RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-09

PHASE II STUDY OF PACLITAXEL, ETOPOSIDE, AND CISPLATIN CHEMOTHERAPY COMBINED WITH TWICE DAILY THORACIC RADIOTHERAPY FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

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SCHEMA

R  Cycle 1 Chemotherapy and Concurrent Radiotherapy

E  Followed by 3 Cycles of Chemotherapy Alone (Cycles are q 21 days for 3 cycles)

G  Thoracic Radiotherapy: (Begins Day 1) 45 Gy in 30 fractions (twice daily), 1.5 Gy per fraction; daily fractions to be separated by at least 6 hours:

I  Chemotherapy: Cycle 1 begins Day 1 (with thoracic RT)

S  Cycle 1 drug doses: Paclitaxel 135 mg/m² i.v. over 3 hours, Day 1 only. Etoposide 60 mg/m² i.v. Day 1;

T  80 mg/m² PO Days 2,3

Cisplatin 60 mg/m² i.v. Day 1

E  Cycles 2-4 Doses: Paclitaxel 175 mg/m² i.v. over 3 hours, Day 1 only

Etoposide as in Cycle 1

R  Cisplatin as in Cycle 1

No G-CSF until radiotherapy concluded,
G-CSF only used as per guidelines in Section 7.2.2

Prophylactic Cranial Radiotherapy (PCI):
Patients with CR or PR should be offered PCI, 2.0 to 2.5 Gy daily fractions for 25 Gy in 10 fractions or 26-30 Gy in 13-15 fractions within 6 weeks of Cycle 4. See Section 6.7.

Eligibility: (See Section 3.0 for details)

- Histologic or unequivocal cytologic proof (fine needle aspiration biopsy or two positive sputa) of SCLC is required.
- Patients must have limited disease, clinical TNM stages I-IIIb (i.e., confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement).
- Patients with minimal pleural effusion visible on CT of the chest, but not evident on CXR, are eligible.
- Patients must have measurable or evaluable disease.
- Age ≥ 18.
- Karnofsky Performance Status ≥ 70.
- No prior chemotherapy, radiotherapy, or biotherapy is permitted.
- Absolute granulocytes ≥ 1500/µl, platelets ≥ 150,000/µl, bilirubin ≤ 1.5 mg/dl, creatinine ≤ 1.5 mg/dl are required. No minimum HGB level is specified. However, HGB level of 9.0 gm/100 ml or better is desirable.
- No pre-existing grade II or worse peripheral neuropathy

Required Sample Size: 52 3/17/98
<table>
<thead>
<tr>
<th>Case #</th>
<th>1. Does the patient have documented histologic or unequivocal cytologic proof of small cell lung cancer?</th>
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<tr>
<td></td>
<td>2. What is the stage?</td>
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<td>3. Does the patient have N3 disease based on contralateral hilar or contralateral supraclavicular nodal involvement?</td>
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<td>4. Is there evidence of pleural effusion? If yes, is the amount of effusion too small to tap under CT guidance and not visible on chest X-ray?</td>
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<td>5. Does the patient have measurable or evaluable disease?</td>
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<td>6. What is the patient's age?</td>
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<td>7. What is the Karnofsky Performance Status?</td>
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<td>8. Has the patient received any prior chemotherapy, radiotherapy, or biotherapy?</td>
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<td>9. State the absolute neutrophil count (ANC).</td>
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<td>10. Report the platelet count (x 1000).</td>
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<td>11. Report the bilirubin results.</td>
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<td>12. State the serum creatinine.</td>
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<td>13. Has the radiation oncologist verified that tumor can be encompassed by radiation fields as defined in Section 6.0 without significantly compromising pulmonary function?</td>
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<td>14. Does the patient have a pericardial effusion?</td>
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<td>15. Has the patient had a myocardial infarction within the last 6 months, symptomatic heart disease, COPD with FEV-1 &lt; 1 liter, or uncontrolled bronchospasms in the unaffected lung?</td>
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<td>16. Is there history of a prior malignancy from which the patient has not been disease free for a minimum of 5 yrs, other than adequately treated basal/squamous skin cancer or in situ cervix cancer?</td>
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<td>17. If female, is the patient pregnant or lactating?</td>
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<td>18. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?</td>
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<th>Case #</th>
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<th>19. Has the patient had a complete tumor resection?</th>
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<th>20. Does the patient have a pre-existing grade II or worse peripheral neuropathy?</th>
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<th>21. Has the patient agreed to be available for followup?</th>
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<td>Y</td>
<td>Has the patient agreed to be available for followup?</td>
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<th>22. Has the patient signed a study-specific consent form?</th>
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<td>Y</td>
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<th>Social Security Number</th>
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<th>Method of Payment</th>
<th>Will any component of the patient’s care be given at a military or VA facility?</th>
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<th>Treatment Assignment</th>
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1.0 INTRODUCTION

Roughly one-fourth of all patients with lung cancer will have small cell lung cancer (SCLC). Although SCLC can be staged by the TNM classification for lung cancer, more typically it is staged as "limited" or "extensive". Limited stage disease shows clinical evidence of involvement of one hemi-thorax and its regional lymph nodes. Extensive disease demonstrates spread beyond these regions. At presentation, roughly 30-40% of all small cell patients will have limited stage disease.\(^1\)

Milestones in the management of limited stage SCLC have included recognition of the following: \(^1\text{-}^{13}\)

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

Currently, the combination of Etoposide (VP-16) with Cisplatin is felt to be one of the most active combinations in the management of SCLC.

The use of twice daily radiotherapy has received substantial attention in the management of both non-small cell and SCLC. In the non-small cell setting Cox, et al. and subsequently, Sause, et al. have confirmed that twice daily radiotherapy results in improved results, as compared to once daily fractionation, for favorable Stage III patients.\(^14,15\) Choi has discussed the rationale and the anticipated limitations for accelerated radiotherapy in SCLC.\(^16\) Subsequently, he has reported for the CALGB that 45 Gy in 30 fractions over 19 elapsed days represents the MTD (maximum tolerated dose) of twice daily radiotherapy when administered with PCE chemotherapy (Cisplatin 33 mg/m² i.v. days 1, 2, 3; cyclophosphamide 500 mg/m²day 1; and etoposide 80 mg/m² i.v. days 1, 2, 3) as judged by a 29% incidence of grade 3 or worse esophagitis and a 43% incidence of grade 4 leukopenia and granulocytopenia.\(^17\)

Turrisi, et al.\(^18,19\) reported their pilot results at the University of Pennsylvania using limited radiotherapy fields and concurrent VP-16 and Cisplatin in doses of 120 mg/m² I.V. days 4, 6, and 8 and 60 mg/m² i.v. day 1, respectively. Radiotherapy was given in 1.5 Gy fractions twice daily with an inter fraction interval of at least 4 hours. Radiotherapy portals were AP/PA AM and PM in week 1, AP/PA in the AM and off cord obliques in the PM during weeks 2 and 3. Radiotherapy volumes included the primary tumor and ipsilateral hilum, involved mediastinal nodes, and inclusion of nodes one level beyond those involved without routine irradiation of contralateral hilum or either supraclavicular region. Their results of 94% CR, 96% local control in patients with non-variant histology, median survival of 21 months and actuarial disease free survival of 45-50% represented the best results reported in limited stage disease. Prophylactic cranial irradiation was administered to all complete responders. These results were confirmed by a joint study of the RTOG (RTOG 88-15) and ECOG using the same chemotherapy regimen with randomization to either 45 Gy in 25 fractions (1.8 Gy once daily) or 45 Gy in 30 fractions (1.5 Gy BID). As reported by Wagner, et al.\(^20\) the CR+PR rate was 81% in both groups, median survival was 18.6 - 20.3 months and two year survival was 41.7 - 44.3% in a study involving 358 eligible patients. Although BID radiotherapy yielded the slightly higher response and survival results, at the time of this preliminary analysis these were not significant. Myelotoxicity in the two groups was the same (40% grade 3 and 4). Grade 3-4 esophageal toxicity was less with once daily radiotherapy (15% vs 31%).

Pending subsequent long term analysis of the above study, the RTOG has elected to continue studies of concurrent BID radiotherapy/Cisplatin/VP-16 with modifications made in the chemotherapy regimen seeking enhanced therapeutic effect with acceptable toxicity. RTOG 93-12, modified the chemotherapy regimen by adding Ifosfamide + Mesna, changing the Cisplatin schedule and using an oral 14 day schedule for VP-16. G-CSF was permitted to rescue from febrile neutropenia and to maintain dose intensity in subsequent cycles. In order to avoid recruitment phenomena that might paradoxically enhance myelotoxicity G-CSF was not initiated until at least 24 hours after the last dose of oral VP-16 or radiation fraction and was stopped 48 hours prior to the initiation of the next cycle of chemotherapy. As of 10/1/95 acute toxicity data are available on 26 patients in this study revealing 8 patients with grade 3 esophagitis (no grade 4 or worse), 3 patients with grade 3 nausea and 7 patients with grade 4 myelotoxicity. There was one grade 4 neurologic
toxicity (not specified) and one grade 4 stomatitis. There were no treatment related deaths.

Pending analysis of mature data from RTOG 93-12 for toxicity and therapeutic outcomes, we propose a second phase II trial building on the theme of BID fractionation/Cisplatin/ VP-16. In this trial our major modification will be the addition of the drug Taxol (paclitaxel).

Paclitaxel has been selected for study in this context for several reasons. In addition to being an exceptionally promising antineoplastic agent in general (see general review by Rowinsky, E.K. and Donehower, R.C.), this drug also was to have substantial single agent activity in both non-small cell and SCLC in phase II studies (response rates of 21-24% in non-small cell and 32-41% in small cell patients). Additionally, there is evidence to suggest that Taxol acts as a radiation sensitizer. The clinical pharmacology and sequencing of combined Taxol and Cisplatin has been well studied. Paclitaxel has been studied as a single agent with radiation in patients with Stage III lung cancer, and paclitaxel has been studied with combination chemotherapy including Cisplatin and/or VP-16 and radiation in patients with lung cancer.

Two phase I studies of paclitaxel, VP-16, and Cisplatin without radiotherapy for patients with extensive stage small cell lung cancer have been described in abstract form. Levitan, et al. found the appropriate drug doses and scheduling for a phase II study with this combination of drugs to be paclitaxel 170 mg/m² i.v. over 3 hours on day 1, Cisplatin 60 mg/m² i.v. on day 1, and Etoposide 80 mg/m² i.v. on days 1, 2, and 3. This regimen is virtually identical to what we have proposed for the non-radiotherapy cycles in our protocol except that by giving the Etoposide PO on days 2 and 3 we may lower the toxicity slightly. Levitan, et al describe this regimen with a lower Paclitaxel dose of 135 mg/m² in 4 patients and observed no grade 3 or 4 toxicity. When the paclitaxel dose was escalated to 170 mg/m², the dose limiting toxicity was diarrhea, a toxicity that should not be increased by thoracic radiotherapy as we are proposing it. We note that Levitan et al did utilize G-CSF in their study. In a second study Kelly et al describe the use of these three drugs as follows in a phase I study. Level 1: Taxol 135 mg/m² i.v. over 3 hours and Cisplatin 80 mg/m² i.v. day 1. Etoposide 50 mg/m² i.v. day 1 and 100 mg/m² PO days 2 and 3. In Level 2, the Etoposide was increased to 80 mg/m² i.v. day 1 and 160 mg/m² days 2 and 3. In Level 3 the Cisplatin dose and Etoposide doses were as in Level 2 and the paclitaxel was increased to 175 mg/m². As of the date of this abstract, they did not feel dose limiting toxicity had been achieved and were escalating the paclitaxel dose further to 200 mg/m². These results, considering the similarity of regimens utilized and the dose effects observed, give us confidence that the doses we are proposing are appropriate and safe for this Phase II study.

Results to date, though preliminary, suggest that the addition of paclitaxel to Cisplatin/Etoposide/radiation may well result in significant enhancement of therapeutic effect. These results also suggest that there is likely to be significant neutropenia, esophagitis, and some risk of radiation pneumonitis. In designing this trial we have attempted to deal with these concerns by choosing conservative drug doses and sequences as indicated by currently available data and by utilizing the "tight" radiation therapy fields of RTOG 88-15 and RTOG 93-12. Paclitaxel will be given as a 3 hour infusion which may help reduce toxicity. Dose and schedule of Etoposide have been selected after considering the significant contribution of this agent toward esophagitis and myelosuppression and, additionally, that the oral bio-availability of this drug may be as high as 76% at the doses utilized.

2.0 OBJECTIVES

2.1 To determine the response rate and progression-free and overall survival in patients with limited stage SCLC treated with paclitaxel, etoposide, and cisplatin and combined with accelerated hyperfractionated thoracic radiotherapy.

2.2 To determine the qualitative and quantitative toxicity and reversibility of toxicity from this approach.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility
3.1.1 Histologic or unequivocal cytologic proof (fine needle aspiration biopsy or two positive sputa) of SCLC is required.

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

3.1.2.1 Patients with minimal pleural effusion visible on CT of the chest, but not evident on CXR, are eligible.

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

3.1.4 Age ≥ 18.

3.1.5 Karnofsky Performance Status ≥ 70 (See Appendix II).

3.1.6 No prior chemotherapy, radiotherapy, or biotherapy is permitted.

3.1.7 Adequate hematologic, hepatic, and renal function as follows: absolute granulocytes ≥ 1500/μl, platelets ≥ 150,000/μl, bilirubin ≤ 1.5 mg/dl, creatinine ≤ 1.5 mg/dl are required. No minimum HGB level is specified. However, HGB level of 9.0 gm/100 ml or better is desirable.

3.1.8 Patients must sign a study-specific consent form.

3.1.9 Patients must be available for active follow up.

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

3.2 Conditions for Patient Ineligibility

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

3.2.2 Patients with complete tumor resection.

3.2.3 Absolute granulocytes < 1500/μl, platelets < 150,000/μl, bilirubin > 1.5 mg/dl, creatinine > 1.5 mg/dl.

3.2.4 Pericardial effusion (regardless of cytology).

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

3.2.6 Previous or concurrent malignancy other than curatively-treated basal or squamous cell skin cancer or carcinoma in situ of cervix. Patients managed for a non-pulmonary invasive malignancy more than 5 years previously with no subsequent clinical, laboratory, imaging, or pathologic evidence of recurrence or persistence of the prior malignancy are eligible for this protocol.

3.2.7 Patients with pre-existing grade II or worse peripheral neuropathy (Grade II = motor: mild objective weakness; = sensory: moderate paresthesia or non-disabling but objective sensory loss; deep tendon reflexes lost).

4.0 PRETREATMENT EVALUATION

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

4.2 Laboratory studies will include a CBC with differential, platelet count, SMA-12, electrolytes, magnesium, and urinalysis done within 2 weeks before study entry.

4.3 Chest X-ray, EKG, CT scans of brain, chest, abdomen, radionuclide bone scan, and bone marrow aspirate and biopsy are required within four weeks before starting treatment. Scans or X-rays used to document measurable or evaluable disease should be done within four weeks before study entry.

4.4 Bronchoscopy, PFT (patients with a pretreatment FEV 1 of less than 1.0 L/sec will not be eligible for this study).

4.5 Location, type and size of all measurable lesions must be reported.

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 following information must be provided:
- Patient’s Name & ID Number
- Institution Name & Number
6.0   **RADIOThERAPY**

6.1   **Thoracic Radiation Dose**

6.1.1   Each fraction will consist of 1.5 Gy to be given twice daily (6-8 hours apart), five days a week for three weeks. Total dose 45 Gy in 30 fractions. Dose is specified at midplane or isocenter.

6.1.2   Irradiation must begin within 24 hours of day one of cycle one chemotherapy.

6.1.3   Patients will be treated two times per day on each treatment day, receiving 1.5 Gy in each treatment. No less than 6 and no more than 8 hours may elapse between each treatment session daily. Treatment times (a.m./p.m.) must be documented in the daily record.

6.1.4   Treatment is administered 5 days/week. A minimum of three days concurrent therapy is required, i.e., therapy should begin no later than Monday, Tuesday, or Wednesday of the first week.

6.1.5   Efforts should be made to avoid interruptions in therapy. Note: Fevers, cytopenias, esophagitis, do not constitute reasons for interruptions (Contact Dr. Abrams to discuss any planned interruption). Routine holidays are understood. Interruptions will be scored as major protocol violations. Document in treatment chart reason for treatment interruption. See also Section 6.5.2.

6.1.6   Week one is given AP/PA in both am and pm sessions. The pm session of weeks 2 and 3 must be given by oblique or lateral fields (rarely, all 3 weeks may require multi-port fields in order to avoid excess dose to normal tissues or compromise target volume dose.) Direct posterior spinal cord blocks are not acceptable.

6.2   **Target Volume**

The target volume that will be treated by AP/PA and oblique or lateral fields includes the primary tumor plus regional (hilar and mediastinal) lymph nodes. In the case of upper lobe tumors, the ipsilateral supracardiac lymph nodes should also be treated. The primary tumor 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 contralateral border of the vertebral bodies. Ipsilateral supracardiac 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 supracardiac treatment is not allowed. Contralateral hilar irradiation should only be delivered if there is demonstrable bulky contralateral mediastinal involvement. The lower field border will be two vertebral bodies or 5 cm below the carina for upper and middle lung field lesions. The lower extent of lower lobe lesions with a 1.0 to 1.5 cm margin 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. The CT for treatment planning should be taken in treatment position.

6.2.1   Target volume for antero-posterior (AP) and postero-anterior (PA) ports must be simulated before initiation of radiotherapy.

6.2.2   Target volumes for AP/PA treatment also define target volumes to be included in oblique or multi-field volume. No posterior spinal cord blocks are allowed other than the most superior laryngeal and spinal cord blocks where the tumor does not exist.

6.3   **Technical Factors**

6.3.1   **Radiotherapy Equipment:** Megavoltage required, with minimum peak energy of 6 MV. Minimum source to isocenter distance is 100 cm. Electron beams, 60Co, 4 MV accelerators and 80 cm SSD are not acceptable. Fifteen MV or higher energy is recommended for oblique and lateral fields.

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 defined in Section 6.2. Oblique or lateral fields should be simulated with a barium swallow to document the length of the irradiated esophagus.

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 recommended 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   **Dose Calculation:** Doses are to be calculated without heterogeneity correction, i.e., no correction is to be made for density differences between air spaces, lung, water-density or bony tissue.
6.3.4.1 Spinal Cord: If compensating filters are not used, the point at which the spinal cord dose is to be calculated is 2 cm below the superior margin of the posterior fields. If compensating filters or wedges are used then the point of maximum dose to the spinal cord must be determined. Maximal spinal cord dose should not exceed 36 Gy at any level.

6.3.4.2 Subcarinal Nodes: Which are assumed to be at mid-plane.

6.3.4.3 Ipsilateral Normal Lung Dose: This is to be calculated at the level of the central rays of the oblique fields at the point of maximum dose in the lung which lies at least 2 cm outside the projected borders of the initial (AP/PA) treatment fields in the ipsilateral lung.

6.3.4.4 Contralateral Normal Lung Dose: This is to be calculated at the level of the central rays of the oblique fields at the point of maximum dose in the lung which lies at least 2 cm outside of the projected borders of the initial (AP/PA) treatment fields in the contralateral lung.

6.3.4.5 Maximum Normal Lung Tissue Dose: This is to be calculated at the level of the central rays of the oblique fields as the maximum total dose that is at least 2 cm outside of the target volume.

6.3.5 Isodose Distribution: In order to ensure homogeneity of dose between +5% contours and isodose plots will be obtained at: a) the central axis level b) 2.0 cm from the top, and c) 2 cm from the bottom of the field. The isodose plans must reflect utilized blocks and compensators. These must be composite plans accounting for the total dose from each component field. Critical structures (spinal cord) and target volume must be clearly delineated on each plot.

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

6.3.7 Maximum Dose to Critical Normal Tissues:

\[
\begin{align*}
\text{a)} & \quad \text{Ipsilateral whole lung} \quad 10 \text{ Gy} \\
\text{b)} & \quad \text{Contralateral portion of lung (non paramediastinal)} \quad 16 \text{ Gy} \\
\text{c)} & \quad \text{Spinal Cord} \quad 36 \text{ Gy} \\
\text{d)} & \quad \text{Esophagus} \quad 45 \text{ Gy} \\
\text{e)} & \quad \text{Entire Heart} \quad 36 \text{ Gy}
\end{align*}
\]

6.4 Treatment Techniques

6.4.1 All doses are to be prescribed and calculated assuming a homogeneous patient, that is there will be no heterogeneity corrections used in the definitions of these doses. The doses shall be prescribed and calculated according to the following RTOG guidelines for external treatments using photons and electrons.

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

6.4.1.2 At mid-separation on the central ray for two opposed coaxial unequally weighted beams.

6.4.1.3 At the center of the target area on the central beam for two opposed coaxial unequally weighted beams.

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

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

6.4.1.6 At the center of the target area for complex treatment arrangements which are not covered above.

6.5 Toxicity from Radiation Therapy

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

6.5.2 Esophagitis

Esophageal complaints are common with combined modality therapy. It does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous xylocaine, carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.
It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event please notify Dr. Abrams.

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

6.7 Prophylactic Cranial Radiotherapy (PCI)
6.7.1 We suggest that all CR patients (and PR patients who desire to receive it) be offered PCI using 2.0-2.5 Gy daily fractions. Acceptable time dose fractions schemes will include 25 Gy in 10 fractions, or 26-30 Gy in 13-15 fractions. PCI should be initiated in those patients after hematologic recovery from the last cycle of chemotherapy or within 6 weeks thereof. Repeat brain imaging prior to initiating PCI should be considered.

6.8 Compliance Criteria
6.8.1 Major Deviations
6.8.1.1 Dose: Deviation of total dose by more than 10%. Deviation in any fractional dose by more than 20%.
6.8.1.2 Treatment Time: Interfractional interval of less than 5.5 hours on more than two occasions.
6.8.1.3 Fields: Failure to use off cord obliques or laterals in weeks 2 and 3.
6.8.1.4 Target Volumes: Less than 5 mm margin on designated target volume uncorrected for predominance of treatment fractions. Inclusion of volume specifically indicated to be excluded, e.g., contralateral mediastinal involvement.
6.8.1.5 Technical Factors: Failure to comply with any factors mentioned in Section 6.3.1. Failure to use custom blocks.
6.8.1.6 Dose to Critical Tissues: Spinal cord dose at any point along the length in excess of 45 Gy. Dose to entire heart more than 45 Gy. Esophageal dose more than 54 Gy. Ipsilateral whole lung dose more than 16 Gy.

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

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

7.1 Treatment Plan
7.1.1 Cycle 1: Patients will receive chemotherapy concurrently with radiotherapy.
7.1.1.1 Paclitaxel: 135 mg/m² intravenously over 3 hours on day 1. The drug is administered first before other chemotherapeutic agents are administered. Premedication: All patients must receive premedication prior to paclitaxel in order to reduce the risk of hypersensitivity reactions. Patients must receive dexamethasone 20mg p.o. 12 and 6 hours before paclitaxel, diphenhydramine 50 mg intravenously 30 minutes prior to paclitaxel and cimetidine 300 mg intravenously 30 minutes prior to paclitaxel. Drug Administration: Following premedication, patients will receive paclitaxel. The drug will be mixed in 500cc 0.9% sodium chloride and administered by continuous i.v. infusion over 3 hours.

7.1.1.2 Etoposide: 60 mg/m² intravenously over 60 minutes on day 1. 80 mg/m² p.o. days 2 and 3. Drug Administration: The drug given intravenously will be mixed in 250cc of normal saline and infused over 45 minutes on day 1. On days 2 and 3 the oral dose is given as shown in Appendix VI using commercially available 50 mg capsules. Oral VP-16 is given in a single daily dose. See Appendix VI.

7.1.1.3 Cisplatin: 60 mg/m² intravenously on day 1 following the administration of the etoposide. Hydration: Patients should receive prehydration prior to Cisplatin with 750-1000cc of
intravenous 1/2 normal saline over 2-3 hours prior to Cisplatin. Following Cisplatin, patients should receive post hydration with 750-1000cc of intravenous 1/2 normal saline over 2-3 hours.

Mannitol: 25 gm intravenous push prior to Cisplatin.

Drug Administration: Cisplatin will be mixed in 250cc of normal saline and given over 1 mg per minute.

7.1.2 Cycles 2-4: Patients will receive chemotherapy without radiotherapy. Cycle 2 to start 21 days after initiation of chemotherapy (Day 22). Subsequent cycles also repeated q 21 days.

7.1.2.1 Paclitaxel: 175 mg/m² intravenously over 3 hours on day 1.

7.1.2.2 Etoposide: 60 mg/m² intravenously over 60 minutes on day 1. 80 mg/m² p.o. days 2 and 3.

7.1.2.3 Cisplatin: 60 mg/m² intravenously on day 1 following the administration of the etoposide.

<table>
<thead>
<tr>
<th>Cycle #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Week</td>
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<tr>
<td>Taxol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP-16</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
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<tr>
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<td>XXXXX</td>
<td>XXXXX</td>
<td>XXXXX</td>
<td>XXXXX</td>
</tr>
</tbody>
</table>

7.2 Chemotherapy

7.2.1 Patients will receive antiemetics prior to chemotherapy at the discretion of the treating physician. Ondansetron (or granisetron) and dexamethasone are recommended.

7.2.2 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 2-4 of chemotherapy in patients who have experienced such a complication. Alternatively, a dose reduction can be instituted. The G-CSF must be separated from administration of both thoracic radiotherapy and chemotherapy, i.e. 24 hours should elapse between either the last day of XRT or the last dose of 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.

7.2.3 All courses will be held pending hematologic recovery to AGC ≥ 1,500/μl and platelets ≥ 100,000/μl.

7.3 Paclitaxel (Taxol) (NSC-125973)

7.3.1 Chemistry: Paclitaxel is a natural product with antitumor activity. The chemical name for paclitaxel is 5,20-Epoxy-1,2-hexahydroxytax-11-en 9-one 4, 10 diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel is a white to off-white crystalline powder with the empirical formula C₄₇H₅₁NO₁₄ and a molecular weight of 853.9. It is extremely lipophilic and melts at around 216-217°C. Paclitaxel is highly insoluble in water.

7.3.2 Mechanisms of Action: Microtubules have been demonstrated to be very strategic targets for antineoplastic agents; however, few antimicrotubule agents have been discovered and encompassed into standard chemotherapeutic regimens. Paclitaxel, a diterpenoid plant product extracted from the bark of the western yew (Taxus brevifolia), has a unique mechanism of action. Unlike other antimicrotubule agents in clinical use (e.g. colchicine, vincristine, and vinblastine) that shift the equilibrium between microtubules and tubulin subunits toward microtubule disassembly, paclitaxel promotes assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. These microtubules are stable even when treated with low temperatures or calcium, conditions that usually promote disassembly. This unusual stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules during mitosis.

7.3.3 Animal Tumor Data: Paclitaxel demonstrated a broad spectrum of activity against murine and human solid tumors and leukemias in studies directed by the National Cancer Institute’s Division of Cancer Treatment. It had its greatest activity against i.p. B16 murine melanoma and subrenal
capsule implants of the MX-1 human breast cancer xenograft in nude mice. Paclitaxel was also active against i.p. P388 and L1210 murine leukemias and human CX-1 colon and LX-1 lung cancer xenografts.

7.3.4 Human Toxicology: The dose limiting toxicities and MTD of paclitaxel administered on a variety of schedules to patients with solid neoplasms were previously evaluated in phase I trials. In these studies, paclitaxel was infused over 1, 3, 6, and 24 h, but severe acute reactions, characterized by bronchospasm, hypotension, stridor, tachy- and bradyarrhythmias, and death, resulted in the temporary discontinuation of all trials. These reactions were attributed to paclitaxel’s Cremophor vehicle, since identical reactions were observed with other drugs formulated with it and when the vehicle alone was administered to animals. Since a higher incidence of these acute reactions was observed with shorter durations of infusion, studies that used shorter infusions were permanently discontinued, and trials that evaluated longer infusion durations (24 h) were resumed using antiallergic pre-medications consisting of corticosteroids, H₁- and H₂- histamine antagonists.

These modifications were associated with a marked reduction in the incidence of acute reactions. Neutropenia was the major dose-limiting toxicity for paclitaxel in phase I solid tumor trials. In addition, a sensory neuropathy, characterized by a glove-and-sock distribution of numbness and paresthesias, was observed at higher doses. Nausea and vomiting, myalgias, mucositis, total-body alopecia, diarrhea, and phlebitis were also observed. The MTD and recommended Phase II doses of Paclitaxel administered as a 6-h infusion were 265 and 212 mg/m², respectively, and 275 and 250 mg/m², respectively, as a 24-h infusion.

7.3.5 Pharmaceutical Data: Formulation: Paclitaxel (TAXOL®) for Injection Concentrate is a clear colorless to slightly yellow viscous solution. It is supplied as a solution in a nonaqueous medium. It is intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5mL) vials. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor®EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

7.3.6 Storage and Stability: Unopened vials of Paclitaxel for Injection Concentrate are stable until the date indicated on the package when stored under refrigeration, 2 - 8 °C (36 °-47°F). Refrigeration is not required for shipping. Freezing does not adversely affect the concentrate. Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.

7.3.7 Administration: Paclitaxel should be given after the patient has received the appropriate premedication as per Section 7.1.1.1.

7.3.8 Supplier: Paclitaxel is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

7.4 VP-16 (Etoposide) (Vepesid) (NSC-141540)

7.4.1 Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllotoxin pletatum, and has antineoplastic properties in experimental animals and in man. The empirical formula C₂₉H₃₂O₁₃ has a molecular weight of 588.

7.4.2 Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human calls in tissue culture suggests effects against DNA, RNA, and protein synthesis.

7.4.3 Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L1210 system, activity was schedule dependent, having greater effect with a twice weekly administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated L1210.

7.4.4 Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats, and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immunosuppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell-mediated immunity).

7.4.5 Human Toxicology: Reversible myelotoxicity has uniformly been the major toxicity of VP-16 and represents the only clinically significant side effect. Following a single I.V. injection, peak
myelotoxicity occurs at seven to nine days. Following daily I.V. injections for five to seven days, myelotoxicity is maximal between 12-16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Transient modest nausea, usually without vomiting, is common. Occasional alopecia is reported. VP-16 does not produce phlebitis, or nephrotoxicity. Hypotension can be managed by infusing the drug over at least a 30 minute period. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, and hepatotoxicity may be a result of VP-16 administration. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other neoplastic agents.

7.4.6 **Pharmaceutical Data:** 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, VP-16 is supplied as 50 mg capsules which should be stored at 2-8°C. At these temperatures the capsules are stable for 24 months.

7.4.7 **Administration:** VP-16 should be given as a slow intravenous infusion (day 1) or as a single oral dose (days 2 and 3) of each cycle. See Section 7.1.1.3.

7.4.8 **Supplier:** VP-16 is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

7.5 **Cisplatin (CDDP) (Platinol) (NSC-119875)**

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

7.5.2 **Human Toxicity:** Human toxicity studies includes anorexia, nausea, vomiting, renal toxicity (*with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient*), otoxicity (*with hearing loss which initially is in the high frequency range, as well as tinnitus*), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with an abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are of taste, allergic reactions, and loss of muscle or nerve function.

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

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

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

7.5.6 **Supplier:** Cisplatin is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

7.6 **G-CSF (r-metHuG-CSF) (NSC-614629)**

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

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

7.6.3 **Pharmacologic Effects:** In phase I studies involving 96 patients with various non-myeloid malignancies, r-metHuG-CSF administration resulted in a dose-dependent increase in circulating neutrophils counts over the dose range 1-70 mcg/kg. This increase in neutrophil counts was observed whether G-CSF was administered intravenously (1-70 mcg/kg [once daily] ) or by continuous subcutaneous infusion (3-22 mcg/kg/day). With discontinuation of therapy, neutrophil counts returned to baseline in most cases within 4 days. The absolute monocyte count was reported to increase, in a dose-dependent manner in most patients receiving r-metHuG-CSF, however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both eosinophils and basophils did not change and were within the normal range. Increase in lymphocyte counts have been reported. WBC differentials obtained during clinical trials have demonstrated a shift towards granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following chemotherapy induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

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

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

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

7.6.6 **Supplier:** G-CSF is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

7.7 **Toxicities to be Monitored and Dosage Modifications**

7.7.1 **Concomitant chemoradiotherapy (cycle 1) dose modifications. (4/28/97)**

7.7.1.1 If 3 out of the first 6 patients entered on study have grade 4 hematologic toxicity or grade 3-4 mucositis, stomatitis, esophagitis or other radiotherapy related toxicity, then subsequent patients would receive 100 mg/M2 of Paclitaxel during the administration of the radiation therapy. See Section 7.8.3. No dose modifications will be made for grades 3 and 4 lymphocytopenia.

7.7.2 **Dosage Modifications for Day 1 of Each Chemotherapy Cycle (cycles 2-4)**

7.7.2.1 For hematologic toxicity

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<th>Granulocyte nadir</th>
<th>Platelet nadir</th>
<th>Modification</th>
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</thead>
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<tr>
<td>&lt; 500 &lt; 5 days</td>
<td>≥ 50,000</td>
<td>No change</td>
</tr>
<tr>
<td>≥ 500 ≥ 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, G-CSF may be used in subsequent cycles as an alternative to dose reduction in the absence of other dose limiting toxicity.

7.7.2.2 For non-hematologic toxicity *(other than renal)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</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>

7.7.2.3 For renal toxicity

- Serum creatinine mg% within 24 hours of anticipated administration
  - 1.6 - 2.0: Decreased to 40 mg/m² until creatinine < 1.6
  - 2.1 to 3.5: Hold one cycle. Cisplatin to be reinstituted at next cycle at 40 mg/m² if serum creatinine < 2.0 otherwise stop Cisplatin.
  - > 3.5: Hold Cisplatin from all remaining cycles.

7.7.3 **Definition of Dose Levels**

<table>
<thead>
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<th>Drug</th>
<th>Dose Level</th>
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<tr>
<td>Paclitaxel <em>(Day 1, IV)</em></td>
<td>175 mg/m²</td>
<td>135 mg/m²</td>
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<td></td>
</tr>
<tr>
<td>Etoposide <em>(Day 1, IV)</em></td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Etoposide <em>(Day 2,3 PO)</em></td>
<td>80 mg/m²</td>
<td>80 mg/m²</td>
<td>80 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Cisplatin <em>(Day 1, IV)</em></td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
<td>60 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

Dose Level 0 is the Dose Level for all patients for Cycle 2 *(first post radiotherapy cycle)*

7.8 **Toxicity Reporting**

7.8.1 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.

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

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

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

7.8.1.4 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.

7.8.2 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

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

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

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

7.8.3.3 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

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study</th>
<th>Days 8, 15</th>
<th>Before Each Course</th>
<th>End Of Induction (Prior to Cycle 2)</th>
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<td>SMA-12, Electrolytes, Magnesium</td>
<td>Xc</td>
<td>Xb</td>
<td>X</td>
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<th>Assessments</th>
<th>Pre-Study</th>
<th>Days 8, 15</th>
<th>Before Each Course</th>
<th>End Of Induction (Prior to Cycle 2)</th>
<th>q3 mos. x1 yr then q6 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity Evaluation</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CT Chest</td>
<td>Xc</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT Abdomen</td>
<td>Xc</td>
<td></td>
<td>X</td>
<td>Xb</td>
<td>Xb</td>
</tr>
<tr>
<td>CT or MRI Brain</td>
<td>Xc</td>
<td></td>
<td>X</td>
<td>Xb</td>
<td>Xb</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>Xc</td>
<td></td>
<td>X</td>
<td>Xb</td>
<td>Xb</td>
</tr>
<tr>
<td>Bone Marrow Asp and BX</td>
<td>X</td>
<td></td>
<td></td>
<td>X</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. Only if indicated based on specific clinical concerns or suspicions. Consider repeat brain imaging shortly prior to initiating PCI.
c. Lab tests must be done within 2 weeks prior to study entry; imaging tests within 4 weeks before study entry, see Sections 4.2 and 4.3.

11.2 Evaluation During Study

11.2.1 Urinalysis with microscopy will be done prior to starting chemotherapy for each cycle. Patients will be followed on days 8, 15 and before each cycle with CBC, differential and platelet count.

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 of 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.

11.3.2.2.1 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.

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 any unequivocal new lesion.

11.4 Criteria for Going Off Protocol
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 grade 4 (excluding myelosuppression).
11.4.3 Non compliance with protocol requirements.
11.4.4 Patient refusal.

11.5 Data and Protocol Management
11.5.1 The attending physician and oncology research nurse 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 cancelled. 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 (3/17/98)
12.1 Summary of Data Submission
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 1 week of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (11)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</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 3, 6, 9, 12 weeks and within 2 weeks</td>
</tr>
</tbody>
</table>
of early termination of chemotherapy or onset of grade $\geq 3$ non-hematologic toxicity.

Follow-Up Form (F1) Every 3 months from treatment start for 1 year; q 6 months x 4 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 One-year overall survival rate and longer term survival rates
13.1.2 Complete and partial response rates
13.1.3 Frequency and severity of treatment morbidity

13.2 Sample Size (3/7/97)

13.2.1 The sample size will be determined by the one year survival rate. We expect the one year survival rate to be 70% and would like to estimate it with a 90% lower confidence bound of 60%. This requires 47 evaluable patients. If the observed one year survival rate is less than 60%, then no further phase III study will be proposed unless later on longer term survival rates turn out to be much better than those from the BID arm of the intergroup trial 0096. (The two and three year survival rates for the BID arm were 46.5% and 30.9%.) Assuming a 10% inevaluability rate (ineligible and canceled patients, see Section 11.4 for definition), the total required sample size is 52 patients.

13.2.2 Suspension of Accrual Due to Morbidity

Section 7.7.1 specifies a monitoring and dose modification schedule for the first six patients. Once the dose is established then all patients treated at that dose will participate in the following stopping rule.

RTOG 93-12 (a phase II SCLC study) had a 40% grade 3 to 4 acute esophagitis rate. The accrual to this trial will be suspended if the expected grade 3 or 4 toxicity rate is greater than 40%. This stopping rule is based upon Fleming’s design to reject if the true rate is greater than 40%. Therefore, suspension of accrual will occur if any of the following numbers of grade 3 or 4 esophagitis is exceeded.

<table>
<thead>
<tr>
<th>Number of Grade 3 or 4 Esophagitis</th>
<th>Total Number of Evaluable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>

Any fatal treatment morbidity will be examined by the study chairs. If more than 2 fatal toxicities are observed then the accrual will be suspended.

13.3 Patient Accrual

From a survey of our member institutions and accrual to RTOG 93-12, we expect that 52 patients can be accrued within one and a half years. If less than 26 patients are accrued in the first one and a half years, the feasibility of continuing the trial will be evaluated by the RTOG Research Strategy Committee.

13.4 Schedule of Analyses

13.4.1 Interim Analyses

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

a) patient accrual rate with a projected completion date for the accrual phase;
b) pretreatment characteristics of all entered patients;
c) compliance rate of treatment delivery with respect to protocol prescription;
d) frequency and severity of the toxicities.

Corrective actions or even accrual suspension may be initiated based on these findings.
13.4.2 *Initial Efficacy Results*

When each patient has been potentially followed for a minimum of one year the initial efficacy results (*Sections 13.1.1 and 13.1.2*), together with what are usually contained in the interim analysis, will be reported.
REFERENCES


APPENDIX I

RTOG 96-09

PHASE II STUDY OF CISPLATIN, PACLITAXEL, ETOPOSIDE, AND CONCURRENT TWICE DAILY THORACIC RADIOTHERAPY 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 and hazards involved. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

Some research studies indicate that radiotherapy given twice a day may improve the outcome of treatment to control the growth of limited stage small cell lung cancer. This clinical research study is to evaluate the effectiveness of taxol plus chemotherapy consisting of cisplatin, and etoposide along with twice a day radiotherapy (given with the chemotherapy) to the chest in the treatment of patients with limited small cell lung cancer. A growth factor for the bone marrow, G-CSF, may be given to help decrease the side effects of the chemotherapy and radiotherapy.

DESCRIPTION OF PROCEDURES

Chemotherapy will consist of three drugs: cisplatin, paclitaxel, and etoposide. Treatment will be given on an outpatient or in-patient basis and will be repeated approximately every 3 weeks for a total of four cycles (times). Each of these drugs will be given through my vein on the first day of each cycle. Etoposide will be given by mouth for two additional days of each cycle. With the first cycle of chemotherapy, radiotherapy to the chest will be given in two treatments per day (6-8 hours apart) for a total of 15 days over a three week period. Radiotherapy will be given Monday through Friday. G-CSF may be used during some treatment periods 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.

<table>
<thead>
<tr>
<th>Cycle #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Etoposide</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>XXXXX</td>
<td>XXXXX</td>
<td>XXXXX</td>
<td></td>
</tr>
</tbody>
</table>

Treatment will be discontinued if at any time the cancer has grown in size or at any time intolerable side effects to treatment occur. Radiotherapy to the brain will be offered to patients whose lung tumors disappear or shrink considerably.

Evaluation at study entry will include blood tests, urinalysis, chest x-ray and other imaging tests such as CAT scans or bone scans or MRI scans and a bone marrow test to look for cancer spread. During treatment, blood counts will be obtained weekly or more often if necessary.
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.

Risks from Chemotherapy

The drugs used in this study have been associated with the following side effects:

Paclitaxel (*Taxol*) commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding. This lowering of blood counts can lead to need for treatment with antibiotics, transfusions, or hospitalization if severe. Other common side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, and fatigue. There is the possibility of skin irritation should paclitaxel leak from my vein. Rarely, paclitaxel can cause severe allergic reactions leading to rash, difficulty breathing, and low blood pressure. Medicines will be used prior to giving the paclitaxel in an effort to avoid this type of problem. In some patients paclitaxel has caused numbness of the hand and feet or rarely has caused a temporarily slowed or irregular heart beat. Paclitaxel may increase the effects and risks of radiotherapy.

Cisplatin (*Platinol*) may cause nausea, vomiting, weakness, hearing loss or ringing in the ears. It may also cause damage to the kidneys. Fluids and medicines will be used to control/prevent these problems. Cisplatin can also lower the blood counts and change the levels of calcium and magnesium in the blood. Other less common side effects include allergic reactions (*sweating, difficulty breathing, rapid heart beat*) and numbness in the fingers or toes. Rarely this drug can lead to restlessness, swelling of the face, loss of coordination, involuntary movements, liver damage, loss of taste, or muscle cramps.

Etoposide (*Vespid, VP-16*) may lower blood counts as noted above. This drug can also cause diarrhea, hair loss, chest pain, blood in the urine, numbness, or skin rash. Less common side effects include low blood pressure, liver damage, fever, chills, or muscle cramps. Acute leukemia has rarely been reported following the use of this and other cancer drugs.

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. Rarely it has been associated with temporary decreases in blood pressure.

Risks from Radiation

Radiation therapy to the chest is commonly associated with difficulty or pain in swallowing. This usually begins during or after the second week of radiotherapy and goes away within one month of completion of radiotherapy. The use of chemotherapy with radiation may increase this risk. I should avoid alcoholic, acidic, or spicy foods and beverages. I may also feel very tired. The skin within the area of radiation treatments may develop a sunburn-like or tan appearance which may itch or burn. This effect usually goes away within 2-6 weeks of completing therapy. Radiation also causes hair loss in the treatment area and a drop in blood counts that may increase the risk of infection and bleeding.

Chest radiotherapy can cause changes in normal lung. These changes can be as unimportant as small amounts of "scarring" seen on x-rays, but not causing 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.

Radiation therapy to the brain may cause scalp redness or soreness, hair loss, hearing impairment, fatigue, dry mouth or altered taste, headaches or weakness. Sometimes radiation to the brain causes late side effects such as mental slowing or changes in behavior. Occasionally radiation can cause severe local damage to normal brain tissue (*necrosis*).

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.

For Women

This clinical treatment would definitely involve risks to both me as a patient and my embryo or fetus if I 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.

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 of 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. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life than would be obtained with non research treatment, but I understand this is not guaranteed.

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 once a day with or without chemotherapy, chemotherapy alone or treatments to make me feel better, but not necessarily cure me or make my disease less. Most oncology doctors would probably offer chemotherapy with VP-16 and platinol plus chest irradiation (once daily) as standard for my problem. An additional alternative is no 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 my doctors. The physicians 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 manufactures, 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
(IUCC-AJCC, 1988)

TNM CATEGORIES (Note Definitions)

T-Primary Tumor

TX  Tumor proven by the presence of malignant cells in broncho-pulmonary secretions but no visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as in a retreatment staging.

T0  No evidence of primary tumor. TIS Carcinoma in situ.

T1  A tumor that is 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.

T2  A tumor more than 3.0 cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.

T3  A tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus or vertebral body, or a tumor in the main bronchus within 2 cm of the carina without involving the carina.

T4  A tumor of any size with invasion of the mediastinum or involving heart, great vessels, trachea, esophagus, vertebral body or carina or presence of malignant pleural effusions.

Definitions

T1  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 classified as T1.

T4  Most pleural effusions associated with lung cancer are due to tumor. There are, however, some few patients in whom cytopathological examination of pleural fluid (on more than one specimen) is negative for tumor, the fluid is non-bloody and is not an exudate. In such cases where these elements and clinical judgment dictate that the effusion is not related to the tumor, the patients should be staged T1, T2 or T3 excluding effusion as a staging element.

N-NODAL INVOLVEMENT

N0  No demonstrable metastasis to regional lymph nodes.

N1  Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension.

N2  Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes.

N3  Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or suprACLAVICULAR lymph nodes.
### Distant Metastasis

**MO**  No (known) distant metastasis  

**M1**  Distant metastasis present - Specify Site(s)

---

**STAGE GROUPING OF CARCINOMA OF THE LUNG**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIS Carcinoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>N1</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIa</strong></td>
<td>T3</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T1-3</td>
<td>N1</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIb</strong></td>
<td>Any T</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>N3</td>
<td>Any N</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).

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

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOR Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

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.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOR sponsored intergroup studies) must also be submitted to RTOR Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOR sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had not previously been
identified as a known side effect.

**Commercial and Non-Investigational Agents (2/14/95)**

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. Form 3500 is to be used in reporting details (see attached). All relevant data forms must accompany the RTOG copy of Form 3500.**

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

iv. **All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting and 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 only a reasonable suspicion.

**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

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.

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

** See attached NCI Adverse Drug Reaction Reporting Form

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

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

Oral Etoposide Dose Schedule  80 mg/m^2  (*Days 2 and 3 of Each Cycle*)

<table>
<thead>
<tr>
<th>BSA</th>
<th>DOSE CALC/2 DAYS</th>
<th>DAY 2 DOSE</th>
<th>DAY 3 DOSE</th>
<th>TOTAL CAPSULES</th>
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<tbody>
<tr>
<td>1.4</td>
<td>224 mg</td>
<td>150 mg</td>
<td>100 mg</td>
<td>5</td>
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<tr>
<td>1.45</td>
<td>232 mg</td>
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