any time intolerable side effects occur.

Evaluation at study entry will include blood tests, chest x-ray, urinalysis, and appropriate tests of the bone, bone marrow, abdomen, and brain to look for cancer spread. During treatment, a blood specimen will be obtained to check my blood counts.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss, ringing of the ears, and numbness of the fingers and toes. It can also cause damage to the kidneys; I will be given extra amounts of fluids and other medications to lessen the risk of kidney injury. It can lower the blood counts and the levels of calcium and
magnesium in my blood. It is possible that I may become anemic and require transfusion. Other less common side effects include allergic reactions such as sweating, difficulty breathing, and rapid heartbeat. Rarely the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps, or acute leukemia.

Etoposide (Vepesid, VP-16) may lower blood counts which could lead to an increased risk of infection, weakness, or bleeding complications. I could require hospitalization, treatment with antibiotics, and/or transfusion if these problems are severe. This drug can cause nausea and vomiting, diarrhea, hair loss, chest pain, blood in the urine, or a skin rash. Less common reactions include low blood pressure, liver damage, fever, chills, muscle cramps, and leukemia.

G-CSF is given by injection under the skin and there is some discomfort associated with this. It also commonly causes mild to moderate muscle/bone aching which is usually relieved with medication like acetaminophen (Tylenol). Rarely it has been associated with transient decreases in blood pressure.

Risks from Radiation:

Radiation Therapy may cause: 1) difficulty, pain or burning sensation on swallowing. This effect usually begins after the second week of radiotherapy and goes away within a month of completion of radiation therapy; 2) fatigue (tiredness) for no apparent reason, which is a temporary effect, resolving within a month of completion of treatment; 3) skin damage within the area of radiation; the skin may develop a sunburn-like area within 2-6 weeks after treatment, the skin will permanently be more dry than other skin, and chest hair (if any) may not regrow: 4) decrease in white blood cells and platelets. Decrease in white cell production may result in bleeding and bruising easily; 5) cough and some difficulty in breathing (radiation pneumonitis and subsequent scarring of the lung). In addition, although uncommon, pericarditis (irritation of the heart sac), myocarditis (irritation of the heart muscle), transverse myelitis (irritation of spinal cord), or esophageal narrowing may occur long after radiation therapy.

This clinical research may involve unforeseeable risks to the participant (or to the embryo or fetus, if the participant is or may 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.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr.________ the investigator in charge at______________________________. In addition, I may contact__________________________at ____________________________for information regarding patients’ rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others.

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

Alternatives which could be considered in my case include radiation therapy with or without chemotherapy, chemotherapy alone or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative) __________________________ Date __________________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</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>
</tr>
</tbody>
</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 cytological 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)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

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

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
<td>TX</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

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

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

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

#### Commercial and Non-Investigational Agents

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

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

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

iv. All relevant data forms must be submitted to RT0G Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

#### Investigational Agents

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

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

i. **Phase I Studies Utilizing Investigational Agents**

- All deaths during therapy with the agent. Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.**

- All deaths within 30 days of termination of the agent. As above
- All life threatening (grade 4) events which may be due to agent.  

As above

- First occurrence of any toxicity (regardless of grade).

Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

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

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.

Report by phone to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

**Report in writing** to RTOG Headquarters and IDB within 10 working days.

**See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**
## APPENDIX VI (9/8/98, 12/14/00, 9/21/01)

### PROTOCOL DOSE SCHEDULE

<table>
<thead>
<tr>
<th>Week</th>
<th>Large Field (1.8 Gy/fx)</th>
<th>Boost (1/8 Gy Bid) x (off cord)</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRT</td>
<td>X X X X X</td>
<td></td>
<td>Arm 1 &amp; 5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td>X X X X X</td>
<td></td>
<td>Arm 2</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td>X X X X X</td>
<td></td>
<td>Arm 3</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td>X X X X X</td>
<td></td>
<td>Arm 4</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td>X X X X X</td>
<td></td>
<td>Arm 6</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>↑ ↑ ↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- **Thoracic Irradiation** = large field, **X** = boost field, **↑** = chemotherapy
- Cisplatin 60 mg/m² day 1; Etoposide iv 120 mg/m² day 1; Etoposide p.o. 240 mg/m² per day, days 2-3. Chemo every 22 days x 4 cycles.
- PCI 2.5 Gy x 10 Fx to 25 Gy for CR after completion chemo/RT
- Grade 3 Esophagitis in only 3 pts in Arm 1: escalate boost dose with increments of 3.6 Gy 2 days. If 1 patient grade 4, treat next 6 patients at same dose.