MEMORANDUM

TO: RTOG Principal Investigators and CRAs

FROM: Elaine Pakula
       Director, Protocol Development

DATE: July 23, 1999

SUBJECT: Protocol Update

Closed to Accrual Effective Immediately

RTOG 97-01       Poor Prognosis Lung       Poor Accrual

Data will no longer be collected; this study has been terminated to both accrual and data submission.

cc: Study Chairmen
    Lung Committee
MEMORANDUM

TO: RTOG Principal Investigators and CRAs
FROM: Elaine Pakulis
       Director, Protocol Development
DATE: April 20, 1998
SUBJECT: Protocol Update

Activated

RTOG 97-01, "Phase III Randomized Trial of Radiation Therapy Alone Versus Concurrent Chemotherapy Plus Radiation Therapy for Poor-Risk Stage III Non-Small-Cell Lung Carcinoma"

RTOG 97-16, "A Prospective Randomized Phase III Trial Comparing Trimodality Therapy (Cisplatin, 5-FU, Radiotherapy, and Surgery) to Surgery Alone for Esophageal Cancer" (C9781)

Revised

RTOG 90-18 (INT 0116) Gastric Rev. #14
RTOG 91-15 (DM90-094) H&N 13-cis Rev. #12
RTOG 93-09 (INT 0139) N2 Lung Rev. #8
RTOG 93-11 3D Lung Rev. #4
RTOG 94-03 (INT 0144) Post Op Rectum Rev. #7
RTOG 9511 (C9334) Talc Slurry Rev. #8
RTOG 97-02 (C9343) Breast > 70 y.o. Rev. #3
RTOG 97-06 Bladder Rev. #1

RTOG 97-01, 93-09, 93-11, and 97-06 will be available on the RTOG website on 4/20/98. The other studies are not coordinated by RTOG and paper copies are enclosed.

cc: Study Chairmen
    Participating Cooperative Groups

Supported by the Division of Cancer Treatment, National Cancer Institute
RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-01

PHASE III RANDOMIZED TRIAL OF RADIATION THERAPY ALONE VERSUS CONCURRENT CHEMOTHERAPY PLUS RADIATION THERAPY FOR POOR-RISK STAGE III NON-SMALL-CELL LUNG CARCINOMA

Study Chairmen

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Activation Date:  April 20, 1998


This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-01

PHASE III RANDOMIZED TRIAL OF RADIATION THERAPY ALONE VERSUS CONCURRENT CHEMOTHERAPY PLUS RADIATION THERAPY FOR POOR-RISK STAGE III NON-SMALL-CELL LUNG CARCINOMA

SCHEMA

<table>
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<td>45 Gy to the primary tumor and regional lymph nodes, 25 fractions 5 days/week, 1.8 Gy daily. 16 Gy boost to gross disease sites, 8 fractions, 5 days/week, 2 Gy daily.</td>
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<thead>
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<td>1. IIIA</td>
<td></td>
<td>Carboplatin and VP-16 Chemotherapy:</td>
</tr>
<tr>
<td>A</td>
<td>2. IIIB</td>
<td>T</td>
<td>Carboplatin (AUC of 3.0) i.v. bolus on days 1, 3, 29 and 31, prior to VP-16 and daily radiation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>VP-16 (50 mg/m²/day) i.v. bolus on days 1-4 and 29-32</td>
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<tr>
<td></td>
<td></td>
<td>M</td>
<td>after carboplatin and approximately 1 hour prior to daily radiation.</td>
</tr>
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<td>I</td>
<td>plus</td>
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<td>Concurrent Chest Radiation Therapy:</td>
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<tr>
<td></td>
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<td>E</td>
<td>45 Gy to the primary tumor and regional lymph nodes, 25 fractions, 5 days/week, 1.8 Gy daily. 16 Gy boost to gross disease sites, 8 fractions, 5 days/week, 2 Gy daily.</td>
</tr>
</tbody>
</table>

Eligibility: *(See Section 3.0 for details)*

- Patients will have a histologically or cytologically proven diagnosis of a single, primary bronchogenic NSCLC *(adenocarcinoma, large cell carcinoma, or squamous cell carcinoma).*
- Patients must have either Stage IIIA or Stage IIIB disease.
- All patients must have measurable or evaluable tumor by chest x-ray or CT scan.
- Patients must have a WBC ≥ 3,500/μl and platelet count ≥ institutional limits of normal.
- The calculated creatinine clearance must be ≥ 20 ml/min.
- The preregistration FEV1 must be ≥ 0.8 liter.
- Patients must have a Karnofsky performance score ≥ 50.
- Patients who are ineligible for other RTOG non small cell lung protocols for reasons including, but not limited to:
  a. Karnofsky performance status < 70, or
  b. Weight loss > 5% over the past 3 months, or
  c. Calculated creatinine clearance < 50 ml/min, or
  d. Significant hearing loss for which the patient is unwilling to accept the potential for worsening due to cisplatin, or
  e. Symptomatic peripheral neuropathy, or
  f. Controlled congestive heart failure which, in the investigator's opinion, may become decompensated due to excessive hydration prior to cisplatin administration
- No prior invasive malignancy unless disease free for ≥ 3 years.
- Signed study-specific consent form.

Required Sample Size: 316
ELIGIBILITY CHECK (4/20/98)

(page 1 of 2)

1. Does the patient have a histologically or cytologically-proven diagnosis of a single, primary bronchogenic NSCLC as specified in Section 3.1.1?

2. Does the patient have Stage IIIA or IIIB disease?

3. Does the patient have measurable or evaluable tumor by chest x-ray or CT scan?

4. Is the WBC ≥ 3500 and platelet count ≥ institutional limits of normal?

5. Is the calculated creatinine clearance ≥ 20 ml as calculated in Section 3.1.5?

6. What is the pre registration FEV-1? (liter)

7. What is the Karnofsky Performance Status?

8. Does the patient have a concurrent invasive malignancy?

9. Does the patient have history of a prior invasive cancer?

   If yes, has the patient been disease free ≥ 3 years?

10. Does the patient suffer from any uncontrolled condition listed in Section 3.2.1?

11. Does the patient have a pleural effusion? (If no, skip to Q 12)

   If yes, has the patient undergone a thoracentesis?

   If no, does a small pleural effusion exist, can it be seen only on CT, and is the effusion volume insufficient to safely perform ultrasound-guided thoracentesis? (If yes, skip to Q 12)

   Is the effusion an exudate or cytologically positive for malignancy?

12. Is the evidence of distant disease on CT of chest or upper abdomen including contralateral chest, liver, and adrenal glands?

13. Is there CNS or skeletal metastasis?

14. Has the patient had prior chemotherapy for lung cancer or prior RT to the chest?

15. Is the patient pregnant?

16. If female, has the patient agreed to use effective methods of contraception?

17. Is the patient ineligible for good risk RTOG stage III NSCLC protocols?

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

[ ] 1. Has the Eligibility Checklist (above) been completed?

[ ] 2. Is the patient eligible for this study?

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

[ ] Patient's Name

[ ] Verifying Physician

[ ] Patient ID #

[ ] Referring Institution # (if different)

[ ] Karnofsky Performance Scale (50-70 vs. 80-100)

[ ] AJC Stage Group (IIIA vs. IIIB)

[ ] Medical Oncologist

[ ] Birthdate

[ ] Sex

[ ] Race

[ ] Social Security Number

[ ] Zip Code (9 digit if available)

[ ] Method of Payment

[ ] Will any component of the patient's care be given at a military or VA facility?

[ ] Treatment Start Date

[ ] Treatment Assignment

Completed by ___________________________ Date ___________________________
INTRODUCTION

Approximately 30% of patients with non-small-cell lung cancer (NSCLC) present with stage IIIA or IIIB disease. Because of the regionally advanced nature of the disease, stage III NSCLC patients are rarely considered resectable for curative intent. The standard therapeutic approach has been primary thoracic radiation therapy (RT) alone 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 stage III patients treated with RT alone.

In carefully selected patients, adding cisplatin-based chemotherapy to RT has been reported to yield favorable survival over RT alone. The survival benefit of chemotherapy in regionally advanced NSCLC has been demonstrated by the Cancer and Leukemia Group B (CALGB) trial 84-33, the French multicenter trial CEBI 138, and the RTOG 88-08/Eastern Cooperative Oncology Group (ECOG) 45-88 trial. The CALGB trial randomized 155 patients to two cycles of vinblastine and cisplatin prior to RT versus RT alone. The 2-year survival rates and MST were 13.8 months versus 9.7 months favoring the chemoradiotherapy arm \( (P=0.0075) \). The superiority of the combined modality arm has remained significant in later reports with 5-year follow-up. The CEBI trial compared a sandwich regimen of induction and post-RT chemotherapy (vincristine, lomustine, cisplatin, and cyclophosphamide) to RT alone and reported a 2-year survival rate advantage of 20% versus 12% \( (P=0.04) \) favoring the combined modality arm. The MST on the CEBI trial was 12 months for the combined modality arm vs. 10 months for RT alone.

A third trial comparing cisplatin-based chemotherapy plus RT vs. RT alone is RTOG 88-08/ECOG 4588. This three arm study compared standard RT, the CALGB regimen of induction chemotherapy \( (vinblastine and cisplatin) \) followed by standard RT, and hyperfractionated RT. Two-year survival and MST were 19% and 11.4 months, 32% and 13.8 months, and 24% and 12.3 months, respectively. Survival for patients receiving chemotherapy plus radiotherapy was statistically superior to survival for patients receiving either standard or hyperfractionated RT alone \( (P=0.03) \).

Although cisplatin-based regimens have been generally well tolerated, the eligibility criteria for these protocols have been very selective. Only good-risk patients with weight loss less than 5% and a Karnofsky performance status of 70 or more were allowed study entry. In addition, patients with impaired renal function or intolerance to the rigorous intravenous hydration required for cisplatin administration are excluded from these trials. A tolerable combined modality regimen for these poor-risk patients is needed.

Carboplatin is an analog of cisplatin with a similar spectrum of antitumor activity. One major advantage over cisplatin is that carboplatin does not require rigorous hydration immediately before and after drug administration. In addition, the incidence of nephropathy, neuropathy, and ototoxicity is low. Myelosuppression is the major dose-limiting toxicity. The reduced toxicity profile of carboplatin makes the drug an attractive alternative to cisplatin for use in combined modality regimens, especially in poor-risk patients.

Phase II studies have demonstrated that carboplatin is an active agent against NSCLC. One phase III ECOG trial suggests that carboplatin, as a single agent at a dose of 400 mg/m², is at least equivalent if not superior to several cisplatin-containing combination regimens in survival time of patients with stage IV NSCLC. A recent EORTC study comparing cisplatin \( (120 \text{ mg/m}²) \) plus VP-16 to carboplatin \( (325 \text{ mg/m}²) \) plus VP-16 shows no significant differences in either response rate or median survival time.

A promising combined modality treatment regimen for poor risk stage III NSCLC patients is two cycles of carboplatin and VP-16 chemotherapy with concurrent daily thoracic RT to 61 Gy. This regimen was found to be reasonably tolerable in a pilot study of 26 patients at UC Davis. The MST was 13 months and the 2-year survival was an encouraging 40%. The tolerability of this regimen was recently confirmed in the phase II Southwest Oncology Group (SWOG) trial 9429 (unpublished data). Grades III/IV toxicities included neutropenia (38%), thrombocytopenia (23%), and esophagitis (15%). There was no grade V toxicity. The MST on the phase II study was also 13 months, impressive for this poor-risk group.
A significant number of patients with stage III NSCLC are not candidates for good-risk trials. This phase III randomized trial compares thoracic RT alone versus concurrent chemotherapy plus RT for these poor-risk patients with stage IIIA or IIIB NSCLC. Patients receive daily single-fraction (1.8-2.0 Gy) thoracic RT to a total dose of 61 Gy. Concurrent with RT, patients randomized to arm 2 of the study also receive VP-16 IV bolus at 50 mg/m²/day on days 1-4 and 29-32, and carboplatin IV bolus at a daily dose calculated with an area under the curve (AUC) of 3.0, on days 1, 3, 29, and 31. Because these drugs do not require rigorous IV hydration, this chemotherapy regimen can be easily administered as an outpatient treatment, even in patients with renal and cardiac diseases.

Quality of Life (QOL) is an important clinical end-point for patients with poor risk stage III lung cancer, particularly if there is differential toxicity and marginal differences in survival between treatment arms. Quality of Life will be assessed using the Lung Cancer Symptom Scale (LCSS), an easy to use brief self-report which is specific for patients with lung cancer. The patients’ perception of six major symptoms (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain) as well as overall symptom distress, functional ability, and global QOL which can be affected by lung cancer and therapy are evaluated. The LCSS has undergone extensive psychometric testing and has proven validity and reliability for use in patients with lung cancer. It has been used in over 1000 patients with lung cancer, the majority with non-small cell, compares favorably to other “gold” standards for QOL, and is sensitive in detecting change over time. This instrument also has a companion objective rater form that will not be used in this trial.) The LCSS is suitable for patients with different levels of symptom burden and undergoing different types of lung cancer treatment, including chemotherapy and radiation therapy. In this trial, the visual analogue form of the instrument has been converted to a ten point Likert-type response format. Scores are obtained from a sum of the nine aggregate questions (range 0-90), with higher scores indicating decreased QOL. Assessment time periods are projected which will capture QOL prior to, during, and post-treatment for both arms: pre-study, week 8 and week 12 (which correspond with toxicity notations, physical exams and assessments of performance status and weight), and at the 6, 9, and 12 month follow-up appointments.

2.0 OBJECTIVES

2.1 To determine if the survival rate of poor-risk patients with Stage III NSCLC is improved by adding two cycles of concurrent carboplatin and VP-16 to standard thoracic RT.

2.2 To determine if QOL is differentially affected by adding two cycles of concurrent carboplatin and VP-16 to standard thoracic RT both during and after the course of treatment.

2.3 To determine if treatment-related esophageal, pulmonary, and hematologic morbidity is significantly increased by adding concurrent chemotherapy to standard thoracic RT in this group of poor-risk patients.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Patients will have a histologically or cytologically proven diagnosis of a single, primary bronchogenic NSCLC (adenocarcinoma, large cell carcinoma, or squamous cell carcinoma). Histology or cytology from involved mediastinal or supraclavicular nodes will be sufficient for diagnosis if a separate primary lesion of the lung parenchyma is evident on radiographs.

3.1.2 Patients must have either Stage IIIA or Stage IIIB disease. Radiographic evidence of mediastinal lymph nodes ≥ 2.0 cm in the largest diameter is sufficient to stage N2 or N3 disease. If the largest mediastinal node is < 2.0 cm in diameter and this is the basis for stage III disease, then at least one of the nodes must be proven positive cytologically or histologically.

3.1.3 All patients must have measurable or evaluable tumor by chest x-ray or CT scan.

3.1.4 Patients must have a WBC ≥ 3,500/ul and platelet count ≥ institutional limits of normal.

3.1.5 The calculated creatinine clearance must be ≥ 20 ml/min as calculated according to the following formula:

\[
\text{Creatinine Clearance} = \frac{(140-\text{Age}) \times \text{Body Wt} \times \text{Kg}}{72 \times \text{Serum Creatinine (mg/ml)}}
\]

Note: R = 1 for male and 0.85 for female.

3.1.6 The preregistration FEV-1 must be ≥ 0.8 liter.

3.1.7 Patients must have a Karnofsky performance score ≥ 50.
3.1.8 Ineligible for other RTOG non small cell lung protocols for reasons including, but not limited to:
a. Karnofsky performance status < 70, or
b. Weight loss > 5% over the past 3 months, or
c. Calculated creatinine clearance < 50 ml/min, or
d. Significant hearing loss for which the patient is unwilling to accept the potential for worsening due to cisplatin, or
e. Symptomatic peripheral neuropathy, or
f. Controlled congestive heart failure which, in the investigator's opinion, may become decompensated due to excessive hydration prior to cisplatin administration

3.1.9 In situ cervical, breast, or bladder cancers are eligible. Adequately treated basal cell or squamous cell skin cancer is also eligible.

3.1.10 Patient must sign a study-specific consent form prior to randomization.

3.2 Conditions for Patient Ineligibility
3.2.1 Patients with medical illnesses including, but not limited to, active infection, unstable congestive heart failure, active angina, unstable cardiac arrhythmias and peptic ulcer disease uncontrolled by appropriate therapy are not eligible.

3.2.2 Patients with a pleural effusion must undergo thoracentesis. Patients are ineligible if the effusion is found to be an exudate or cytologically positive for malignancy. Patients with small pleural effusions seen only on CT scan are eligible provided that the effusion volume is insufficient to safely perform ultrasound guided thoracentesis.

3.2.3 Evidence of distant metastasis on CT scan of the chest and upper abdomen including the contralateral chest, liver and adrenal glands.

3.2.4 Evidence of CNS metastasis.

3.2.5 Evidence of skeletal metastasis.

3.2.6 Prior chemotherapy for lung cancer or prior RT to the chest.

3.2.7 Pregnant women are ineligible because of the teratogenic effects of therapy. Women of reproductive potential must agree to use effective contraceptive methods.

3.2.8 Concurrent malignancy; prior invasive malignancies unless disease free for ≥ 3 years.

4.0 PRETREATMENT EVALUATIONS
4.1 History and physical examination including Karnofsky performance status, neurologic assessment, weight loss over past 3 months, concurrent non-malignant disease and therapy.

4.2 Chest X-ray, CT scan of the chest and upper abdomen (including liver and adrenal glands), CT scan or MRI of the brain with contrast (only if abnormal neurological signs or symptoms are present), and radionuclide bone scan (only if patient has bone pain or elevated alkaline phosphatase) within 6 weeks prior to randomization.

4.3 Pulmonary function tests including VC, FEV1, and DLCO.

4.4 CBC with differential and platelet count within 14 days prior to randomization.

4.5 Electrolytes, BUN, creatinine, albumin, calcium, phosphorus, glucose, uric acid, alkaline phosphatase, LDH, total bilirubin, SGOT, and SGPT within 14 days prior to randomization.

4.6 Patient completion of QOL Lung Cancer Symptom Scale prior to any study treatment. Request a set of data forms from RTOG in advance so the appropriate forms are available for the patient.

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
6.0 RADIATION THERAPY

6.1 Radiation Dose

6.1.1 Daily chest radiation will begin on day 1 of the protocol. The primary tumor, adjacent mediastinum and other targeted lymph nodes shall receive 45 Gy in 25 fractions, 5 days/week at 1.8 Gy daily. A 16 Gy boost to areas of gross disease will be delivered through reduced fields in 8 fractions, 5 days/week at 2.0 Gy daily.

6.1.2 Thoracic irradiation is identical on Arm 1 and Arm 2. For Arm 2, day 1 of chemotherapy and radiation must be a Monday or Tuesday.

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 ICRU recommendations for external beam treatments using photons and electrons:

6.2.2.1 For two opposed coaxial equally weighted beams: On the central axis midway between the beam entrances.

6.2.2.2 For two opposed coaxial unequally weighted beams: On the central axis at the center of the target volume.

6.2.2.3 For an arrangement of two or more intersecting beams which are not coaxial: At the point of intersection of the central axes of the beams.

6.2.2.4 For a single electron beam: At the depth of maximum dose (d-\text{max}) for a single electron beam with electron beam energy chosen such that the minimum dose at 3 cm depth is 80\% of the maximum dose. Electron treatment is allowed only for supraclavicular lymph node boost.

6.2.2.5 For complex treatment arrangements not covered above: At the center of the target volume.

6.3 Target Volumes

6.3.1 Two different target volumes shall be considered: The Initial Target Volume which includes the primary tumor and regional lymph nodes at risk, and the Boost Target Volume which includes all gross disease defined pathologically or radiographically.

6.3.2 Initial Target Volume: Includes the primary tumor and regional lymph nodes at risk. The complete extent of visible primary tumor as defined radiographically must be included with a 1.5 cm block margin around the mass. More margin may be necessary because of physiological movement with respiration which should be checked by fluoroscopy. In cases with extensive atelectasis and/or pneumonia where tumor margins are obscure, field boundaries are left to the judgment of the participating radiation oncologist. In these instances, large generous fields are encouraged which may be later reduced as radiographic clearing occurs. Weekly chest x-ray and/or weekly port films are recommended for this purpose. Every attempt is being made to minimize the irradiated volume in this poor risk population. The following lymph nodes are at high risk for having microscopic or occult disease and are to be included under the following conditions:

6.3.2.1 Ipsilateral supraclavicular lymph nodes - included only if involved by tumor (≥ 1.5 cm by CT, physical examination, or biopsy positive). Margins: The superior margin of the field shall adequately cover the supraclavicular fossa. The larynx, cervical spinal cord and upper esophagus should be blocked unless the area is involved by tumor or in close proximity to tumor. The lateral margin should not extend beyond two-thirds the length of the clavicle unless clinically indicated. The inferior margin shall be in continuity with the fields irradiating the mediastinum and lung as needed, or 1 cm below the lower border of the clavicle.

6.3.2.2 Bilateral supraclavicular lymph nodes - included only if the ipsilateral or contralateral supraclavicular lymph nodes are grossly involved (≥ 1.5 cm by CT scan, physical examination or biopsy positive). Margins: As above.

6.3.2.3 Ipsilateral hilar lymph nodes - always (1.5 cm margin).

6.3.2.4 Superior mediastinal lymph nodes (above carina) - always. Margins: The superior margin shall be at the suprasternal notch or 2 cm above known tumor, whichever is greater (if supraclavicular lymph nodes not treated). A 1.5 cm ipsilateral and 1.0 cm contralateral
margin is required. Do not extend the contralateral field edge greater than 1.5 cm beyond
the vertebral body. Do not treat the contralateral hilar nodes unless involved by tumor (≥1.5

cm by CT scan or biopsy positive).

6.3.2.5 Subcarinal lymph nodes - always. **Margins:** The inferior margin shall extend at least 5 cm or
two vertebral bodies below the carina. Lateral margins as above.

6.3.2.6 Inferior mediastinal lymph nodes - extend the inferior border of the mediastinal field at least 2.0

cm below the lowest clinically involved lymph nodes (≥1.5 cm or CT scan or biopsy positive).

6.4 Irradiation Portals

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

6.4.1 **Initial Target Volume Irradiation:** The primary and lymph node target volume (as defined in
Section 6.3.2) shall receive 45 Gy with AP-PA fields. The maximum dose at any point within the
spinal cord shall not exceed 50 Gy.

6.4.2 **Boost Target Volume Irradiation:** The primary and gross nodal tumor shall receive a boost of 16
Gy through reduced oblique fields with a 1.5 cm normal tissue margin between the gross tumor
volume and the field edge. These reduced fields shall not include the spinal cord. If the boost
target volume is adjacent to the spinal cord and all efforts at providing a 1.5 cm normal tissue
margin while excluding the spinal cord are unsuccessful, a reduction in the normal tissue
margin for the boost target volume will be allowed. The use of AP-PA fields with a PA spinal
cord block is not allowed. Lateral fields are discouraged because of increased dose to the
contralateral lung. During the designing of these reduced fields, every effort should be made to
exclude as much uninvolved normal tissue as possible.

6.5 Technical Factors

6.5.1 **Beam Energy:** Megavoltage equipment is required, with photon energies of 4 MV or higher.
The choice of beam energy should consider both the improved depth dose and skin sparing of
high energy photons, and the possible loss of lateral electronic equilibrium in low density
structures. If photon energies of 10 MV or higher are used, bolus is recommended for the
supraclavicular lymph node areas if these are treated, such that the 90% dose in the build-up
region is at no more than 1 cm depth. Electron beams are discouraged and may be used only to
treat the supraclavicular lymph nodes.

6.5.2 **Treatment Distance:** The minimum treatment distance shall be 80 cm to the skin for SSD
techniques and 100 cm to the isocenter for SAD techniques.

6.5.3 **Blocking:** Treatment fields must be individually shaped to exclude structures and lung not
within the target volume as defined in Section 6.3. Divergent custom-made blocking or
multileaf collimator is highly recommended.

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:** Each field will be treated every session. Adherence to the fractionation scheme is
required, although slight variations in the daily dose fraction are allowed (± 5%).

6.5.6 **Therapy Interruptions:** If interruptions of therapy up to two weeks become necessary, irradiation
should be completed to the prescribed doses. Total number of fractions and elapsed days
should be carefully recorded. Radiotherapy interruptions or delays will be permitted only for
febrile neutropenia or grade 4 esophagitis/mucositis. Interruptions longer than one week
should be discussed with Dr. Leigh or Dr. Gandara.

6.5.7 **Treatment Planning:** CT scanning of the chest in the treatment position (on a flat table-top) is
recommended for all patients. Two sets of composite isodose plans (one without lung corrections
and the other corrected for lung transmission) at the level of the tumor should be submitted. The
volume occupied by the tumor, heart, lungs and spinal cord should be clearly displayed on
each treatment plan. The isodose lines should be expressed either in total cGy (or Gy) or as a
percentage of prescribed dose to the target volume. The following off axis-points of calculation
shall be carried:

6.5.7.1 Spinal cord dose. If compensating filters or wedges 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, the point of maximum dose to the spinal cord must be determined. Maximum spinal cord dose should not exceed 50 Gy at any level.

6.5.7.2
Supraclavicular lymph node point - measured at 3 cm depth below the anterior surface
(when applicable).

6.6 Evaluation Criteria

6.6.1 Dose

<table>
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<tr>
<th>Total Dose Variation</th>
<th>Overall Evaluation</th>
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<td>≤ 5%</td>
<td>Per Protocol</td>
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<tr>
<td>&gt; 5% ≤ 10%</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&gt; 10%</td>
<td>Deviation Unacceptable</td>
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6.6.2 Field Borders (Except Contralateral Mediastinum on Initial Target Volume)

1.0 cm to 2.0 cm

<table>
<thead>
<tr>
<th>MIN</th>
<th>MAX</th>
<th>Per Protocol</th>
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<tr>
<td>0.5 to 1.0 cm</td>
<td>2.0 to 2.5 cm</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&lt; 0.5 cm</td>
<td>&gt; 2.5 cm</td>
<td>Deviation Unacceptable</td>
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</tbody>
</table>

6.6.3 Contralateral Mediastinum Field Borders (Initial Target Volume Only)

1.0 cm to 1.5 cm

<table>
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<tr>
<th>MIN</th>
<th>MAX</th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 to 1.0 cm</td>
<td>1.5 to 2.5 cm</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&lt; 0.5 cm</td>
<td>&gt; 2.5 cm</td>
<td>Deviation Unacceptable</td>
</tr>
</tbody>
</table>

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 Chemotherapy Plan (Arm 2)

7.1.1 The first cycle of chemotherapy begins on day 1 concurrent with initiation of radiation. The daily chemotherapy of each cycle is delivered prior to the daily radiation. Day 1 of chemotherapy and radiation must be a Monday or Tuesday.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>AUC=3 mg/ml-min</td>
<td>i.v.</td>
<td>1, 3, 29, 31</td>
<td>Give over 5-15 min prior to VP-16</td>
</tr>
<tr>
<td>VP-16</td>
<td>50 mg/m²/day</td>
<td>i.v.</td>
<td>1-4, 29-32</td>
<td>Give over 30-60 min approx. 1 hour prior to radiation</td>
</tr>
</tbody>
</table>

7.1.2 On days 1, 3, 29 and 31, carboplatin will be given as an i.v. bolus at a dose calculated with an AUC of 3.0 mg/ml x min by the modified Calvert formula\(^\text{14}\) given prior to RT on the same day.

Carboplatin Dose (mg) = AUC \times (CrCL + 25)

where AUC = 3.0 mg/ml x min

AND

Creatinine clearance = \(\frac{(140-\text{Age}) \times \text{Body Wt (Kg)}}{\text{R}}\)
Note: R = 1 for male patients and 0.85 for female patients.

Note: CrCl is calculated based on the pretreatment weight and serum creatinine before each cycle of chemotherapy.

7.2 Carboptatin (NSC-241240)

7.2.1 Mechanism of Action and Pharmacology: The mode of action of carboptatin is similar to that of the bifunctional alkylating agents, producing intrastrand and interstrand cross-links of DNA. Following a IV infusion, plasma carboptatin decays in a biphasic manner with the initial plasma half-life of 1.1-2 hrs and the elimination half-life of 2.6-5.9 hrs. Carboptatin itself is not bound to plasma protein but platinum from carboptatin is bound to plasma protein and is slowly eliminated with a minimum half-life of 5 days. The major route of carboptatin elimination is renal excretion. Patients with creatinine clearance of 60 ml/min or greater excrete 65% of the dose in the urine within 12 hrs and 71% by 24 hrs.

7.2.2 Human Toxicity: Human toxicity may include nausea and vomiting, diarrhea, weight loss, fever, hair loss, lowering of blood counts, which could cause an increased risk of infection, easy bruising or bleeding or tiredness. A decrease in the blood cell count may necessitate a blood transfusion. Less common side effects may include damage to the liver and kidney. The damage is usually detected by blood tests and usually reverts to normal when the drug is stopped. Also hearing loss, cessation of menses, allergic reactions including dizziness or blurred vision, a decrease in calcium or magnesium levels may occur. These lowered levels have gone back to normal when the drug has been stopped.

7.2.3 Pharmaceutical Data: Carboptatin (Paraplatin) is supplied as a white lyophilized powder in 50-mg, 150-mg and 450-mg vials to be reconstituted with 5, 15 ml and 45 ml, respectively, of sterile water, 5% dextrose in water or normal saline for injection, USP.

7.2.4 Storage and Stability: Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature (27°C). The reconstituted solution is stable for 8 hours at room temperature.

7.2.5 Administration: Carboptatin will be administered intravenously over 5-15 minutes.

7.2.6 Supplier: Carboptatin is commercially available.

7.3 VP-16 (Etoposide, Vepesid) (NSC-141540)

7.3.1 Mechanism of Action and Pharmacology: The major mode of action of VP-16 is inhibition of topoisomerase II resulting in the stabilization of the DNA-protein cleavable complex, which prevents the rejoining of DNA and leads to double-strand DNA breaks.

7.3.2 Human Toxicity: Human toxicity may include diarrhea, marked or complete hair loss, chest pain, blood in the urine, or rashes. Low blood pressure, liver toxicity, fever, chills, and intermittent muscle cramps may also be experienced. Sometimes patients experience spasms of the lung, numbness and tingling in the fingers and toes, headaches, and allergic reactions. It also can lower blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. In rare instances, acute leukemia has been reported in patients treated with VP-16 when given with other cancer agents.

7.3.3 Pharmaceutical Data: IV formulation: VP-16 is supplied as an 100-mg ampule in 5 ml of clear solution. The ampule has to be diluted with 20-50 volumes of 5% dextrose in water of normal saline to yield a final concentration of 0.2-0.4 mg/ml.

7.3.4 Storage and Stability: Unopened vials of Vepesid are stable for 24 months when stored at room temperature (25°C). The reconstituted solutions of 0.2 mg/ml and 0.4 mg/ml are stable for 96 and 48 hours, respectively, at room temperature.

7.3.5 Administration: VP-16 will be administered intravenously over 30-60 minutes.

7.3.6 Supplier: VP-16 is commercially available.

7.4 Recommended Antiemetic Regimen:

Ondansetron (Zofran) 24 mg, dexamethasone (Decadron) 10 mg IV, and Compazine Spansule 15 mg p.o. 30 minutes prior to carboptatin administration, followed by Compazine Spansule 15 mg p.o. q 12 hours for 3 days after carboptatin. Ondansetron 10 mg IV on days the patient is given VP-16 only. Lorazepam 1-2 mg p.o. is given prn.

7.5 Dose Modifications for Toxicity
7.5.1 chemotherapy adjustment for hematologic toxicity on or before day 29 (Arm 2 patients only):
- Day 29 ANC ≥ 1,000/µl, and platelets ≥ 100,000/µl - give full dose on cycle 2 (Day 29).
- Day 29 ANC < 1,000/µl, or platelets < 100,000/µl, delay chemotherapy one week.
- Febrile neutropenia during cycle 1, or nadir ANC < 500/µl or platelets < 40,000/µl, reduce cycle 2 carboplatin dose to AUC = 2.0 on days 29 and 31 (do not reduce VP-16).

7.5.2 therapy interruptions/delays:
Interruptions and delays of radiotherapy and chemotherapy will be allowed for up to two weeks for febrile neutropenia, grade 4 mucositis/esophagitis, or grade 4 nausea/vomiting. If the treatment delay exceeds 2 weeks, the patient will be taken off protocol therapy but followed as the other patients. Further treatment of this patient is at the discretion of the treating physicians.

7.6 adverse drug reaction reporting
7.6.1 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 and telephoned to RTog Data Management and to the Study Chair within 24 hours of discovery:

7.6.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.6.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.6.1.3 Any death on study if clearly related to the commercial agent(s).
7.6.1.4 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.

7.6.2 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
fax (301) 230-0159

7.6.3 Any death regardless of cause, which occurs during protocol treatment must be reported to RTog Headquarters by telephone within 48 hours of discovery.

8.0 Surgery
Not applicable to this study.

9.0 other therapy
Not applicable to this study.

10.0 Pathology
10.1 RTog tissue bank
10.1.1 Patients entered on this study with histologically-confirmed tumor should also participate in the RTog Tissue Bank.
10.1.2 The following must be provided:
10.1.2.1 One paraffin block of tumor or 15 unstained slides. 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 source of the enclosed materials (primary or nodes) and that it is being submitted for the RTog Tissue Bank.
10.1.3 RTog will reimburse pathologists from submitting institutions $100. per case if proper materials are submitted (send invoice to RTog Administration, ATT: Path Reimbursement).
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).
11.0 PATIENT ASSESSMENTS
11.1 Study Parameters

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</tbody>
</table>

a. Arm 2 patients only.
b. Follow-up: One month after completing RT, then every 3 months x 1 year; then every 6 months x 2 years, then annually.
c. CT chest every 6 months for 3 years, then as indicated by signs, symptoms or other tests.
d. Follow-up bone scan, and CT or MRI of brain only if relevant signs or symptoms appear.
e. And at 6, 9, and 12 month followup appointments.
f. Only for bone pain or elevated alkaline phosphatase.
g. Only for abnormal neurological signs or symptoms.
h. Not required if baseline LCSS was not done.

11.2 Evaluation During Study
11.2.1 CBC with differential and platelet count every other week for Arm 1 patients, weekly for Arm 2 patients.
11.2.2 History and physical examination with particular attention to drug-induced side effects (Arm 2 patients), along with documentation of the patient's weight and performance status every 4 weeks during treatment.
11.2.3 Creatinine, BUN, total bilirubin, LDH, Ca++, electrolytes, and Mg++ at least every 4 weeks during treatment or as frequently as needed to define drug toxicity (Arm 2 patients only).

11.2.4 Tumor measurements, response of each lesion, site, and overall response at 12 weeks and during follow-up.

11.2.5 After completing therapy, patients will be seen at 12 weeks and then every three months x one year, then every 6 months x 2 years, then annually. Required follow-up studies are listed in Section 11.1.

11.2.6 LCSS will be completed by patients at eight and 12 weeks and at the 6, 9, and 12 month followup appointments.

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.

11.3.4 QOL is defined as the total score obtained from the LCSS self-report.

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 lesions 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 duration is 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.

11.4.5 Quality of Life will be determined by the LCSS score (possible scores range from 0-90). Better QOL: lower scores on the LCS

Poorer QOL: higher scores on the LCSS

Changes in QOL will be assessed by time and by treatment arm and are defined as:

Improved: decreased overall score on the LCSS
Declined: increased overall score on the LCSS
No change: no change in the LCSS score.

11.5 Criteria for Discontinuing Therapy

11.5.2 The development of unacceptable toxicity defined as unpredictable, irreversible, or Grade 4.

11.5.3 Patient refusal.

11.5.4 All patients will be followed.
12.0 DATA COLLECTION
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of randomization</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (for histologically-confirmed patients only) (P2)</td>
<td></td>
</tr>
<tr>
<td>PreTreatment Quality of Life LCSS (QL)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Flowsheets (M1) (Arm 2) (to include pre tx lab values)</td>
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</tr>
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</table>

Initial Dosimetry Information:

<table>
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</thead>
<tbody>
<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>
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<tr>
<td>Calculations (T4)</td>
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</tr>
<tr>
<td>Chemotherapy Flowsheets (M1) (Arm 2)</td>
<td>Following completion cycle 1, within 2 weeks of completing cycle 2 and at one month of completion of all protocol chemotherapy.</td>
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Final Dosimetry Information:

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<tbody>
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<td>Isodose Distribution (T6)</td>
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<td>Boost Film (simulation and portal) (T8)</td>
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</table>

Quality of Life LCSS (SS) At 2, 3, 6, 9, and 12 months from start of treatment

Follow-up Form (F1) At one month after completion of protocol treatment, q 3 months for one year, then q 6 months x 2 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 Quality of life will be compared between the two treatment regimens.

13.1.3 The frequency of severe (≥ grade 3) toxicities will be examined.

13.2 Sample Size

By evidence presented in Section 1.0, it is estimated that the two-year survival rate for the radiation alone arm is 15%. By adding two cycles of concurrent chemotherapy, it is hypothesized that the two-year survival rate will be 26%. Assuming constant hazard rates and uniform accrual, we have designed our study to have 80% power to test the null hypotheses of same survival against the alternative hypothesis of improved survival for the chemoradiation arm at 5% (two sided) significance level. Using group sequential design with shape parameter 0.20 the maximum number of deaths needed is approximately 298. The maximum patient accrual and study duration depends on the accrual rate.
The primary hypothesis for quality of life is improved QOL on the concurrent chemotherapy arm compared to RT alone. A difference of 1 point on the Lung Cancer Symptom Scale is considered clinically significant. The estimated standard deviation is 1.81. Therefore, assuming 90% of all patients participate in the QOL component, then there will be 99% statistical power to find a 1 point difference in QOL change scores between the two treatment regimens. Comparing follow-up scores from the LCSS to baseline, the change scores will be compared across treatment arms.

13.3 Patient Accrual

Though there are no previous randomized studies for the patient group eligible for this study, from a survey of RTOG member institutions, we project that 70 eligible and evaluable patients can be accrued each year. Based on the study design in Section 13.2, we set 300 as the expected accrual of eligible and evaluable patients. Adding 5% to that number because of ineligible and inevaluable patients, the total accrual required is 316 patients, and the accrual period will take 4.5 years. If the accrual rate is less than half the projected accrual rate, this study will be evaluated for feasibility.

13.4 Randomization Scheme

The stratified treatment allocation scheme as described by Zelen\textsuperscript{21} will be used. There will be stratification on Karnofsky Performance Score (50-70 vs. 80-100) and by AJCC Stage (IIIA vs. IIIB).

13.5 Analyses Plans

13.5.1 Interim Analyses of Accrual and Toxicity Data

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 with respect to pretreatment characteristics;

c) the frequency and severity of the toxicities.

13.5.2 Interim Analyses of Study Endpoints

There will be two 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># of Deaths</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>149</td>
<td>.0058</td>
</tr>
<tr>
<td>75%</td>
<td>224</td>
<td>.0264</td>
</tr>
<tr>
<td>100%</td>
<td>275</td>
<td>.0478</td>
</tr>
</tbody>
</table>

The results of these interim analyses will be reported, in a blinded fashion, only to the RTOG Data Monitoring Committee (DMC) as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the DMC, 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.

13.5.3 Analysis and Reporting of Initial Treatment Results

This major analysis will be undertaken when each patient has been potentially followed until 275 deaths have been observed. 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.

i. Survival will be estimated using the Kaplan-Meier method and compared using the Prentice-Marek modified Wilcoxon.

ii. The treatment arms will be compared by changes in scores in the LCSS at 8 and 12 weeks and at 6, 9 and 12 months. Treatment comparisons will be performed on individual timepoints using the Wilcoxon inversion test. A repeated measures model will be used to compare the results across the five time points.
Further subgroup analyses may be conducted (depending upon the sizes within the subgroups) for the purpose of identifying patterns of treatment responses.

### 13.6 Inclusion of Women and Minorities

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 an 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/to race and treatments. The participation rates of men and women will be examined according to Section 13.5.1. Gender and minority accruals are estimated below:

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian or Pacific Islander</th>
<th>Black, not of Hispanic Origin</th>
<th>Hispanic</th>
<th>White, not of Hispanic Origin</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>102</td>
<td>1</td>
<td>121</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>3</td>
<td>46</td>
<td>3</td>
<td>138</td>
<td>2</td>
<td>195</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>6</td>
<td>55</td>
<td>6</td>
<td>240</td>
<td>3</td>
<td>316</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX 1

RTOG 97-01

PHASE III RANDOMIZED TRIAL OF RADIATION THERAPY ALONE
VERSUS CONCURRENT CHEMOTHERAPY PLUS RADIATION THERAPY
FOR POOR-RISK STAGE III NON-SMALL CELL LUNG CARCINOMA

SAMPLE PATIENT CONSENT FORM

RESEARCH STUDY

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

PURPOSE OF THE STUDY

I have been diagnosed with a lung cancer that cannot be completely removed and that further treatment is recommended. There is now evidence that the best treatment for my condition involves the use of radiation therapy. Radiation therapy is a form of cancer treatment using high energy x-rays. Chemotherapy, a form of treatment involving the use of special medications, may also be useful.

Previous studies have shown that chemotherapy given with radiation therapy is reasonably safe for patients with lung tumors such as mine. This may allow both treatments to work together in shrinking a lung tumor. The purpose of this study is to determine whether getting radiation at the same time as chemotherapy is more effective than radiation treatments alone.

DESCRIPTION OF PROCEDURES

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

Treatment 1: Chest radiation therapy alone will be given once a day, five days a week for seven weeks.

Treatment 2: Chest radiation therapy will be given once a day, five days a week for seven weeks. In addition to the radiation therapy, Carboplatin chemotherapy will be given by i.v. over 5-15 minutes on days 1, 3, 29 and 31. In addition, VP-16 chemotherapy will be given by i.v. over 30-60 minutes on days 1 to 4 and 29 to 32 (after the carboplatin) approximately one hour before my daily radiation treatment.

At regular intervals during the first year, I will be asked to complete a short questionnaire describing any symptoms relating to my lung cancer.

Also, at the time of my diagnosis by biopsy, 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.

Carboplatin may cause nausea and vomiting, diarrhea, weight loss, fever, hair loss, lowering of blood counts, which could cause an increased risk of infection, easy bruising or bleeding or tiredness. A decrease in the blood cell count may even necessitate a blood transfusion. Less common side effects may include damage to the liver and kidney. The damage is usually detected by blood tests and usually reverts to normal when the drug is stopped. Also hearing loss, cessation of menses, allergic reactions including dizziness or blurred vision, and decreased calcium or magnesium levels may occur. These lowered levels have gone back to normal when the drug has been stopped.

Etoposide (VP-16) may cause diarrhea, marked or complete hair loss, chest pain, blood in the urine, or rashes. Low blood pressure, liver toxicity, fever, chills, and intermittent muscle cramps may also be experienced. Sometimes patients experience spasms of the lung, numbness and tingling in the fingers and toes, headaches, and allergic reactions. It also can lower blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, need hospitalization, and transfusions if these problems are severe. In rare instances, the occurrence of acute leukemia has been reported 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 within a month of completion of radiation therapy; 2) fatigue (tiredness) for no apparent reason, which is a temporary effect, resolving within a month of completion of treatment; 3) skin damage within the area of radiation; the skin may develop a sunburn-like area within 2-6 weeks after treatment. The skin will permanently be more dry than other skin, and chest hair (if any) may not regrow; 4) decrease in white blood cells and platelets. Decrease in white cell production may result in bleeding and bruising easily; 5) cough and some difficulty in breathing (radiation pneumonitis and subsequent scarring of the lung). In addition, although uncommon, pericarditis (irritation of the heart sac), myocarditis (irritation of the heart muscle), transverse myelitis (irritation of spinal cord), or esophageal narrowing may occur long after radiation therapy.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood 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 unforeseeable 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; however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____________________________ the investigator in charge at ____________________________. In addition, I may contact _________ at ____________________________ for information regarding patients’ rights in research studies.
BENEFITS

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

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 that could be considered in my case include radiation therapy and chemotherapy either alone or together given off study 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. 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 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 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

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

100  Normal; no complaints; no evidence of disease
90   Able to carry on normal activity; minor signs or symptoms of disease
80   Normal activity with effort; some sign or symptoms of disease
70   Cares for self; unable to carry on normal activity or do active work
60   Requires occasional assistance, but is able to care for most personal needs
50   Requires considerable assistance and frequent medical care
40   Disabled; requires special care and assistance
30   Severely disabled; hospitalization is indicated, although death not imminent
20   Very sick; hospitalization necessary; active support treatment is necessary
10   Moribund; fatal processes progressing rapidly
  0   Dead
APPENDIX III
ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 1997)

TNM CATEGORIES (Note Definitions)

Primary Tumor (T)

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

T0 No evidence of primary tumor.

Tis Carcinoma in situ.

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

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

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

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

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

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

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph nodes metastasis.

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

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

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

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 1997)

**Distant Metastasis** *(M)*

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

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

**STAGE GROUPING**

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

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.

INSTRUCTIONS

4. Refer to detailed toxicity guidelines in the protocol, or to RTOG Headquarters for toxicity not covered on this table.
5. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
6. An accurate baseline prior to start of therapy is necessary.

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>- 0 -</th>
<th>- 1 -</th>
<th>- 2 -</th>
<th>- 3 -</th>
<th>- 4 -</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>=&gt; 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>WNL</td>
<td>75.0 - normal</td>
<td>50.0 - 74.9</td>
<td>25.0 - 49.9</td>
<td>&lt; 25.0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>WNL</td>
<td>10.0 - normal</td>
<td>8.0 - 10.0</td>
<td>6.5 - 7.9</td>
<td>&lt; 6.5</td>
</tr>
<tr>
<td>Granulocytes/Bands</td>
<td>=&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>=&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Hemorrhage (Clinical)</td>
<td>None</td>
<td>Mild, no transfusion</td>
<td>Gross, 1-2 units transfusion per episode</td>
<td>Gross, 3-4 units transfusion per episode</td>
<td>Massive &gt; 4 units transfusion per episode</td>
</tr>
<tr>
<td>Infection</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Nausea</td>
<td>None</td>
<td>Able to eat/reasonable intake</td>
<td>Intake significantly decreased but can eat</td>
<td>No significant intake</td>
<td>- - - - - - - -</td>
</tr>
<tr>
<td>Vomiting</td>
<td>None</td>
<td>1 episode in 24 hrs.</td>
<td>2-5 episodes in 24 hrs.</td>
<td>6-10 episodes in 24 hrs.</td>
<td>&gt; 10 episodes in 24 hrs, requiring parenteral support</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>Increase of 2-3 stools per day over pre-Rx</td>
<td>Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>Increases of 7-9 stools/day or incontinence or severe cramping</td>
<td>Increase of =&gt; 10 stools/day or grossly bloody diarrhea, or need for parenteral support</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>None</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Painful erythema, edema or ulcers but can eat</td>
<td>Painful erythema, edema or ulcers and cannot eat</td>
<td>Requires parenteral or enteral support</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>WNL</td>
<td>- - - - - - - -</td>
<td>&lt; 1.5 X N</td>
<td>1.5 - 3.0 X N</td>
<td>3.0 X N</td>
</tr>
<tr>
<td>Transaminase (SGOT, SGPT)</td>
<td>WNL</td>
<td>=&gt; 2.5 X N</td>
<td>2.6 - 5.0 X N</td>
<td>5.1 - 20.0 X N</td>
<td>&gt; 20.0 X N</td>
</tr>
<tr>
<td>Alkaline Phosphatase or S'nucleotidase</td>
<td>WNL</td>
<td>=&gt; 2.5 X N</td>
<td>2.6 - 5.0 X N</td>
<td>5.1 - 20.0 X N</td>
<td>&gt; 20.0 X N</td>
</tr>
<tr>
<td>Liver клинический</td>
<td>No change from baseline</td>
<td>- - - - - - - -</td>
<td>Precoma</td>
<td>Hepatic coma</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>WNL</td>
<td>&lt; 1.5 X N</td>
<td>1.5 - 3.0 X N</td>
<td>3.1 - 6.0 X N</td>
<td>&gt; 6.0 X N</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>No change</td>
<td>1 + or &lt; 0.3 g% or &lt; 3 g/l</td>
<td>2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l</td>
<td>4+ or &gt;1.0 g% or &gt;10 g/l</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Negative</td>
<td>Micro only</td>
<td>Gross/no clots</td>
<td>Gross + clots</td>
<td>Requires transfusion</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>- 0 -</td>
<td>- 1 -</td>
<td>- 2 -</td>
<td>- 3 -</td>
<td>- 4 -</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Alopecia</td>
<td>No loss</td>
<td>Mild hair loss</td>
<td>Pronounced or total hair loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>None or no change</td>
<td>Asymptomatic with abnormality in PFT's</td>
<td>Dyspnea on significant exertion</td>
<td>Dyspnea at normal level of activity</td>
<td>Dyspnea at rest</td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
<td>None</td>
<td>Asymptomatic/Transient/Requiring no therapy</td>
<td>Recurrent or Persistent/no therapy required</td>
<td>Requires treatment</td>
<td>Requires monitoring or hypotension or ventricular tachycardia or fibrillation</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>None</td>
<td>Asymptomatic/Decline of resting ejection fraction by 20% of baseline value</td>
<td>Asymptomatic/Decline of resting ejection fraction by &gt;20% of baseline value</td>
<td>Mild CHF, responsive to therapy</td>
<td>Severe or refractory CHF</td>
</tr>
<tr>
<td>Cardiac/ischemia</td>
<td>None</td>
<td>Non-specific T-wave flattening</td>
<td>Asymptomatic/ST and T wave changes suggesting ischemia</td>
<td>Angina without evidence for infarction</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Cardiac/pericardial</td>
<td>None</td>
<td>Asymptomatic effusion/no intervention required</td>
<td>Pericarditis (rub, chest pain, ECG changes)</td>
<td>Symptomatic effusion: drainage required</td>
<td>Tamponade/drainage urgently required</td>
</tr>
<tr>
<td>Hypertension</td>
<td>None or no change</td>
<td>Asymptomatic/Transient increase by &gt; 20 mmHg (D) or to &gt; 150/100 if previously WNL/No treatment required</td>
<td>Recurrent or persistent increase by &gt;20 mmHg (D) or to &gt; 150/100 if previously WNL/No treatment required</td>
<td>Requires therapy</td>
<td>Hypertensive crisis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None or no change</td>
<td>Changes requiring no therapy/including transient orthostatic hypotension</td>
<td>Requires fluid replacement or other therapy but not hospitalization</td>
<td>Requires therapy and hospitalization/resolves within 48 hours of stopping the agent</td>
<td>Requires therapy and hospitalization for &gt; 48 hours after stopping the agent</td>
</tr>
<tr>
<td>Neurological/sensory</td>
<td>None or no change</td>
<td>Mild paresthesias/loss of deep tendon reflexes</td>
<td>Mild or moderate objective sensory loss/moderate paresthesias</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
<td>-</td>
</tr>
<tr>
<td>Neurological/motor</td>
<td>None or no change</td>
<td>Subjective weakness/no objective findings</td>
<td>Mild objective weakness without significant impairment of function</td>
<td>Objective weakness with impairment of function</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Neurological/cortical</td>
<td>None</td>
<td>Mild somnolence or agitation</td>
<td>Moderate somnolence or agitation</td>
<td>Severe somnolence, agitation, confusion, disorientation or hallucinations</td>
<td>Coma, seizures, toxic psychosis</td>
</tr>
<tr>
<td>Neurological/cerebellar</td>
<td>None</td>
<td>Slight incoordination/dysdiadokinesia</td>
<td>Intention tremor, dystemtria, slurred speech, nystagmus</td>
<td>Locomotor ataxia</td>
<td>Cerebellar necrosis</td>
</tr>
<tr>
<td>Neurological/mood</td>
<td>No change</td>
<td>Mild anxiety or depression</td>
<td>Moderate anxiety or depression</td>
<td>Severe anxiety or depression</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Neurological/headache</td>
<td>None</td>
<td>Mild</td>
<td>Moderate or severe but transient</td>
<td>Unrelenting and severe</td>
<td>-</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>- 0 -</td>
<td>- 1 -</td>
<td>- 2 -</td>
<td>- 3 -</td>
<td>- 4 -</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Neurological/constipation</td>
<td>None or no change</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Ileus &gt; 96 hours</td>
</tr>
<tr>
<td>Neurological/hearing</td>
<td>None or no change</td>
<td>Asymptomatic/hearing loss on audiometry only</td>
<td>Tinnitus</td>
<td>Hearing loss interfering with function but correctable with hearing aid</td>
<td>Deafness not correctable</td>
</tr>
<tr>
<td>Neurological/vision</td>
<td>None or no change</td>
<td>- - - - - - -</td>
<td>- - - - - - -</td>
<td>Symptomatic subtotal loss of vision</td>
<td>Blindness</td>
</tr>
<tr>
<td>Skin</td>
<td>None or no change</td>
<td>Scattered macular or papular eruption or erythema that is asymptomatic</td>
<td>Scattered macular or papular eruption or erythema with pruritis or other associated symptoms</td>
<td>Generalized symptomatic macular, papular, or vesicular eruption</td>
<td>Exfoliative dermatitis or ulcerating dermatitis</td>
</tr>
<tr>
<td>Allergy</td>
<td>None</td>
<td>Transient rash/drug fever &lt; 38°C, 100.4°F</td>
<td>Urticaria, drug fever = 38°C, 100.4°F/mild bronchospasm</td>
<td>Serum sickness, bronchospasm, requiring parenteral medication</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Fever in absence of infection</td>
<td>None</td>
<td>37.1 - 38.0°C, 98.7 - 100.4°F</td>
<td>38.1 - 40.0°C, 100.5 - 104.0°F</td>
<td>&gt; 40.0°C/104.0°F for less than 24 hours</td>
<td>&gt; 40.0°C/104.0°F for more than 24 hrs. or fever accompanied by hypotension</td>
</tr>
<tr>
<td>Local</td>
<td>None</td>
<td>Pain</td>
<td>Pain and swelling with inflammation or phlebitis</td>
<td>Ulceration</td>
<td>Plastic surgery indicated</td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>&lt; 5.0%</td>
<td>5.0 - 9.9%</td>
<td>10.0 - 19.9%</td>
<td>=&gt; 20.0%</td>
<td>- - - - - - -</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>&lt; 116</td>
<td>116 - 160</td>
<td>161 - 250</td>
<td>251 - 500</td>
<td>&gt; 500 or ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>&gt; 64</td>
<td>55 - 64</td>
<td>40 - 54</td>
<td>30 - 39</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Amylase</td>
<td>WNL</td>
<td>&lt; 1.5 X N</td>
<td>1.5 - 2.0 X N</td>
<td>2.1 - 5.0 X N</td>
<td>&gt; 5.1 X N</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>&lt; 10.6</td>
<td>10.6 - 11.5</td>
<td>11.6 - 12.5</td>
<td>12.6 - 13.5</td>
<td>=&gt;13.5</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&gt; 8.4</td>
<td>8.4 - 7.8</td>
<td>7.7 - 7.0</td>
<td>6.9 - 6.1</td>
<td>&lt;= 6.0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>&gt; 1.4</td>
<td>1.4 - 1.2</td>
<td>1.1 - 0.9</td>
<td>0.8 - 0.8</td>
<td>&lt;= 0.5</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>WNL</td>
<td>0.99 - 0.75 X N</td>
<td>0.74 - 0.50 X N</td>
<td>0.49 - 0.25 X N</td>
<td>&lt;= 0.24 X N</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>WNL</td>
<td>1.01 - 1.25 X N</td>
<td>1.26 - 1.50 X N</td>
<td>1.51 - 2.00 X N</td>
<td>&gt; 2.00 X N</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>WNL</td>
<td>1.01 - 1.66 X N</td>
<td>1.67 - 2.33 X N</td>
<td>2.34 - 3.00 X N</td>
<td>&gt; 3.00 X N</td>
</tr>
</tbody>
</table>

APPENDIX IV
<table>
<thead>
<tr>
<th><strong>RTOG Acute Radiation Morbidity Scoring Criteria</strong></th>
<th><strong>APPENDIX IV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>[0]</strong> SKIN</td>
<td><strong>[4]</strong> Ulceration, hemorrhage, necrosis</td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating</strong></td>
</tr>
<tr>
<td><strong>Tender or bright erythema, patchy moist desquamation / moderate edema</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[3]</strong> Confluent, moist desquamation other than skin folds, pitting edema</td>
<td></td>
</tr>
<tr>
<td><strong>MUCOUS MEMBRANE</strong></td>
<td><strong>Injection / may experience mild pain not requiring analgesic</strong></td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Patchy mucositis which may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia</strong></td>
</tr>
<tr>
<td><strong>Confluent fibrinuous mucositis / may include severe pain requiring narcotic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Ulceration, hemorrhage or necrosis</td>
<td></td>
</tr>
<tr>
<td><strong>EYE</strong></td>
<td><strong>Mild conjunctivitis with or without scleral injection / increased tearing</strong></td>
</tr>
<tr>
<td><strong>No change</strong></td>
<td><strong>Moderate conjunctivitis with or without keratitis requiring steroids &amp;/or antibiotics / dry eye requiring artificial tears / iritis with photophobia</strong></td>
</tr>
<tr>
<td><strong>Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Loss of vision (unilateral or bilateral)</td>
<td></td>
</tr>
<tr>
<td><strong>EAR</strong></td>
<td><strong>Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline</strong></td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Moderate external otitis requiring topical medication/ serous otitis media/ hypeacusis on testing only</strong></td>
</tr>
<tr>
<td><strong>Severe external otitis with discharge or moist desquamation / symptomatic hypeacusis/ tinnitus, not drug related</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Deafness</td>
<td></td>
</tr>
<tr>
<td><strong>SALIVARY GLAND</strong></td>
<td><strong>Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals</strong></td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Moderate to complete dryness / thick, sticky saliva / markedly altered taste</strong></td>
</tr>
<tr>
<td><strong>Severe dysphagia or odynophagia with dehydration or weight loss &gt;15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Acute salivary gland necrosis</td>
<td></td>
</tr>
<tr>
<td><strong>PHARYNX &amp; ESOPHAGUS</strong></td>
<td><strong>Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet</strong></td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet</strong></td>
</tr>
<tr>
<td><strong>Severe dysphagia or odynophagia with dehydration or weight loss &gt;15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Complete obstruction, ulceration, perforation, fistula</td>
<td></td>
</tr>
<tr>
<td><strong>LARYNX</strong></td>
<td><strong>Mild or intermittent hoarseness/ cough not requiring antitussive / erythema of mucosa</strong></td>
</tr>
<tr>
<td><strong>No change over baseline</strong></td>
<td><strong>Persistent hoariness but able to vocalize / referred ear pain, sore throat, patchy fibrotous exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive</strong></td>
</tr>
<tr>
<td><strong>Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>[4]</strong> Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary</td>
<td></td>
</tr>
<tr>
<td><strong>UPPER G.I.</strong></td>
<td><strong>Anorexia with &lt;= 5% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &amp;/or vomiting requiring tube or parenteral support/ abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)</strong></td>
</tr>
<tr>
<td><strong>No change</strong></td>
<td><strong>Anorexia with &lt;=15% weight loss from pretreatment baseline/ nausea &amp;/or vomiting requiring tube or parenteral support/ abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)</strong></td>
</tr>
<tr>
<td><strong>[4]</strong> ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/ abdominal pain requiring tube decompression or bowel diversion.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0]</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>LOWER G.I.</td>
<td>No change</td>
</tr>
<tr>
<td>INCLUDING PELVIS</td>
<td></td>
</tr>
<tr>
<td>LUNG</td>
<td>No change</td>
</tr>
<tr>
<td>GENITOURINARY</td>
<td>No change</td>
</tr>
<tr>
<td>HEART</td>
<td>No change over baseline</td>
</tr>
<tr>
<td>CNS</td>
<td>No change</td>
</tr>
<tr>
<td>HEMATOLOGIC</td>
<td></td>
</tr>
<tr>
<td>WBC (X 1000)</td>
<td></td>
</tr>
<tr>
<td>PLATELETS</td>
<td></td>
</tr>
<tr>
<td>(X 1000)</td>
<td></td>
</tr>
<tr>
<td>NEUTROPHILS</td>
<td></td>
</tr>
<tr>
<td>(X 1000)</td>
<td></td>
</tr>
<tr>
<td>HEMOGLOBIN</td>
<td></td>
</tr>
<tr>
<td>(GM %)</td>
<td></td>
</tr>
<tr>
<td>HEMATOCRIT</td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease and treatment related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

* ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.
<table>
<thead>
<tr>
<th>ORGAN/ TISSUE</th>
<th>0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt;10% linear measurement</td>
<td>Necrosis</td>
<td></td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucous</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Fibrosis</td>
<td></td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Mono, para quadriparesis</td>
<td></td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dysesthesia)</td>
<td>Seizures or paralysis; Coma</td>
<td></td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment; Severe glaucoma</td>
<td>Panophthalmitis; Blindness</td>
<td></td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Necrosis</td>
<td></td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Severe respiratory insufficiency; Continuous O2; Assisted ventilation</td>
<td></td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low O2R</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Tamponade; Severe heart failure; Severe constrictive pericarditis</td>
<td></td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilatation required</td>
<td>Necrosis; Perforation; Fistula</td>
<td></td>
</tr>
<tr>
<td>SMALL/ LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily; Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;6 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding; requiring surgery</td>
<td>Necrosis; Perforation; Fistula</td>
<td></td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis; Hepatic coma or encephalopathy</td>
<td></td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg/dL; Creatinine 1.5-2.0 mg/dL; Creatinine clearance &gt;75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60 mg/dL; Creatinine &gt;4.0 mg/dL (50-74%)</td>
<td>Severe albuminuria; Severe hypertension; Persistent anemia (&lt;10g%); Severe renal failure; Urea &gt;60 mg/dL; Creatinine &gt;4.0 mg/dL; Creatinine clearance &lt;50%</td>
<td>Malignant hypertension; Uremic coma; Urea &gt;100%</td>
<td></td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria; Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt;150 cc)</td>
<td>Necrosis; Contracted bladder (capacity &lt;100 cc); Severe hemorraghic cystitis</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
<td>Necrosis; Spontaneous fracture</td>
<td></td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis; Complete fixation</td>
<td></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. **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 Report by phone to RTOG Headquarters and the Study Chairman within 24 hours
investigational agent.

- 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.

**A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

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.

** See attached NCI Adverse Drug Reaction Reporting Form
ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:
- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:
- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:
- you're not certain the product caused the event
- you don't have all the details

Report product problems — quality, performance or safety concerns such as:
- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:
- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:
- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 for more information or to report quality problems
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:
Reports Clearance Officer, PHS
Hubert H. Humphrey Building,
Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
ATTN: PRA

and to:
Office of Management and Budget
Paperwork Reduction Project
9010-0230
Washington, DC 20503

Please do NOT return this form to either of these addresses.