A THREE-ARM PHASE III STUDY OF CONCOMITANT VERSUS SEQUENTIAL CHEMOTHERAPY AND THORACIC RADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED INOPERABLE NON-SMALL CELL LUNG CANCER

Study Chairmen
Radiation Oncology Walter J. Curran, Jr., M.D. (215) 955-6700 FAX# (215) 955-0412
Co-Chair Ritsuko Komaki, M.D. (713) 792-3420 FAX# (713) 792-3642
Medical Oncology Corey J. Langer, M.D. (215) 728-2985 FAX# (215) 728-3639
Co-Chair Jin S. Lee, M.D. (713) 792-6363 FAX# (713) 796-8655
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SCHEMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Arm 1: VBL/cisDDP; STD RT begins at day 50</th>
<th>Arm 2: VBL/cisDDP; STD RT begins at day 1</th>
<th>Arm 3: Oral VP-16/cisDDP x 2 cycles; HFX RT begins at day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Vinblastine 5 mg/m² i.v. bolus weekly first 5 weeks</td>
<td>Vinblastine 5 mg/m² i.v. bolus weekly first 5 weeks</td>
<td>Oral VP-16 50 mg b.i.d. x 10 only on RT treatment days 1-5, 8-12, 29-33, and 36-40 (75 mg/day if body surface area &lt; 1.7 m²)</td>
</tr>
<tr>
<td>T</td>
<td>Cisplatin 100 mg/m² i.v. over 30-60 minutes, days 1 &amp; 29</td>
<td>Cisplatin 100 mg/m² i.v. over 30-60 minutes, days 1 &amp; 29</td>
<td>Cisplatin 50 mg/m² i.v. over 30-60 minutes on days 1 and 8 and 29 and 36</td>
</tr>
<tr>
<td></td>
<td>RT: 63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx then 2.0 Gy x 9 fx) beginning day 50</td>
<td>RT: 63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx then 2.0 Gy x 9 fx) beginning day 1</td>
<td>RT: 69.6 Gy/6 wks/58 x 1.2 Gy twice daily fractions (at least 6 hours apart) beginning day 1</td>
</tr>
</tbody>
</table>

ELIGIBILITY (See Section 3.0 for details)

- Medically inoperable stages II & IIIA or unresectable stages IIIA & IIIB non-small cell lung cancer
- KPS ≥ 70, age ≥ 18
- Weight loss ≤ 5% in 3 months prior to diagnosis
- No distant metastasis, prior chemo- or radiation therapy
- Serum creatinine ≤ 1.5, Hgb ≥ 8.0, absolute granulocyte count (AGC) ≥ 2000, platelets ≥ 100,000, bilirubin and SGOT ≤ 1.5 institutional upper limit
- No recurrent disease or prior complete tumor resection
- No prior chemotherapy or RT to the thorax or neck
- Prior malignancy ≥ 3 years and currently disease-free
- Study-specific consent form
- Patients with pleural effusion appearing only after thoracotomy or other invasive thoracic procedure are eligible.
- Ineligible for RTOG 93-09 (refer to Eligibility Checklist [Q 20] and Section 3.1.9)

Required Sample Size: 597

9/1/94
2/14/95
6/3/96
Institution #

RTOG 94-10

ELIGIBILITY CHECK (2/14/95, 2/1/96)

Case #

(page 1 of 2)

(Y) 1. Does the patient have histologic proof of non-small cell lung cancer documented by biopsy or cytology?

(II-IIIB) 2. What is the stage?

(Y) 3. Is the patient free of metastatic disease?

(N) 4. Is there a synchronous lung primary?

(N) 5. Prior surgical resection of the lung tumor?

(N) 6. Has the patient had any prior malignancy other than skin within the past 3 years?

(N) 7. Has the patient received any prior chemotherapy or radiation to the thorax or neck?

(N) 8. Has the patient had a weight loss of > 5% in the three months prior to diagnosis?

(Y/N) 9. Is there evidence of pleural effusion?
   ______ (Y) If yes, did it appear only after a thoracotomy or other invasive thoracic procedure was attempted?

(≥ 18) 10. What is the patient's age?

(≥ 70) 11. State the KPS.

(≤ 1.5) 12. Report the serum creatinine.

(≥ 8) 13. Report the hemoglobin.


(≥ 100) 15. Report the platelet count (x 1000).

(Y/N) 16. Is the bilirubin and SGOT ≤ to 1.5 times the institutional upper limits of normal?
   ______ (Y) If no, is the serum bilirubin and/or SGOT abnormality caused by documented benign disease?

(N) 17. Has the patient had a myocardial infarction within the last 6 months or symptomatic heart disease, including angina, CHF or uncontrolled arrhythmia?

(N/NA) 18. If female, is the patient pregnant or lactating?

(Y/NA) 19. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?
20. Reason for not entering this patient to RTOG 93-09?
   1. Does not meet eligibility criteria
   2. Deemed ineligible by thoracic surgeon
   3. Medically ineligible
   4. Patient refusal
   5. Institution not participating
   6. Other reason, specify ____________________________________________

21. Has the patient signed a study-specific consent form?

   ____________________________________________  Patient's Name
   ____________________________________________  Verifying Physician
   ____________________________________________  Patient ID #
   ____________________________________________  Referring Institution # (if different)
   ____________________________________________  Medical Oncologist
   ____________________________________________  Birthdate
   ____________________________________________  Sex
   ____________________________________________  Race
   ____________________________________________  Social Security Number
   ____________________________________________  Zip Code (9 digit if available)
   ____________________________________________  Method of Payment
   ____________________________________________  Treatment Start Date
   ____________________________________________  Treatment Assignment

Completed by ____________________________  Date _________________
1.0 INTRODUCTION

The standard therapeutic approach to patients with clinical stage III NSCLC has been fractionated thoracic RT to a total dose of 60 Gy. Median survival times (MST) of 9-13 months and two-year survival rates of 15-20% have been reported in most institutional and cooperative group studies of such patients treated with RT alone.1-3 Because of these disappointing results and because of the growing global epidemic of tobacco-related cancers, stage III NSCLC is appropriately the subject of intense clinical investigation and controversy. Efforts to improve the survival results with thoracic RT alone have included such non-operative approaches as altered fractionation RT, concurrent or sequential chemoradiotherapy, conformal RT, and endobronchial brachytherapy. For stage III NSCLC patients with marginally resectable tumors, a variety of pre-operative chemotherapy and/or RT regimens have been created to render such patients resectable. While the benefit of surgery for such patients is under evaluation in the current intergroup trial RTOG 93-09, most clinical stage III NSCLC tumors are not anatomically suitable to such an approach. The challenge for oncologists charged with the care of patients with such tumors is to optimize a treatment strategy using available non-operative therapies.

The recognition that chemotherapy response rates for untreated locally advanced NSCLC are higher than for metastatic tumors led to the testing of induction chemotherapy prior to thoracic RT.4 There are at least six published reports of randomized trials with more than one hundred patients comparing RT alone to induction chemotherapy followed by RT.5-10 Two of these trials have demonstrated a survival advantage favoring the induction chemotherapy and RT arm, and these are the Cancer and Leukemia Group B (CALGB) trial 84-33 and the French multicenter trial CEBI 138. The CALGB trial randomized 155 patients to two cycles of vinblastine and cisplatin prior to RT versus RT alone. The MST and 5-year survival rates were 13.7 months and 19% versus 9.6 months and 7%, favoring the chemoradiotherapy arm ($P=0.01$).5 The French trial formulated a “sandwich” regimen of induction and post-RT chemotherapy (vinodesine, lomustine, cisplatin, and cyclophosphamide) and reported a two year survival rate advantage of 20% vs 12% ($P=0.04$) favoring the combined modality arm.6

To confirm the survival advantage reported by CALGB in a larger patient population and to test encouraging observations from an RTOG phase I/II trial of hyperfractionated RT (RTOG 83-11),11 the RTOG and Eastern Cooperative Oncology Group (ECOG) initiated a three arm phase III trial for locally advanced NSCLC in 1988 (RTOG 88-08/EST 4588). Four hundred ninety patients were randomized between: (1) standard RT (60 Gy/once-daily/6 weeks); (2) hyperfractionated RT (69.6 Gy/twice daily/six weeks); and (3) induction vinblastine/cisplatin followed by standard RT. With nineteen months of follow-up since the closure to patient entry, the one year survival rates and MST of the three arms are: (1) standard RT: 46% and 11.4 months; (2) hyperfractionated RT: 51% and 12.3 months; (3) chemoradiotherapy: 60% and 13.8 months. The Wilcoxon statistic $p$-value of a pairwise comparison between the chemoradiotherapy arm and either the hyperfractionated RT arm or the standard RT arm is significant, at 0.03 and 0.008, respectively. The comparison of the hyperfractionated RT and standard RT arms has a Wilcoxon $p$-value statistic of $p=0.83$.12 Based on this preliminary result, the RTOG now considers induction vinblastine and cisplatin followed by standard thoracic RT to be the optimal regimen against which future nonoperative approaches should be tested. This conclusion should be restricted to the patient subgroup eligible for RTOG 88-08 or CALGB 84-33, those with < 5% weight loss and a good performance status (Zubrod Performance Status 0-1 or Karnofsky Performance Status 70-100).

An alternative method of interdigitating chemotherapy and thoracic RT is by simultaneous or concomitant delivery. There are at least three large published randomized trials comparing RT alone to RT and concomitant cisplatin chemotherapy.13-15 No survival difference was observed in the trials conducted by the Hoosier Oncology Group13 or by Trovo, et al.14 In a three arm trial conducted by the European Organization Research in the Treatment of Cancer (EORTC 08844) comparing low dose daily cisplatin/RT to weekly cisplatin/RT to RT alone, a significant survival advantage favored the daily low dose cisplatin/RT arm, with two-year survival rates of 32% vs 17% and 14%, respectively.15

The improvement in survival rates over RT alone in the two published trials using induction chemotherapy (CALGB 84-33 and CEBI 138) appears related to a decrease in detectable distant metastases. Such patterns of tumor recurrence information are as yet unavailable from RTOG 88-08. The survival advantage observed in EORTC 08844 with low dose daily cisplatin during thoracic RT was associated with improved control of the intrathoracic tumor burden. Presumably, the simultaneous delivery of low dose cisplatin with RT enhanced local tumor response,
and the use of higher drug doses in the induction regimens deterred the progression of micrometastatic disease. The incorporation of both of these features into a combined modality regimen with acceptable morbidity has been a major goal of recent activities within the RTOG Lung Committee and in other cooperative groups.

The RTOG has completed four phase II trials evaluating the concomitant delivery of high dose cisplatin-based chemotherapy and thoracic RT for unresectable stage III NSCLC. In RTOG 88-04 thirty patients received both induction vinblastine and cisplatin as well as concomitant cisplatin during a standard RT course. Although nearly 30% of enrolled patients did not meet the performance status and eligibility criteria of RTOG 88-08, the survival results were quite encouraging, with a MST of 16.1 months and 2-year survival rate of 34%. RTOG 90-15 registered 42 patients to a regimen of immediate hyperfractionated RT with cisplatin and vinblastine. Toxicity was primarily hematologic, and in this unfavorable patient population (76% ineligible for RTOG 88-08), the MST was 12.1 months. Among the 10 patients in this protocol fulfilling the favorable weight loss and performance status criteria of RTOG 88-08, the MST was 17.5 months. In RTOG 91-06, 76 patients received immediate hyperfractionated RT and concomitant cisplatin and oral etoposide. As recently analyzed, the estimated one-year survival rate is 67%, and the MST has been estimated at 19.7 months. Grade 4 hematologic toxicities in RTOG 90-15 and RTOG 91-06 were 43% and 57%, respectively, comparable to the 48% grade 4 hematologic toxicity rate seen in the induction chemotherapy arm of RTOG 88-08. RTOG 92-04 was a randomized phase II trial evaluating the regimens studied in RTOG 88-04 and 91-06 among patients fulfilling favorable performance status and weight loss criteria. This study was closed to accrual March 1994, and preliminary data suggest a decline in grade 4 hematologic toxicity from the prior studies.

With the expected acceptance of cisplatin-based chemotherapy and thoracic RT as the standard of care for selected patients with unresected, locally advanced NSCLC, the issue of timing becomes increasingly important. The simultaneous delivery of multi-agent chemotherapy and thoracic RT could result in supra-additive anti-tumor synergism through the immediate application of all active modalities. The principal disadvantage of concomitant therapy is the enhancement of normal tissue toxicity, both hematologic and esophageal, resulting in unnecessary patient morbidity and attenuation of RT and/or chemotherapy delivery. The temporal relationship of multiagent chemotherapy to thoracic RT has been successfully addressed in phase III trials for limited stage small cell lung cancer, most recently by Murray, et al. of the National Cancer Institute of Canada (NCIC). In this trial, a survival advantage was identified favoring immediate over delayed concomitant thoracic RT/chemotherapy. No randomized trials have yet addressed such important chemotherapy/RT sequencing issues for patients with locally advanced NSCLC.

There are new systemic agents with encouraging activity levels against NSCLC, and in conjunction with thoracic RT, some of these may improve the outcome of patients with locally advanced NSCLC. While both CALGB 84-33 and RTOG 88-08 used vinblastine and cisplatin in their induction regimens, other agents may be equally or more efficacious in such a multimodality regimen. Oral etoposide is among the most promising "new" agents, with higher single agent response rates among metastatic or recurrent NSCLC than intravenous etoposide and with a documented synergistic relationship to radiation and cisplatin. The remarkable, although preliminary, survival results from RTOG 91-06, the phase I/II trial of concomitant cisplatin, oral etoposide, and hyperfractionated RT (MST: 19.7 months), strongly support further investigation of such a regimen.

The present three-arm phase III trial will evaluate both the critical issue of chemoradiation sequencing and the encouraging results from RTOG's own phase II trials. To isolate the issue of sequencing, the two cycles of cisplatin and vinblastine delivered in the best arms of CALGB 84-33 and RTOG 88-08 will be given as pre-RT induction therapy in the control arm (Arm 1) and concurrent with RT in Arm 2. While Arm 2 closely resembles the regimen tested in RTOG 90-15 (MST: 17.5 mo. in selected patients), the RT will be delivered once daily, thus allowing for an unobstructed evaluation of the sequencing question. The other investigational arm (Arm 3) includes concomitant cisplatin, oral etoposide, and hyperfractionated RT to 69.6 Gy as in RTOG 91-06 and will be tested against the standard induction chemoradiation regimen (Arm 1). While survival is the primary endpoint, it is possible that treatment-related esophageal and hematologic morbidity may be higher in the two investigational arms than in Arm 1. The grade 3 or worse esophageal toxicity rates of the induction chemoradiation arm in RTOG 88-08, 90-15 and 91-06 were 1%, 24%, and 36%, respectively. The extent of this toxicity difference will be followed as an important secondary endpoint.
2.0 OBJECTIVES

2.1 To determine if the survival rate of selected patients with locally advanced, unresectable NSCLC is improved by the concomitant administration of two cycles of vinblastine and cisplatin chemotherapy and thoracic RT versus sequential delivery of the same chemotherapy regimen prior to once daily thoracic RT.

2.2 To determine if the survival rate of such patients is improved by the concomitant administration of cisplatin, oral etoposide, and hyperfractionated thoracic RT versus the sequential delivery of two cycles of vinblastine and cisplatin and once daily thoracic RT.

2.3 To determine if treatment-related esophageal and hematologic morbidity is increased with concomitant versus sequential chemoradiation.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (9/1/94, 2/14/95)

3.1.1 Patients with unresected loco-regionally advanced non-small cell lung cancer without evidence of hematogenous metastases, Stages II, IIIA, or IIIB, (See Appendix III).

3.1.2 Age ≥ 18.

3.1.3 Karnofsky performance status ≥ 70 (Appendix II).

3.1.4 Weight loss ≤ 5% in three months prior to diagnosis.

3.1.5 No pleural effusion unless it appeared only after a thoracotomy or other invasive thoracic procedure was attempted.

3.1.6 Serum creatinine ≤ 1.5, hemoglobin ≥ 8.0, absolute granulocyte count ≥ 2000, platelets ≥ 100,000.

3.1.7 Serum bilirubin and SGOT must be ≤ 1.5 times the institutional upper limits of normal unless the abnormality is caused by documented benign disease.

3.1.8 Patients must sign a study-specific consent form.

3.1.9 Patients cannot be eligible for RTOG 93-09 (confirmed N2 involvement). At institutions participating in RTOG 93-09, patients with clinical or pathologic stage IIIA (N2) disease must either a) have been evaluated by a thoracic surgeon and deemed ineligible for 93-09, b) must be medically ineligible for 93-09, or c) must have refused participation in RTOG 93-09.

3.2 Conditions for Patient Ineligibility

3.2.1 Evidence of small cell histology.

3.2.2 Stage I or stage IV non-small cell cancer.

3.2.3 Patients who have undergone complete (or incomplete) tumor resection.

3.2.4 Patients with post-resection intrathoracic tumor recurrence.

3.2.5 Patients with a synchronous or prior invasive malignancy, unless disease-free for ≥ 3 years except for non-melanomatous skin cancer.

3.2.6 Patients with prior chemotherapy or thoracic or neck RT.

3.2.7 Patients with myocardial infarction within the preceding six months or symptomatic heart disease, including angina, congestive heart failure, uncontrolled arrhythmias.

3.2.8 Pregnant women (patients with childbearing potential must practice appropriate contraception).

4.0 PRETREATMENT EVALUATIONS

4.1 A complete medical history and physical examination to include Karnofsky performance status, neurologic assessment, recent weight loss, usual weight, concurrent non-malignant disease and therapy.

4.2 CBC with differential, platelet count, SMA-12, electrolytes, Mg++, and urinalysis within 14 days before randomization.

4.2.1 SMA-12: Total Protein, Albumin, Calcium, Inorganic Phosphorus, Glucose, BUN, Uric Acid, Creatinine, Alk. Phos., LDH, Total Bilirubin, SGOT and SGPT.

4.3 Chest X-ray, CT scans of the brain and chest (including liver and adrenal glands), and radionuclide bone scan within 4 weeks before randomization.

4.4 EKG and pulmonary function tests including VC, FEV1, and DLCO.

4.5 Location, type, and size of measurable lesion prior to treatment must be recorded.

5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191,
Monday through Friday 8:30 am to 5:00 pm 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:
- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY

6.1 Radiation Dose

6.1.1 Arm 1: Radiation therapy will commence on day 50 of the chemotherapy dose schedule. Total dose to the involved areas will be 63 Gy. This will be administered at 1.8 Gy daily 5 times a week to deliver 45 Gy target dose in 5 weeks to the large field. An additional 18 Gy will be delivered at 2 Gy daily to initial tumor with reduced fields. Positive nodes ≥ 2 cm will receive 63 Gy. The total dose will be 63 Gy in 34 fractions in 34 treatment days in 7 weeks.

6.1.2 Arm 2: Radiation therapy will commence on day 1 of the chemotherapy dose schedule. Total dose to the involved areas will be 63 Gy. This will be administered at 1.8 Gy daily 5 times a week to deliver 45 Gy target dose in 5 weeks to the large field. An additional 18 Gy will be delivered at 2 Gy daily to initial tumor with reduced fields. Positive nodes ≥ 2 cm will receive 63 Gy. The total dose will be 63 Gy in 34 fractions in 34 treatment days in 7 weeks.

6.1.3 Arm 3: Radiation therapy will commence on day 1 of the chemotherapy dose schedule. Total dose to the involved areas will be 69.6 Gy. This will be administered at 1.2 Gy twice daily at least 6 hours apart (time of each treatment to be recorded in daily treatment record) 5 days a week in 42 fractions in 21 treatment days in 4 weeks (50.4 Gy) to the primary and mediastinum plus a boost to the primary and involved nodes of 19.2 Gy in 2 weeks. The total dose will be 69.6 Gy in 58 fractions in 29 treatment days in 6 weeks. Positive nodes ≥ 2 cm will receive 69.6 Gy. The initial treatment volume must be treated with fields which keep the maximum spinal cord dose ≤ 45 Gy. For example, a field arrangement sparing the spinal cord could begin at 43.2 Gy. (9/1/94)

6.2 Treatment Techniques

6.2.1 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.

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

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

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

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

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

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

6.2.1.7 At the depth of maximum dose for a single electron beam with an electron beam energy chosen at least 90% dose at 3 cm. depth.

6.3 Target Volumes

6.3.1 Two different target volumes shall be considered, the initial large field target volume consisting of primary and mediastinum and the boost target volume consisting of the primary, involved nodes and nodes ≥ 2.5 cm. in diameter only. In treating the initial fields, various sets of fields may be used.

6.3.2 In all regimens, no part of the primary lesion and ipsilateral hilar and mediastinal lymph nodes (within a 2 cm. margin) will receive a dose less than 45 Gy from the initial large fields. In cases where the central rays of the large fields do not intercept the center of the boost target volume, it will be necessary to calculate the contribution from the initial sets of fields to the center of the boost target volume. The maximum dose in any part of either target volume should not exceed the prescribed dose more than 15%.
6.3.3 Deviations of the daily dose of up to 5% are allowed. In patients where the difference in dose between
the initial large field target volume and boost target volume is such that a 5% change in the boost dose
would not result in the proper final dose being delivered by the prescribed number of fractions, then
additional fraction(s) can be added to reach the prescribed total dose. As an example of the above for
Arms 1 or 2, assume that a patient who is being treated according to the protocol receives 43 Gy to the
center of the boost target volume after 45 Gy has been delivered along the central rays of the initial fields
at the point of mid-separation of the beams. The center of the target volume has received 2 Gy less than
prescribed. This patient could then receive one extra fraction of 2 Gy to the boost field.
As an example of the above for Arm 3, assume that a patient who is being treated according to the
protocol receives 48.4 Gy to the center of the boost target volume after 50.4 Gy has been delivered
among the central rays of the initial fields at the point of mid-separation of the beams. The center of the
target volume has received 2 Gy less than prescribed. This patient could then receive one extra fraction
of 2 Gy to the boost field.

6.4 Irradiation Portals

   The irradiation target volume must be defined by the individual shaped ports with secondary lead blocking
   or tailor-made blocks.

6.4.1 Target volume of primary tumor

6.4.1.1 Includes complete extent of visible primary tumor as defined radiographically with a minimum of 2
   cm. and the maximum of 2.5 cm. around the mass. For patients in Arm 1 (induction chemotherapy),
   the extent of tumor present at randomization should be used to define the RT treatment volume with
two exceptions: 1) in the case of primary tumor or nodal progression during chemotherapy, the
   extent of disease at day 50 should define the treatment volume. 2) if post-obstructive atelectasis is
   present at initial presentation and a chemotherapy-induced response results in better tumor/uninvolved
   lung definition, then the post-chemotherapy tumor volume should be used to define
   the RT treatment volume.

6.4.1.2 Entire lung may be included for extensive lesions if complicated by atelectasis or pneumonitis.

6.4.2 Target volume of lymph nodes. The following nodes must be included:

6.4.2.1 Supraclavicular lymph nodes -- if primary is in upper lobes and mainstem bronchus lesions. It is
   acceptable to treat the ipsilateral supraclavicular nodes only.

6.4.2.2 Ipsilateral hilar lymph nodes -- always(2 cm. margin). (9/1/94)

6.4.2.3 Superior mediastinal lymph nodes (above carina) -- always (ipsilateral 2 cm. margin).

6.4.2.4 Subcarinal lymph nodes (include the contralateral mainstem bronchus and extend field at least to 5
   cm. below carina) -- always.

6.4.2.5 Inferior mediastinal nodes to the diaphragm (to bottom of T10) for patients with lower lobe lesions or
   inferior mediastinal involvement. (9/1/94)

6.4.2.6 Contralateral hilar lymph nodes for patients with contralateral mediastinal, subcarinal, or contralateral
   hilar involvement-(1 cm. margin) . (9/1/94)

6.5 Technical Factors

6.5.1 Beam Energy: Megavoltage equipment is required with minimum peak photon energies of 6 MeV.
   Electrons with at least 90% dose at 3 cm. depth may be used to boost supraclavicular lymph nodes and
   should be specified to Dmax.

6.5.2 Treatment Distance: Minimal treatment distance to skin should be greater than 80 cm. for SSD
   technique and minimum isocenter distance should be 100 cm. for SAD techniques.

6.5.3 Blocking:

6.5.3.1 In the case of x-ray beams, the primary collimation may be used, and blocking will be required only
   for shaping of the ports to exclude volume of tissues that are not to be irradiated.

6.5.4 Compensating Filters or Wedges:
   In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in
   large patients, compensating filters are recommended. A wedge may also be used as a 2 dimensional
   tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive
   irradiation to critical structures.

6.5.5 Fractionation:

6.5.5.1 Each field to be treated every session. There should be at least 6 hours between daily fractions
   (actual time to be recorded in daily record) for patients receiving twice daily irradiation in Arm 3.

6.5.5.2 Adherence to the fractionation schemes is required although slight deviations in the daily dose
   fraction are allowed (± 5%).

6.5.6 Therapy Interruptions: (6/3/96)
6.5.6.1 If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.

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

6.5.6.3 Radiotherapy interruptions or delays will be permitted only for febrile neutropenia or grade ≥ 3 esophagitis/mucositis. Interruptions longer than 3 days should be discussed with Dr. Curran, or in his absence, Dr. Komaki.

6.5.6.4 If neutropenic fever occurs and radiation is withheld, G-CSF may be initiated to expedite neutrophil recovery.

6.5.7 Treatment Planning:

6.5.7.1 Treatment planning should be performed in accordance with the prescribing doses (Section 6.2) to each target volume, together with restrictions in dose to normal tissues as given Section 6.6. Treatment planning simulation is required. It is recommended that CT-based treatment planning be utilized whenever possible.

6.5.7.2 One set of isodose distributions at the midplane transverse plane of the boost target volume should be submitted. Sagittal dose distributions are encouraged.

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

1) The Spinal Cord Dose. 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 field. 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 48 Gy at any level. (2/1/96)**

2) Subcarinal Nodes. Which are assumed to be at mid-plane.

3) Ipsilateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost fields at the point of maximum dose in the lung which lies at least 2 cm. outside the projected border of the initial treatment fields in the ipsilateral lung.

4) Contralateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost field at the point of maximum dose in the lung which lies at least 2 cm. outside of the projected border of the initial treatment fields in the contralateral lung.

5) Maximum Normal Tissue Dose. This is to be calculated at level of the central rays of boost fields as the maximum total dose at least 2 cm. outside of the target volume.

6.5.8 Localization Films:

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

6.5.9 Dosimetry Monitoring:

The American Association of Physicists in Medicine (Radiological Physics Center, Houston, Texas) may conduct a field survey of equipment.

6.6 Anticipated Side Effects or Toxicities (2/14/95)

6.6.1 Suggested Maximum Doses to Critically Sensitive Normal Structures

<table>
<thead>
<tr>
<th>Organ</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Lung</td>
<td>25 Gy</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td></td>
</tr>
<tr>
<td>CONTRALATERAL (ONLY IF NECESSARY)</td>
<td>20 Gy</td>
</tr>
<tr>
<td>Spinal Cord (Maximum Dose)</td>
<td>48 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>ENTIRE ORGAN</td>
<td>45 Gy</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>50 Gy</td>
</tr>
<tr>
<td>Esophagus</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

6.6.2 The dose to the spinal cord must be limited to 45 Gy. **A POSTERIOR SPINAL CORD SHIELD WILL NOT BE AN ACCEPTABLE TECHNIQUE.** Oblique or lateral field arrangements with custom shielding are recommended to limit spinal cord dose. The use of a spinal cord shield (block) will result in an unacceptable variation score in the RT Quality Assurance review.

6.6.3 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiation pneumonitis and subsequent fibrosis of the lung will occur in 100% of all
patients receiving ≥ 40 Gy to the lung, usually within the first six months after initiation of treatment so it is essential to spare all normal lung possible.

6.6.4 Radiation therapy may be interrupted for periods of up one week for significant (≥ grade 3) esophagus toxicity: i.e., inability to tolerate liquids, whenever weight loss occurs and/or supplemental feedings are necessary. Sucralfate slurries may provide symptomatic relief of mucositis and esophagitis.

6.6.5 Post-treatment pneumonitis thought due to radiation should be treated with prednisone after excluding microbial causes.

6.6.6 Adverse reactions will be reported as described in Appendix V.

6.7 Criteria for Removal from Protocol Treatment

6.7.1 Disease progression at any time during therapy or the follow-up period. The patient should be restaged and sites of recurrence and/or progression documented. Rebiopsy is strongly encouraged.

6.7.2 Unacceptable toxicity.

6.7.3 The patient may elect to withdraw from study treatment at any time for any reason.

6.7.4 Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up.

6.7.5 All reasons for discontinuation of treatment must be documented.

6.7.6 All patients will be followed until death.

7.0 DRUG THERAPY

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

7.1 Chemotherapy Pharmaceutical Data

7.1.1 Cisplatin (DDP)

7.1.1.1 Formulation: Vial containing 10 mg cisplatin with 10 mg and 9 mg sodium chloride.

7.1.1.2 Storage: Refrigeration.

7.1.1.3 Preparation: One vial diluted with 10 mg of sterile water for injection.

7.1.1.4 Administration: Drug should be given immediately after preparation as an intravenous injection over 30-60 minutes.

7.1.1.5 Pharmacology: The dominant mode of action appears to be the inhibition of incorporation of DNA precursors although protein and RNA synthesis are also inhibited. Cross-linking of DNA has also been shown. Plasma levels of Cisplatin decay in a biphasic mode with an initial half-life of 25-49 minutes and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and standard alkylating agents. Also, there appears to be potentiation of other anti-tumor agents by cisplatin in tissue culture, animal tumor models and in early human work. Studies have shown that cisplatin has no cell-cycle dependency and that cytotoxicity of this agent is similar in all stages of the cell cycle.

7.1.1.6 Toxicity: Toxicity includes nausea, vomiting, renal toxicity (with elevation of BUN, creatinine and impairment of endogenous creatinine clearance), ototoxicity (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 tract. Myelosuppression, often with delayed erythrosuppression, is expected. The nadir white cell and platelet counts occur at about two weeks with recovery generally at about three weeks after initiation of therapy. Peripheral neuropathy and acute myeloid leukemia have been reported in a few cases where long-term cisplatin was used in combination with other forms of therapy. (2/14/95)

7.1.1.7 Supplier: Commercially available

7.1.2 Vinblastine, (Velban)

7.1.2.1 Formulation: Vials containing 10 mg of the drug in the form of a lyophilized powder.

7.1.2.2 Storage: Refrigeration. Reconstituted solution may be kept refrigerated up to 30 days without loss in potency.

7.1.2.3 Preparation: Reconstitute with 10 mL Bacteriostatic Sodium Chloride Injection, USP (preserved with benzyl alcohol).

7.1.2.4 Administration: Drug is administered as a weekly bolus i.v. 5 mg/m² for five weeks. Caution: It is extremely important that the needle be properly positioned in the vein before this product is injected. If leakage into surrounding tissue should occur during intravenous administration of vinblastine
sulfate, it may cause considerable irritation. The injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

7.1.2.5 **Pharmacology:** Vinblastine is a vinca alkaloid and binds to tubulin monomers and interferes with microtubular assembly, thereby interfering with several critical cell functions.

7.1.2.6 **Toxicity:** Dose limiting toxicities of vinblastine include transient myelosuppression (especially leukopenia) and a peripheral neuropathy which may be prolonged (N.B. cisplatin shares this potential toxicity. A careful inquiry about symptoms and motor strength exam prior to each dose should be made).

7.1.2.7 **Supplier:** Commercially available.

7.1.3 **Etoposide (VP-16) (6/3/96)**

7.1.3.1 **Formulation:** 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 polyethyleneglycol 400.

7.1.3.2 **Storage:** Refrigeration. The capsules are stable for 24 months. Do not freeze.

7.1.3.3 **Administration:** Drug is administered orally at 100 mg/day (50 mg b.i.d) for 10 days, giving it only on the days of RT during the first two weeks of each cycle (days 1-5 and 8-12). If, however, treatment is delayed and radiation is completed before etoposide is due to be completed, patients will complete oral etoposide as scheduled. If body surface area is < 1.7 m\(^2\), administer 75 mg/day. Repeat cycle on day 29.

7.1.3.4 **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.

7.1.3.5 **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.

7.1.3.6 **Supplier:** Commercially available

7.2 **Chemotherapy Plan: (6/3/96)**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 29</th>
<th>Day 50</th>
<th>Day 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>V#1</td>
<td>V#2</td>
<td>V#3</td>
<td>V#4</td>
<td>V#5</td>
</tr>
</tbody>
</table>

8
Chemotherapy will be initiated on Day 1 in both Arms 1 and 2 and is identical in dose and schedule. The difference between the arms is whether thoracic RT is delayed to Day 50 (Arm 1) or started on Day 1 (Arms 2 and 3). For Arms 2 and 3, chemotherapy should ideally be started on the same day. If however, due to logistic reason, this is impossible, a 24-hour delay before initiating chemotherapy is reasonable.

**Arms 1 and 2**

**Vinblastine** 5 mg/m² i.v. bolus will be administered weekly for five weeks. Because it is a vesicant, it must be administered through a freely running intravenous line with a good blood return.

**Cisplatin** will be administered at a dose of 100 mg/m² over 30-60 minutes intravenously on Days 1 and 29, using the following hydration schema:

**Over 2-4 hours prior to cisplatin, the patient will receive hydration with at least 1.5-2.0 liters intravenously. Recommended intravenous solution will include D5 0.45 Normal Saline with 20 mEq KCl and 16 mEq MgSO₄. Concentration can be adjusted according to the patient’s serum potassium and magnesium levels.**

**Just prior to cisplatin administration, patients will receive mannitol: 12.5 gm. intravenously over 10 minutes.**

**Cisplatin will be given over 30-60 minutes, as described.**

**After cisplatin is administered, patients will receive 2-3 liters of intravenous fluids over 6-8 hours. If patients are unable to keep any oral fluid because of nausea and vomiting, intravenous fluid will be kept over 16-24 hours, with fluid components and electrolyte concentration tailored to each patient (9/1/94).**

**Arm 3** (6/3/96)

**Etoposide** will be given p.o. on days 1-5 and on days 8-12, 50 mg. b.i.d. if body surface area (BSA) is ≥ 1.7 m² or 75 mg./day (oral etoposide 50 mg. one day alternating with 50 m.g. b.i.d.) if BSA < 1.7 m². The first dose of oral etoposide will be given 20-60 minutes before the planned RT.

**Cisplatin** 50 mg/m² will be given i.v. over 30-60 minutes on days 1 and 8. The following hydration sequence is recommended.

**A calculated dose of cisplatin will be given i.v. in 500 of 0.9% normal saline + 10 mEq KCl + 5 mEq MgSO₄ + 12.5 gm. Mannitol. Prior to and after cisplatin infusion, all patients should receive 500-1000 ml. of D5/0.45 normal saline, i.v. over 2 hours, respectively; oral fluid intake should be encouraged after discharge. Alternatively, post cisplatin hydration can be adjusted based on electrolytes at investigator's discretion.**

The intervals between etoposide and cisplatin and the intervals between etoposide and radiation therapy fractions must be recorded in "real time" in the institutional record. The intervals will be reported on the data collection forms.

When etoposide is administered b.i.d., the second dose should precede the RT fraction by not less than 30 minutes and not more than 60 minutes.

The choice of anti-emetic regimen is left to the local investigator. Ondansetron, at 0.15 mg/kg i.v. hours 0, 4, and 8 is an acceptable alternative anti-emetic.
7.2.3.2.5 *Repeat cycle beginning day 29.* The second course of chemotherapy shall not be started until adequate recovery from myelosuppression is documented \((\text{granulocytes} \geq 1,500 \text{ and platelets} \geq 100,000)\).

7.2.4 *Anti-Emetic:* The choice of anti-emetic regimens will be left to the discretion of individual investigators. Ondansetron at a dose of 32 mg intravenously prior to cisplatin is recommended. Alternatively, a combination of lorazepam: 1 mg; metoclopramide: 1 mg/kg; dexamethasone 10-20 mg; diphenhydramine \((\text{benadryl})\): 25-50 mg, repeated at reasonable intervals is appropriate. In addition, prophylaxis against delayed nausea and vomiting is recommended; e.g., a tapering dose of dexamethasone, with or without lorazepam, metoclopramide, and Benadryl.

7.3 **Dose Modifications for Toxicity on both Arms 1 & 2 (9/1/94, 2/14/95, 6/3/96)**

7.3.1 *Nephrotoxicity:* If serum creatinine is > 1.5 mg/dl when the second cycle of cisplatin is due \((\text{Day 29})\), the patient should receive aggressive hydration and have serum electrolytes, serum BUN, and creatinine rechecked within 24 hours. The patient may proceed with treatment if the serum creatinine is \(\leq 1.5\) mg/dl. If the creatinine value is between 1.5 and 2.0 mg/dl, the patient should receive 50% cisplatin dose reduction as well as aggressive hydration. Dr. Langer, the medical oncology principal investigator, should be contacted.

7.3.2 *Myelosuppression:* Dose modification for both vinblastine and cisplatin depend on blood counts on the day of administration as well as nadir blood counts.

7.3.2.1 *Cisplatin:* If the granulocyte count is \(\geq 1500\) and the platelet count is \(\geq 100,000\) on day 29, then full dose cisplatin \((100\%)\) should be given.

7.3.2.2 If the granulocyte count is between \(1000 - < 1500\), and/or the platelet count is between \(75,000 - < 100,000\) on Day 29, the cisplatin should be administered at 75% of target dose.

7.3.2.3 If the granulocyte count is \(< 1000\) and/or the platelet count is \(< 75,000\) on Day 29, cisplatin should be withheld until those hematologic levels are reached. At that time, cisplatin should be administered at 75% of target dose.

7.3.2.4 *Vinblastine:* If the granulocyte count is \(\geq 1000\) on Day 29, vinblastine should be administered at full doses \((100\%)\). If the granulocyte count is between 500-1000 on Day 29, vinblastine should be administered at 50% of target dose. If the granulocyte is \(< 500\) on Day 29, vinblastine should be withheld until day 36 and counts repeated. If granulocytes are \(\geq 500\), dose is given as above. If by day 36, counts remain \(< 500\), no further vinblastine is to be administered.

7.3.2.5 *Nadir Blood Counts:* If the nadir granulocyte count is \(< 500\) or if nadir-related sepsis occurs, subsequent vinblastine and cisplatin doses will be reduced by 25%.

7.3.2.6 During days 8, 15, 22, vinblastine dose will be withheld for ANC \(< 750\) or platelets \(< 75,000\). Vinblastine will be given at full dose if counts are above these levels. If omitted on days 8, 15, or 22, vinblastine will not be made up at the end of five weeks. If day 29 treatment is withheld, it will be given on day 36.

7.3.2.7 If dose reduction guidelines conflict, observe the more stringent.

7.4 **Dose Modifications for Toxicity on Arm 3**

7.4.1 *During treatment course:* Administration of oral VP-16 will be discontinued if the granulocyte count falls below 750 or platelets fall below 50,000 on day 8. Cisplatin dose on day 8 will be withheld if the granulocyte count falls below 750 or platelets fall below 50,000 or serum creatinine rises above 2.0 mg. on day 8 of treatment. If serum creatinine rises above 1.5 mg., but is less than or equal to 2.0 mg. on day 8, cisplatin dose will be reduced by half.

7.4.2 *For the second course:* No attempt will be made to escalate the chemotherapy doses for a given patient. However, if the granulocyte nadir count falls below 750 or the platelet nadir count falls below 50,000, the second course of VP-16 will be given at 25% reduction; the cisplatin dose will be reduced by 20%. However, if cisplatin has been already reduced by 50% because of an elevated serum creatinine, the cisplatin dose should not be further reduced because of the drop in nadir white blood cell and platelet counts. If at the time chemotherapy is to be given, serum creatinine rises above 1.5 mg. but is less than or equal to 2.0 mg, the cisplatin dose will be reduced by half and if the serum creatinine rises above 2.0 mg., cisplatin will be discontinued.

7.4.2.1 The second course of chemotherapy shall not be started until adequate recovery from myelosuppression is documented \((\text{granulocyte} > 1,500 \text{ and platelets} > 100,000)\).

7.4.3 *Modifications of Route of Etoposide*
If patient is unable to take Etoposide by mouth, or gastrointestinal absorption is not predictable due to nausea/vomiting/diarrhea, or oral Etoposide is not available/affordable, intravenous route can be used by giving one half of oral dose i.v. Etoposide must be given a half hour before radiotherapy.

7.5 **Adverse Drug Reaction 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 the FDA form 3500 (*Appendix V*) and mailed to:

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

8.0 **SURGERY**

Not applicable to this study.

9.0 **OTHER THERAPY**

Not applicable to this study.

10.0 **PATHOLOGY (2/1/96)**

10.1 **Fixed Tumor Repository Study (Optional)**

10.1.1 Patients entered on this study are also eligible for the Fixed Tumor Repository.

10.1.2 To receive an additional RTOG case credit, the following must be provided to RTOG:

10.1.2.1 One additional paraffin block of tumor or 15 unstained slides (*maximum thickness of 5 microns each*). Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the Fixed Tumor Repository.

10.1.3 To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides.

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.1.5 Materials will be sent to:

Pathology Coordinator  
RTOG Headquarters  
1101 Market Street  
Philadelphia, PA 19107

10.2 **Fresh Tissue Repository (Optional)**

10.2.1 Fresh Specimens are eligible for RTOG 93-08, the fresh/frozen tumor repository study.

11.0 **PATIENT ASSESSMENTS**

11.1 **Study Parameters (6/3/96)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pretreatment (within 2 weeks of study entry)</th>
<th>Weekly During RX</th>
<th>Prior To DDP</th>
<th>After RXa</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neurological Assessment</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Weight &amp; KPS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray, PA &amp; LAT</td>
<td>Xd</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest CT Scan</td>
<td>Xd</td>
<td></td>
<td>Xb</td>
<td></td>
</tr>
<tr>
<td>Tumor Measurement</td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC, platelets, serum creatinine</td>
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<tr>
<td>SMA-12, electrolytes, Mg++</td>
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</tr>
<tr>
<td>Urinalysis</td>
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<tr>
<td>VC, FEV1,DLCO, EKG</td>
<td>Xd</td>
<td></td>
<td>Xc</td>
<td></td>
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<tr>
<td>Metastatic Evaluation</td>
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<td>Toxicity Evaluation</td>
<td></td>
<td>Xe</td>
<td>Xf</td>
<td></td>
</tr>
<tr>
<td>Swallowing Assessment</td>
<td></td>
<td>Xf</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. After completing radiation therapy, patients will be seen one month later then every 3 months for two years, then every six months for three years then annually.
b. Every 6 months for 2 years after RT, then annually
c. When appropriate for new symptoms or findings
d. Within 4 weeks before study entry
e. Prior to start of RT
f. Daily during RT and for 6 weeks following RT

11.2 Evaluation During Study

11.2.1 An interval history and physical examination with particular attention to drug-induced side effects along with documentation of the patient's weight and performance status on each visit.

11.2.2 Weekly CBC, platelet count, differential AGC count, and serum creatinine.

11.2.3 An SMA-12, electrolytes, and Mg++ shall be performed at least every 4 weeks or as frequently as needed to define drug toxicity.

11.2.4 Tumor measurements, response of each lesion, site and overall response before each chemotherapy cycle.

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

11.2.6 After completing radiation therapy, patients will be seen according to the schedule in Section 12.1. Required studies for follow-up are listed in Section 11.1.

11.2.7 Patient swallowing assessment diary is done prior to start of RT, daily during RT, and for 6 weeks following RT.

11.3 Criteria for Response

11.3.1 A measurable lesion is defined as a lesion with clearly defined perpendicular diameters seen on physical examination, chest x-ray, CT scan, or ultrasonic examination. The longest diameter and its perpendicular will be measured. All measurable lesions will be measured in centimeters prior to each course of therapy. Measurements should be made and recorded by the physician or the oncology research nurse under his or her supervision.

11.3.2 An evaluable lesion is defined as a lesion which is clinically apparent but not bidimensionally measurable.

11.3.3 An estimate of overall objective and subjective response will be made and recorded at each visit.

11.4 Response Definitions

11.4.1 Patients with measurable indicator lesions:

Complete Response (CR): Disappearance of all clinical evidence of tumor persisting for a minimum of four weeks. The patient must be free of all symptoms of cancer.

Partial Response (PR): 50% or greater decrease in the sum of the products of diameters of all measured lesions persisting for a minimum of 4 weeks. No lesions may increase in size and no new lesion may appear.

No Change (NC): Any regression of indicator lesions not fulfilling the criteria of partial remission and no evidence of progression as defined below. NC is considered a failure, but should be noted as a possible signal of biologic activity.
Progressive Disease (PD): An increase of ≥ 25% in the sum of the products of diameters of any measurable lesion or appearance of an unequivocal new lesion.

11.4.2 Patients with evaluable (non-measurable) indicator lesions:

- **Complete Remission**: Disappearance of all clinical evidence of disease on physical examination, x-rays, and CT scans for a minimum of four weeks.
- **Improved**: Definite decrease (≥ 50%) in the size of the evaluable lesions for a minimum of four weeks; this must be concurred in by at least 3 observers, including the referee radiologist if the evaluable lesion is assessed by its x-ray appearance. No simultaneous increase in the size of other lesions or the appearance of new lesions may occur.
- **No Change**: Any regression of indicator lesions not fulfilling the criteria of complete remission or improved and no evidence of progression as defined below.
- **Progression**: Unequivocal worsening of any evaluable lesions or the appearance of new lesions.

11.4.3 **Response Duration**: Response durations are measured from the time of response (not the beginning of treatment) until there is evidence of progressive disease.

11.4.4 **Survival Duration**: The survival of patients will be measured from the date of randomization.

11.5 **Criteria for Discontinuing Therapy**

- **Progressive disease after a minimum of one course chemotherapy**.
- **The development of unacceptable toxicity defined as unpredictable, irreversible, or Grade 4**.
- **Patient refusal**.
- **All patients will be followed**.

12.0 **DATA COLLECTION**

12.1 **Summary of Data Submission (2/1/96, 6/3/96)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 1 week of registration</td>
</tr>
<tr>
<td>Medical Oncology Treatment Planning Form (M2)</td>
<td></td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 weeks of registration</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>For Fixed Tumor Repository (see Section 10.1)</td>
<td>Within 4 weeks of randomization</td>
</tr>
<tr>
<td>Pathology Report (P6)</td>
<td></td>
</tr>
<tr>
<td>Pathology Blocks/Slides (P7)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Flowsheets (M1)</td>
<td>Following completion of course 1, within 4 weeks of completion of all protocol chemotherapy.</td>
</tr>
<tr>
<td>completing course 2 and at one month</td>
<td></td>
</tr>
<tr>
<td>Post Induction Treatment Form (F0) (Arm 1)</td>
<td>Within 1 week after completion of chemotherapy</td>
</tr>
<tr>
<td>Initial Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
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<tr>
<td>Films (simulation and portal) (T3)</td>
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</tr>
<tr>
<td>Calculations (T4)</td>
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</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
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<td>Treatment Record (T5)</td>
<td>Within 1 week of RT end</td>
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<tr>
<td>Isodose Distribution (T6)</td>
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</tr>
<tr>
<td>Boost Film (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Swallowing Diary (DP)</td>
<td>Within 1 week of RT end (to include pre-RT assessment) and at 6 weeks post RT.</td>
</tr>
</tbody>
</table>
Follow-up Form (F1)

At one month after completion of protocol treatment, q 3 months for two years, then q 6 months x 3 years, then annually. Also at progression/relapse, onset of severe or unusual toxicity and at death.

Autopsy Report, final/microscopic (D3)

As applicable

**13.0 STATISTICAL CONSIDERATIONS**

**13.1 Study Endpoints**

13.1.1 The primary endpoint of this trial is overall survival.

13.1.2 The frequency of severe (≥ grade 3) toxicities will be examined, with emphasis on esophageal toxicity.

**13.2 Sample Size**

The data from RTOG 90-15 was utilized to estimate the median survival (17.5 months) for the study population treated with concomitant chemotherapy and standard radiotherapy (CCT+RT). RTOG 91-06 tested a CCT regimen different from RTOG 90-15 and hyperfractionated radiotherapy (HFX) and estimated the median survival to be 19.7 months. The data from the sequential chemotherapy and radiotherapy (SCT+RT) arm of RTOG 88-08 were used to estimate the median survival (13.8 months) for the standard arm. The median survival for RTOG 91-06 is 19.7 months for all patients compared to 13.8 months for the SCT+RT arm. The Makuch and Simon sample size formula which assumes constant proportionality of the hazards was utilized to calculate the sample size. Assuming an ineligibility/inevaluability (no data) rate of 8%, then **597 patients will be needed** (199 per arm) to ensure an 80% (=0.20, type II error) probability of detecting a minimum 43% relative improvement in median survival between the worst and best regimen, while rejecting the null hypothesis at the 95% level (=0.05).

This sample size is analogous to the method by Chen and Simon. Utilizing the same parameters and the forward selection method, this sample size will ensure an overall power of 89.75%. This sample size will be sufficient to detect an absolute 10% difference in acute grade 3 or worse esophageal toxicity rate. The above sample size will provide at least 90% probability of detecting a 10% difference in acute grade 3 or worse esophagitis (baseline rate of 10%), while rejecting the null hypothesis at the 99% level (two-sided), without correction for multiple tests.

**13.3 Patient Accrual**

The patient accrual is projected to be 12-16 patients per month, based upon the accrual of this patient group to RTOG 88-08. This trial should complete the accrual phase in 3.1-4.2 years. If the monthly accrual is less than 6 cases per month, the study will be re-evaluated with respect to feasibility.

**13.4 Inclusion of Women and Minorities (6/3/96)**

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer. However, the RTOG did not show this to be the case in a recent analysis. Furthermore, an analysis of race did not indicate and association with outcome. 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/race and treatments. The participation rates of men and women will be examined according to Section 13.6.1.

**13.5 Randomization Scheme**

The treatment allocation will be one using a randomized a permuted block within strata to balance for patient factors other than institution. The stratifying variables are Stage II versus Stage IIIa versus Stage IIIb and KPS 70-80 versus 90-100.

**13.6 Analyses Plans**

**13.6.1 Interim analyses of accrual and toxicity data (6/3/96)**

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

a) the patient accrual rate with projected completion date for the accrual phase;

b) the distribution of patients including women and minorities with respect to pretreatment characteristics;

c) the frequency and severity of the toxicities.

**13.6.2 Interim analyses of study endpoints**

There will be three interim analyses of the primary study endpoint (survival). The interim analyses will proceed according to the following table:

<table>
<thead>
<tr>
<th>Total Accrual</th>
<th>Length of Follow-up</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In order to assess the impact of CCT versus SCT patients on the CCT+RT and CCT+HFX arms will be combined and compared to the SCT+RT arm for the interim analyses only. This will increase the power to detect a statistically significant difference between CCT and SCT at each interim analysis point. Furthermore, a blinded analysis of the two CCT arms will be performed in order to assure justification for combining the patients. If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be suspended. The results of these interim analyses will only be reported, in a blinded fashion, the RTOG data monitoring committee as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the lung committee, which responsible for this study and, if necessary, the RTOG executive committee, so that corrective action can be taken.

13.6.3 Analysis and reporting of initial treatment results

This major analysis will be undertaken when each patient has been potentially followed for a minimum of two years. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.

Further subgroup analyses may be conducted (depending upon the sizes within the subgroups) for the purpose of identifying patterns of treatment responses. The forward selection method of Chen and Simon will be utilized to select the best treatment if no Arm has been dropped at interim analysis. The forward selection specifies that Arm 1 versus Arm 2 will be compared at the p=0.0553 level and the superior arm will be compared to Arm 3 at the p=0.069 level to select the best arm. If Arm 1 is dropped at interim analysis, then Arm 2 will be compared to Arm 3 at the p=0.04025 level. If there is no statistical difference in survival between Arms 2 and 3, then the arm with the least toxicity will be selected as best.
REFERENCES


* added 6/3/96
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 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

I understand that I have been diagnosed with a lung cancer which cannot be completely removed and that further treatment is recommended. My doctors believe that my participation in this study may be helpful. There is now evidence that the best treatment for my condition involves the use of both radiation therapy and chemotherapy. Radiation therapy is a form of cancer treatment using high energy x-rays. Chemotherapy is a form of treatment involving the use of special medications.

Previous studies have shown that chemotherapy given prior to radiation therapy may be more effective for patients with lung tumors such as mine than radiation treatments alone. Another method of delivering radiation and chemotherapy is to begin both treatments at the same time. This may allow both treatments to work together in shrinking a lung tumor. The purpose of this study is to determine whether the delivery of radiation at the same time as chemotherapy is more effective than the same chemotherapy followed by radiation treatments.

DESCRIPTION OF PROCEDURES (9/1/94, 2/1/96)

This study involves at random (by chance) assignment to one of the three treatment arms. It is not clear at the present time which of the three regimens is better. For this reason the therapy which is to be offered to me will be based upon a the method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the three regimens by computer. The chance of my receiving one of the three therapies is approximately equal. I will be assigned to one of three treatments:

Arm 1: Cisplatin chemotherapy will be delivered by vein on days 1 and 29, and vinblastine chemotherapy will be given by vein once-weekly for five weeks. Radiation therapy will be given after the completion of chemotherapy, starting on day 50 and delivered once-daily for seven weeks.

Arm 2: Cisplatin chemotherapy will be delivered by vein on days 1 and 29, and vinblastine chemotherapy will be given by vein once-weekly for five weeks. Radiation therapy will be delivered during the chemotherapy starting on day 1 and delivered once-daily for seven weeks.

Arm 3: gives Cisplatin four times, on days 1, 8, 29 and 36 intravenously with radiation therapy. Etoposide will be given by mouth daily for 20 days over 6 weeks (10 days on, 14 days off, 10 days on, no weekends). All start together. Radiation therapy is given twice daily separated by at least 6 hours, 5 days per week for six weeks.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for
additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified.

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_ frequently causes loss of appetite, nausea, vomiting, hearing loss, damage to kidneys, and bone marrow suppression (which can lead to anemia, infections, bruising or bleeding). Other less common but serious side effects include neurological toxicity (nerve damage), allergic reactions and chemical abnormalities of the blood.

_Vinblastine (Velban)_ can cause nausea and vomiting, inflammation of the mouth and mucous membranes, and a lowering of the white blood cell and platelets counts which could increase the risk of infections, bruising, or bleeding. Hair loss is likely but reversible. It may also cause reversible nerve damage with loss of sense of touch or strength.

_Etoposide (VP-16)_ may cause bone marrow suppression (which can lead to infections, bruising, or bleeding), hair loss, liver dysfunction, low blood pressure, nausea vomiting, fever and chills. Less common side effects include redness of the skin, neurological toxicity, shortness of breath, rapid heartbeat and abnormal spasms in the lung. Also the occurrence of acute leukemia has been reported rarely in patients treated with VP-16 when used with other cancer drugs.

_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 with in 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 difficult in breathing due to the lung (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.

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.

This clinical research may involve unforseeable risks to 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.

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 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 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 and chemotherapy either alone or together 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. 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 tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

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>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><strong>Stage 0</strong></td>
<td>TIS</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIa</strong></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIb</strong></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><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 RTOG 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 RTOG sponsored intergroup studies) must also be submitted to RTOG 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 RTOG 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**

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.

- **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 NCI Adverse Drug Reaction Reporting Form**