RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-05

PHASE II STUDY OF POSTOPERATIVE ADJUVANT THERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE II AND STAGE IIIA NON-SMALL CELL LUNG CANCER

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SCHEMA

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PROTOCOL TREATMENT PLAN:

*Concurrent XRT*

50.4 Gy/28 fractions/6 weeks
(1.8 Gy/day 5 days/week)
10.8 Gy/6 fractions boost to nodal stations if extracapsular extension of nodal metastases

*Chemotherapy to begin within 24 hours of initiation of XRT*

Carboplatin
AUC = 5 mg/m^2/min over 30-60 minutes IV, days, 1, 22 (cycles 1 and 2)
AUC = 6 mg/m^2/min over 30-60 minutes IV days 43, 64 (cycles 3 and 4)*

Paclitaxel
3 hr infusion days 1, 22, 43, 64
135 mg/m^2 with XRT (cycles 1 and 2)
225 mg/m^2 (cycles 3 or 4)*

*If radiation boost to be given, cycle 3 will be delayed until completion of the radiation therapy.

Eligibility: (See Section 3.0 for details)

- Patients with Stage II and IIIa NSCLC which has been surgically resected,
- KPS ≥ 70,
- Post-op FEV ≥ 1.0,
- ANC ≥ 2000, platelets ≥ 100,000, serum creatinine ≤ 1.5 mg/dl,
- ≥ 18 yrs of age
- Signed study-specific consent form

Required Sample Size: 79 (4/17/98)
1. Has a diagnosis of non-small cell of the lung been histologically confirmed?  
2. Is patient 18 years or older?  
3. Is the surgery in compliance with Section 8.0 of the protocol?  
4. What was the stage at the time of surgical resection?  
5. Were contralateral mediastinal lymph nodes sampled?  
   Yes, were the locations designated according to the map in Appendix VI?  
   If no, were there no nodes or were there nodes less than 1 cm visible on the contrast CT scan?  
6. Are all bronchial and vascular margins negative?  
7. Does this patient have bronchioalveolar carcinoma with lobar or multi-lobar involvement?  
8. Was all gross disease resected?  
9. Any evidence of superior vena cava syndrome?  
10. Does patient have any medical contraindications to chemotherapy, surgery or irradiation?  
11. Has each of the attending physicians (medical oncologist, thoracic surgeon, radiation oncologist) approved the stage?  
12. Has patient had any prior malignancy other than surgically treated carcinoma in situ of the cervix and squamous or basal cell of the skin within the past 5 years?  
13. Has patient received any prior chemotherapy, thoracic radiation, or immunotherapy within 5 years of study entry?  
14. Will protocol therapy begin within the time frame specified in Section 6.0?  
15. Is patient's Karnofsky ≥ 70?  
16. Is patient's ANC ≥ 2000?  
17. Are patient's platelet ≥ 100,000?  
18. Is serum creatinine ≤ 1.5 mg/dl or clearance creatinine > 60 ml/min?
19. Are the results of the postoperative pulmonary function tests in compliance with Section 3.1.7? 

20. Were laboratory values obtained within 2 weeks prior to registration?

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

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?

Patient’s Name
Verifying Physician
Patient ID #
Referring Institution # (if different)
Medical Oncologist
Provide T classification
Is there pathologic proof of extracapsular spread in a mediastinal node?
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 ___________________________
Lung cancer is the most common cause of death due to cancer in both men and women in the United States.\textsuperscript{1} Surgical resection of the cancer offers the patient the best chance for cure. Thirty percent of patients are able to undergo apparent complete resection of their disease.\textsuperscript{2} Based on the staging system for lung published in 1986,\textsuperscript{3} patients with pathologic stage II and IIIa have a 5-year survival of 30-60% and 15-29% respectively.\textsuperscript{4,7}

Despite surgery for “cure” in patients with lung cancer, treatment failures occur. Such failures are either local-regional recurrences, distant metastases or a combination of both. Because of these failures, the use of adjuvant therapies have been evaluated in patients with pathologic stage II and III disease.

The Lung Cancer Study Group reported the results of three randomized studies which suggested that adjuvant therapy could potentially improve survival in surgically resected lung cancer patients. Local regional control was dramatically improved with postoperative radiotherapy. However, this did not translate into a survival benefit. What was needed was “effective” systemic therapy. Etoposide plus cisplatin was felt to be that systemic therapy.

In 1991, RTOG began their participation in an intergroup randomized study (\textit{INT 0115}) evaluating postoperative adjuvant therapy in patients with completely resected stage II and stage IIIa NSCLC. The study compared thoracic radiation therapy to concurrent thoracic radiation therapy plus etoposide/cisplatin. A total of four cycles of chemotherapy was administered. The study was closed in December 1996. The data is being analyzed. Until the data of the intergroup study is known, the next generation of adjuvant therapies for patients with resectable NSCLC needs to be developed using newer state-of-the-art systemic chemotherapy agents along with thoracic radiotherapy.

One of the new drugs effective against NSCLC is paclitaxel. In two studies utilizing paclitaxel 250 mg/m\textsuperscript{2} given as a 24-hour infusion in patients with metastatic NSCLC, the overall response rate was 21% and 24% with 1-year survival of 40% and 38.5% respectively.\textsuperscript{11,12} In an ECOG randomized advanced NSCLC study comparing standard therapy with etoposide plus cisplatin vs. cisplatin plus low dose paclitaxel to high dose paclitaxel plus cisplatin along with G-CSF, the response rates for the three regimens were 12% 26% and 31% respectively ($p < 0.05$); Median Survival was 7.4 months, 9.6 months and 10 months respectively.\textsuperscript{13}

Carboplatin is felt to be equivalent to cisplatin in its activity in NSCLC especially in regard to survival rates. However, the drug has significantly less non-hematologic toxicity especially neurotoxicity. Because of the neurotoxicity associated with the paclitaxel plus cisplatin regimen, the combination of paclitaxel plus carboplatin has been evaluated in NSCLC.\textsuperscript{14-19}

Three studies evaluated paclitaxel given as a 24-hour infusion along with carboplatin\textsuperscript{14-16} in patients with lung cancer. The overall response rate ranged from 39%-62%. In two studies the median survival was 38 and 54 months with the 1-year survival of 41% and 54%.\textsuperscript{14,15} Three studies evaluated paclitaxel given as a 3-hour infusion along with carboplatin.\textsuperscript{17-19} The response rates ranged from 47%-65%.

A study has been conducted which utilized concurrent radiation therapy with paclitaxel and carboplatin to treat locally advanced NSCLC.\textsuperscript{20} Induction chemotherapy was given with paclitaxel 175 mg/m\textsuperscript{2} as a 3-hour infusion followed by carboplatin AUC of 7.5. G-CSF was given. Following 2 cycles of induction therapy, starting on day 43, thoracic radiotherapy 60 Gy/30 fraction/5 days per week was initiated with concurrent chemotherapy. Paclitaxel 135 mg/m\textsuperscript{2} was given on days 43 and 64 with radiation therapy with no dose limiting toxicity. The carboplatin was dosed at an AUC of 6.25. One episode of grade 4 esophagitis occurred at the completion of the thoracic radiation therapy and 3 episodes of delayed grade 3 steroid responsive pulmonary toxicity occurred 2-6 months after completion of all treatment.

Based on the above information, adjuvant therapy utilizing paclitaxel given as a 3-hour infusion along with carboplatin and concurrent thoracic radiation therapy will be evaluated in patients with completely resected stage II and IIIa NSCLC.
2.0 OBJECTIVES

2.1 To determine the progression-free and overall survival in patient with completely resected stage II and IIIa NSCLC treated with paclitaxel plus carboplatin combined with thoracic radiotherapy.

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

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologic documentation of non-small cell lung cancer.

3.1.2 Stage II ($T_1$-$T_2N_1M_0$) or Stage IIIa ($T_1$-$T_2N_2M_0$, $T_3N_0M_0$, $T_3N_1$-$T_3N_2M_0$) disease according to the International Staging System Criteria (Appendix III). A pathologic diagnosis of Stage II/IIIa must have been made at the time of surgical resection (i.e., by postoperative pathologic diagnosis) to be included in the study.

3.1.2.1 Cervical mediastinoscopy is required for any patient whose CT scan shows a mediastinal lymph node $\geq 1.5$ cm in cross-sectional diameter. If the tumor is in the left upper lobe or left hilar region, level 5/6 lymph nodes with a cross-sectional diameter $\geq 1.5$ cm must be biopsied by extended mediastinoscopy or thoracoscopy. A complete cervical mediastinal staging includes nodal stations 2R, 4R, 10R, 7, 10L, or 4L, 2R if possible. At minimum, three stations must be sampled: one ipsilateral, 7 and one contralateral. If microscopic disease is present in one mediastinal nodal level, the patient is eligible for the study. If more than one level has tumor, or if extranodal disease is present in even one level, the patient is not eligible. Patients who are NOT required to undergo cervical mediastinoscopy and who are found to have extranodal disease at the time of surgical biopsy are eligible.

3.1.3 Surgery consisting of lobectomy, sleeve resection, bilobectomy or pneumonectomy, as determined by the attending surgeon based on the intraoperative findings.

3.1.3.1 Surgery within 56 days prior to adjuvant therapy.

3.1.4 A complete nodal dissection is recommended but not required. For right thoracotomy lesions, the minimal mediastinal lymph nodes that must have been biopsied or resected include levels IV, VII and X (Appendix VI). For left thoracotomy tumors, the minimum required for dissection of the mediastinum must include levels V, VI and VII. All surgical margins of resection must be negative for tumor.

3.1.5 Karnofsky performance status of $\geq 70$.

3.1.6 Consults by an attending thoracic surgeon, medical oncologist, and radiation oncologist.

3.1.7 Post operative FEV$_1$ ($\geq 1.0$) sufficient for patient to tolerate protocol radiation therapy.

3.1.8 ANC $\geq 2000$ and platelet count $\geq 100,000$; serum creatinine $\leq 1.5$ mg/dl or creatinine clearance $> 60$ ml/min. Laboratory values must be obtained $\leq 2$ weeks prior to registration.

3.1.9 $\geq 18$ years of age.

3.1.10 Signed study-specific informed consent.

3.1.11 N2 pre-operative patients should be considered for the NCI High Priority Study, RTOG 93-09 (INT 0139).

3.2 Conditions for Patient Ineligibility

3.2.1 Prior chemotherapy (other than topical therapy), prior thoracic irradiation, or prior immunotherapy within 5 years of study entry.

3.2.2 No prior or concurrent malignancies other than surgically treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin are allowed within the preceding five years.

3.2.3 Medical contra-indication to chemotherapy, surgery, or irradiation.

3.2.4 The presence of Stage IIb (i.e., contralateral N2 or N3) disease or Stage IV (M1) disease.

3.2.5 Incompletely resected gross disease.

3.2.6 Microscopic positive bronchial or vascular margins.
3.2.7 Small cell lung carcinoma (including “mixed” histology).
3.2.8 Bronchioalveolar carcinoma with lobar or multi-lobar involvement.
3.2.9 Karnofsky performance status < 70.
3.2.10 Superior vena cava syndrome.
3.2.11 Surgery performed more than 8 weeks (56 days) prior to start of RT.

4.0 PRETREATMENT EVALUATION

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

4.2 Laboratory studies will include a CBC with differential, platelet count, LFTs, electrolytes, creatinine, magnesium, total protein, albumin and urinalysis done within 2 weeks (14 calendar days) before study entry. Creatinine clearance is required if serum creatinine > 1.5 mg/dl.

4.3 Chest X-ray, EKG, CT scans of brain (for neurologically symptomatic patients), chest, upper abdomen to include liver and adrenals. radionuclide bone scan (mandatory for symptomatic patients or alkaline phosphatase ≥ 2 x upper normal), are required within 6 weeks prior to definitive surgery. Maximum interval between scans and start of RT is 14 weeks.

4.4 PFTs must be obtained postoperatively since it is required for RT planning.

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. Patients may also be registered via computer modem 24 hours a day, 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY

Radiation therapy is to be initiated no earlier than 4 weeks following pneumonectomy or sleeve resection. Following a lobectomy or bilobectomy, radiation therapy is to begin ≥ 14 days post surgery. Radiation therapy must begin by no later than 8 weeks after surgery.

6.1 Equipment

All patients will be treated with isocentric equipment with a minimum SAD of 80 cm. Treatment should be given with photon energies of 4-18 MeV. The use of electron beams is not permitted.

6.2 Treatment Planning

All patients must be simulated prior to the start of radiation therapy. Both the initial portion of treatment, which is to be given with AP/PA portals and the off-cord boost to be given with lateral and/or oblique portals should be simulated at this time with the patient in the same position for both phases of treatment to facilitate the construction of composite isodose plans. Portal verification films should be taken of each field copied and submitted for review. The use of custom immobilization and support devices such as styrofoam molds is encouraged but not required. A CT scan of the chest for radiation treatment planning may suffice for the postoperative scan.

6.3 Target Volume

The desired target volume for treatment on this study will encompass the mediastinal and ipsilateral hilar nodes. The tumor bed is to be included only if invasion of the parietal pleura is documented in the operative pathology report. The target volume is thus to be defined in terms of anatomic landmarks rather than the preoperative appearance of the tumor. A postoperative CT scan is
required to document post surgical anatomic changes and to serve as a baseline study for comparison with follow-up studies. The target volume will include the hilum ipsilateral to the primary tumor as well as bilateral peritracheal nodes. Neither the contralateral hilum nor the supraclavicular fossae are to be included on a routine basis. If, however, it is necessary to treat the tumor bed for a T3 lesion of the upper lobe, the supraclavicular fossa may be included. The exact placement of the field borders will vary somewhat from case to case depending on the postoperative shift of the mediastinal structures. See Appendix VII for suggested radiation fields for initial AP/PA portals. The following are guidelines:

6.3.1 Superior border at the level of the lung apex (*typically about C5*) for patients with N1 disease. Supraclavicular fossa for patients with N2 disease.

6.3.2 Inferior border - 5 cm below the carina for upper lobe lesions and 8 cm below the carina for lesions of the lower or middle lobe, or for lesions of any primary site if the subcarinal nodes are histologically involved.

6.3.3 Ipsilateral border - 2 cm beyond the tracheal edge and encompassing the ipsilateral hilum with a 2 cm margin. In patients who have undergone pneumonectomy, the bronchial stump and associated peribronchial nodes should be included with margins based on the preoperative appearance of the hilum.

6.3.4 Contralateral border - 2 cm lateral to the edge of the trachea as defined on the postoperative simulator film and CT scan.

6.3.5 In patients in whom nodal (*N1 or N2*) disease breaches the nodal capsule, these nodal stations as mapped on the intraoperative staging forms, and not the entire mediastinum, will be included in a boost field which should encompass the nodal region with 1 cm margins.

6.4 Treatment Technique

6.4.1 The initial portion of the treatment will be given with parallel opposed AP/PA portals with equal weighing. These will typically be used for approximately 36-42 Gy of the planned total of 50.4 Gy to the full mediastinal volume.

6.4.2 To deliver the remainder up to 50.4 Gy, the same mediastinal target volume will be used excluding the spinal cord from high dose region. The spinal cord should not receive greater than 45 Gy. Specifically, the supraclavicular areas should be excluded from the oblique field. Oblique fields using angles between 20 and 40 degrees, with medial borders defined by the ipsilateral pedicle of the spine and including the subcarinal space and contralateral mainstem bronchus, are the preferred method. Lateral fields may be used, but for no more than 10 Gy. Direct posterior spinal cord shields are not acceptable.

6.4.3 If the boost is required (*Section 6.5*), then the target volume should be reduced to include only the involved lymph node area or area of T3 invasion plus a 1 cm margin.

6.5 Dose

The entire mediastinal target volume will receive 50.4 Gy/28 fractions/6 weeks/daily. 1.8 Gy once a day for 5 weeks. Patients requiring mediastinal boost of 10.8 Gy in 6 fractions include: (1) patients with pathologically documented extracapsular extension of the nodal metastasis and (2) T3 lesions. This boost is not optional.

6.5.1 Dose will be prescribed to the midplane for AP/PA treatment and to the isocenter for oblique and/or lateral treatment.

6.5.2 Dose inhomogeneity corrections (*lung corrections*) will NOT be used.

6.5.3 The dose inhomogeneity across the target volume in the central transverse plane will be no more than +/- 5%. A composite isodose distribution will be calculated, copied and submitted in one transverse plane at the central axis.

6.5.4 Tissue compensators for sloping chest surfaces are required if separations measured from top-to-bottom of the field result in variations in top-to-bottom dose of ≥ 10%, or if the slope between the upper and lower borders has a difference in depth of ≥ 2 cm.

6.6 Suggested Maximum Doses to Critically Sensitive Normal Structures

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<th>Organ</th>
<th>Maximum Dose</th>
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Spinal Cord 45 Gy
Heart Not more than 35 Gy to > 50% cardiac volume
Lung 20 Gy to entire lung
Esophagus Will tolerate doses required by protocol

6.7 Treatment Interruption
The majority of treatment induced esophageal complaints occur between week 2 and 3 of treatment. Dietary and medicinal regimens of local choice are encouraged. The majority of these complaints are self-limited and do not require breaks, which are specifically discouraged. Indications for interruption include > 10% weight loss and the inability to swallow solids and liquids (all 3 parameters required). In this event, chemotherapy should NOT be delayed. Radiation therapy should not be held for neutropenia, thrombocytopenia or anemia. Please call Dr. Mary Graham (314) 362-8503 with questions.

6.8 Treatment is to be given 5 days per week, once each day. If there are holidays, equipment failure, or treatment interruption, the treatment should recommence as early as possible, and the cause of the delays documented.

7.0 DRUG THERAPY

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

7.1 Treatment Plan (3/17/98)

7.1.1 Cycles 1 and 2: Patients will receive chemotherapy concurrently with radiotherapy.

7.1.1.1 Paclitaxel: 135 mg/m² intravenously over 3 hours on day 1. The drug is administered first, before other chemotherapeutic agents are administered.

Premedication: All patients must receive premedication prior to paclitaxel in order to reduce the risk of hypersensitivity reactions. Patients must receive dexamethasone 20 mg p.o. 12 and 6 hours before paclitaxel, diphenhydramine 50 mg intravenously 60 minutes prior to paclitaxel and cimetidine 300 mg intravenously (or equivalent, ranitidine 50 mg or famotidine 20 mg) 60 minutes prior to paclitaxel.

Drug Administration: Following premedication, patients will receive paclitaxel. The drug will be mixed in 500 cc 0.9% sodium chloride and administered by continuous i.v. infusion over 3 hours.

7.1.1.2 Carboplatin (AUC 5.0): intravenously on day 1

The Calvert formula will be used to calculate the Carboplatin dose (mg).

Carboplatin dose (mg) = AUC x (GFR + 25) The Cockroft-Gault formula can be used to calculate the creatinine clearance (CCR) which can be substituted for the GFR in the Calvert formula.

Calculate C_{CR} = \left(\frac{140 - \text{patient's age}}{\text{patient's weight in kilograms}}\right) \times 72 \times \text{patient's serum creatinine}

(For females, multiply the result by 0.85).

Calculations are to be based upon the serum creatinine value on the day of treatment (or within two days of treatment) for each cycle 1-4.

Drug Administration: Immediately following paclitaxel, and immediately before use, the content of each vial of carboplatin must be reconstituted with either sterile water, 5% Dextrose in water of 0.9% Sodium Chloride and administered over 30-60 minutes.

7.1.2 Cycles 3 and 4: Patients will receive chemotherapy without radiotherapy. Cycle 3 to start 21 days after cycle number 2 of chemotherapy.

7.1.2.1 If radiation boost is required, delay start of cycle 3 until radiation therapy is completed.

7.1.2.2 Paclitaxel 225 mg/m² intravenously over 3 hours on day 1.

7.1.2.3 Carboplatin (AUC 6.0) intravenously over 30-60 minutes immediately following the administration of paclitaxel.

7.2 Chemotherapy

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

7.2.2 G-CSF may be given S.C. or I.V. at 5 \mu g/kg/d to protect against new episodes of febrile neutropenia in cycles 3-4 of chemotherapy in patients who have experienced such a complication. Alternately,
a dose reduction can be instituted as noted in Section 7.6.2.1 and 7.6.3. The G-CSF will not be given in cycles 1 and 2 when radiation therapy is also administered.

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

7.2.4 Amifostine may not be given in this study.

7.3 Paclitaxel (Taxol®) (NSC-125973)

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

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

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

7.3.4 Human Toxicology: The dose limiting toxicities and MTD of paclitaxel administered on a variety of schedules to patients with solid neoplasms was previously evaluated in phase I trials. In these studies, paclitaxel was infused over 1, 3, 6, and 24 h, but severe acute reactions, characterized by bronchospasm, hypotension, stridor, tachy- and bradyarrhythmias, and death, resulted in the temporary discontinuation of all trials. These reactions were attributed to paclitaxel's Cremophor vehicle, since identical reactions were observed with other drugs formulated with it and when the vehicle alone was administered to animals. Since a higher incidence of these acute reactions were observed with shorter duration of infusion, studies that used shorter infusions were permanently discontinued, and trials that evaluated longer infusion durations (24 h) were resumed using antiallergic pre-medications consisting of corticosteroids, H₁ and H₂ histamine antagonists. These modifications were associated with a marked reduction in the incidence of acute reactions. Neutropenia was the major dose-limiting toxicity for paclitaxel in phase I solid tumor trials. In addition, a sensory neuropathy, characterized by a glove-and-sock distribution of numbness and paresthesias, was observed at higher doses. Nausea and vomiting, myalgias, mucositis, total-body alopecia, diarrhea, and phlebitis were also observed. The MTD and recommended phase II doses of paclitaxel administered as a 6-h infusion were 265 and 212 mg/m², respectively, and 275 and 250 mg/m², respectively, as a 24-h infusion.

7.3.5 Formulation: Paclitaxel (Taxol®) for Injection Concentrate is a clear colorless to slightly yellow viscous solution. It is supplied as a solution in a nonaqueous infusion. Paclitaxel is available in 30 mg (5mL) vials. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor®EL (polyoxyethylated castor oil) and 49.7% 9 (v/v) dehydrated alcohol, USP.

7.3.6 Storage and Stability: Unopened vials of paclitaxel for Injection Concentrate are stable until the date indicated on the package when stored at 2°-25°C (36°-77°F). Refrigeration is not required for shipping provided the temperature falls within this range. Freezing does not adversely affect the
concentrate. Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.

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

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

7.4 **Carboplatin (Paraplatin) (NSC-241240)**

7.4.1 **Chemistry:** Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0’]- (SP-4-2). Carboplatin is a crystalline powder with the molecular formula of C₆H₁₂N₂O₄Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/ml, and the pH of a 1% solution is 5-7.

7.4.2 **Mechanism of Action:** Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links. This effect is apparently cell-cycle non-specific.

7.4.3 **Animal Tumor Data:** It is active against several National Cancer Institute tumor panel malignancies including B16 melanocarcinoma, CD8F1 mouse mammary carcinoma, murine colon 26 adenocarcinoma and human breast carcinoma xenografts.

7.4.4 **Human Toxicology:** In phase I trials, carboplatin was not associated with significant neurotoxicity or nephrotoxicity as was in the case of cisplatin. The dose-limiting toxicity of carboplatin is myelosuppression, particularly thrombocytopenia. Carboplatin can be administered without hydration. It is associated with less nausea and vomiting compared with cisplatin. Carboplatin is not significant toxic to the kidneys, however, pretreatment renal function markedly affects the severity of carboplatin-induced thrombocytopenia. Thrombocytopenia more prevalent in patients whose pretreatment glomerular filtration rate (GFR) was reduced. Approximately 70% of an administered dose of carboplatin is excreted in the urine. The renal clearance of carboplatin is closely correlated with the GFR. A dosage formula has been derived from a retrospective analysis of carboplatin pharmacokinetics in patients with various pretreatment GFRs. The formula is known as the Calvert formula (Carboplatin dose (mg) = AUC x (GFR + 25) [for females, multiply the results by 0.85].

7.4.5 **Formulation:** Carboplatin (paraplatin) is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Immediately before use the content of each vial must be reconstituted with either sterile water, 5% Dextrose in water or 0.9% sodium chloride. Vial strengths of 50 mg, 150 mg and 450 mg will be diluted with a volume of 5 ml, 15 ml, 45 ml respectively to produce a carboplatin concentration of 10 mg/ml.

7.4.6 **Storage and Stability:** Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature (59°F-86°F) and protected from light. When prepared, carboplatin solutions are stable for 8 hours at room temperature.

7.4.7 **Administration:** Carboplatin should be given after paclitaxel administration as per Section 7.1.1.2.

7.4.8 **Supplier:** Carboplatin is commercially available and should be obtained through a third party. The drug will not be supplied by the NCI.

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

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

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

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

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

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

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

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

7.6 Toxicities to be Monitored and Dosage Modifications

7.6.1 Concomitant Chemoradiotherapy (cycle 1-2) Dose Modifications

7.6.1.1 If patients during cycle 1 have grade 4 hematologic toxicity (excluding grade 4 lymphopenia) or grade 3-4 mucositis, stomatitis, esophagitis or other significant radiotherapy related toxicity, patients receiving cycle 2 would receive 100 mg/m² of paclitaxel and carboplatin (AUC of 4) during the administration of the radiation therapy. See Section 7.6.3.

7.6.2 Dose Modifications for Day 1 of Each Chemotherapy Cycle (cycles 3-4)

7.6.2.1 For hematologic toxicity

<table>
<thead>
<tr>
<th>Granulocyte Nadir</th>
<th>Platelet Nadir</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 &lt; 5 days and</td>
<td>&gt; 50,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 &gt; 5 days or</td>
<td>&lt; 50,000</td>
<td>Decrease 1 level (see Section 7.6.3)</td>
</tr>
<tr>
<td>Infection or</td>
<td>Bleeding</td>
<td>Decrease 1 level (see Section 7.6.3)</td>
</tr>
</tbody>
</table>

In the case of febrile neutropenia, G-CSF may be used in subsequent cycles as an alternative to dose reduction in the absence of other dose limiting toxicity.

7.6.2.2 For non-hematologic toxicity (excluding alopecia, nausea and vomiting)

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

7.6.3 Definition of Dose Levels

Dose Level 0 is the Dose Level for all patients for Cycle 3 (first post radiotherapy cycle)

Drug               Dose Level:
-------------------:-------------------:---:---
                    0                     -1   -2
PACLITAXEL (Day I, IV) 225 mg/m² 135 mg/m² 100 mg/m²
carboplatin (Day I, IV) (AUC 6) (AUC 5) (AUC 4)

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

7.7.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.7.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.7.1.3 Any death on study if clearly related to the commercial agent(s).
7.7.1.4 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.

7.7.2 The ADR report should be documented on Form FDA 3500 and mailed to:
Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
(301) 230-2330 available 24 hours

7.7.3 Special Reporting for this Study (fax 215/928-0153)
7.7.3.1 All grade ≥ 3 non hematologic toxicities must be reported to RTOG within 24 hours.
7.7.3.2 All grade ≥ 4 hematologic toxicities except lymphopenia must be reported to RTOG within 24 hours.
7.7.3.3 Data submission must adhere to the timetable specified in Section 12.0 and the patient calendar issued by RTOG.

8.0 SURGERY (PRE REGISTRATION)
8.1 Accurate intraoperative surgical staging will be ensured by strict attention to the anatomic boundaries between nodal groups described by the American Thoracic Society regional nodal stations definitions (Appendix VI).

8.1.1 A pathologically complete surgical resection of the tumor mass by lobectomy, bilobectomy, sleeve resection, or pneumonectomy will be performed.

8.1.2 A complete mediastinal lymph node dissection or nodal sampling is recommended but not required. Complete lymph node dissection is recommended. Complete lymph node dissection involves removing all lymph nodes of the anatomically defined level. Lymph node sampling necessitates opening the pleura and removing representative tissue from each lymph node level. All nodal tissue obtained must be carefully labeled by lymph node level. This must be performed by the operating surgeon in the operating room. Complete mediastinal dissection or sampling includes the following nodal levels:
- Levels 2 and 4*
- Levels 8
- Levels 5 and 6 in all patients when the primary lesion is located in the left lung
- Level 7
- Level 9
- Level 10

*It is recognized that Levels 2L and 4L are often difficult to dissect.

All ipsilateral lymph node levels 11-13 should be removed en bloc with the primary surgical specimen. In addition, any lymph nodes which are not mentioned above but which appear grossly abnormal at surgery should be removed and their locations identified. The presence or absence of evidence of invasion of the nodal capsule must be noted on the pathology reports for hilar and/or mediastinal nodes. Patients in whom there is extracapsular extension of nodal metastases will have these nodal stations boosted with an additional 10.8 Gy in 6 fractions.

9.0 SUPPORTIVE THERAPY
9.1 All supportive measures consistent with optimal patient care will be given throughout the study.
9.2 The use of non protocol radiotherapy and corticosteroids should be clearly indicated on the flow sheets, as should dose and reason for continuation.
9.3 Hyperalimentation may be used, but details must be clearly outlined on data forms.

10.0 PATHOLOGY
Not applicable to this study.

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters (3/17/98)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Registration</th>
<th>Weekly During XRT</th>
<th>Every 3 weeks During CTX</th>
<th>Follow-Up</th>
<th>At Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; PE, KPS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CBC, Differential,</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Platelet Count</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LFTs(^a)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lytes, Mg(^++)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray, PA &amp; Lateral</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre-Registration</th>
<th>Weekly During XRT</th>
<th>Every 3 weeks During CTX</th>
<th>Follow-Up</th>
<th>At Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest CT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head CT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PFTs</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis (micro)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: When filling out these pre-study results on the RTOG flow sheets, please make sure that ALL relevant dates are clearly given. Record the actual dates. Do NOT put all the results under the date for Day 1 of protocol treatment unless they were actually done that day.

a. LFTs = bilirubin, SGOT, alkaline phosphatase, LDH.
b. Must be obtained post operatively and is required for radiation therapy planning, however, a CT simulation may suffice for radiation therapy planning. This scan does not have to be done prior to entering the study.
c. Abdominal CT not necessary if a chest CT includes the entire liver and the adrenal glands. Any adrenal gland showing loss of normal contour, regardless of size, must be biopsied.
d. Head CT is required only in neurologically symptomatic patients. At relapse, patients should undergo a head CT scan to document status of CNS only if they are neurologically symptomatic.
e. A pre-registration bone scan is desirable but not required in an asymptomatic patient with a normal alkaline phosphatase. A bone scan is required if the patient has bone tenderness or bone pain or an alkaline phosphatase twice the upper limits of normal or higher.
f. CBC, differential, and platelet count should be obtained weekly during XRT and weekly during chemotherapy following completion of XRT.
g. PFTs should be obtained prior to the initiation of XRT. In addition, repeat PFTs should be obtained at the first follow-up visit upon completion of XRT, and 1 year after completion of XRT.

h. Obtain chest CT if symptoms. If no symptoms, obtain chest CT every 6 months years 1 and 2, every 12 months thereafter up to 5 years.

i. Obtain if serum creatinine > 1.5 mg/dl.

j. Lytes = Nx, K, Cl, BUN, HCo3.

k. As clinically indicated.

l. These tests should be done within 48 hours of the day of chemotherapy.

m. Prior to chemotherapy for each cycle.

11.2 Evaluation During Study

11.2.1 Patients will be followed on days 8, 15 and before each cycle with CBC, differential and platelet count.

11.2.2 A brief interim history and directed physical examination will be done weekly regarding radiation-related toxicity.

11.2.3 History and physical with performance status and weight will be recorded before each course of chemotherapy.

11.2.4 Electrolytes, magnesium, and urinalysis with microscopic analysis will be performed before each course.

11.2.5 Chest x-ray will be performed before each course of chemotherapy.

11.2.6 All relevant information regarding drug dosage, laboratory data and treatment-related toxicity must be recorded on the data forms.

11.3 Duration of Therapy

11.3.1 Patients will receive 4 cycles of adjuvant chemotherapy. Regardless of the actual number of cycles of chemotherapy received, all patients will be evaluated for toxicity and survival.

11.3.2 Development of local, regional or distant recurrence (including CNS metastases) is grounds for discontinuing study treatment. This must be documented on the data forms. Biopsy of recurrence is encouraged.

11.3.3 Unacceptable toxicity from therapy despite attempts to modify toxicity of treatment will constitute grounds for a patient’s discontinuation of treatment. This must be documented on the data forms.

11.4 Measurement of Effect

Outcome measures will include recurrence, disease-free survival, survival and toxicity.

11.4.1 Recurrence

11.4.1.1 The development of a loco-regional and/or distant recurrence. Whenever possible, recurrence should be histologically confirmed. However, to confirm recurrence in some organs, invasive diagnostic procedures might be required. In this case biopsy may be deferred because the clinical course will clarify the time of recurrence in almost all patients. An abnormal chest, abdominal or head CT scan consistent with metastatic disease is considered sufficient evidence to document recurrent disease. Abnormal blood studies are not adequate for documentation of recurrence (e.g., elevated LFTs, CEA, etc.).

11.4.1.2 Definitions of Site of Recurrence
Local - within RT port
Chest - outside RT port
Distant - brain, other

11.4.2 Disease-Free Survival
Date of definitive resection to the date of first treatment failure (recurrence or death before recurrence). Survival is defined as the time from definitive resection until death.

11.4.3 Survival
The cause of death (cancer versus non-cancer related) should be documented and explained. Survival is measured from the date of definitive resection to the date of death.

11.5 Criteria for Going Off Protocol

11.5.1 Increasing disease at any time during therapy.

11.5.2 The development of unacceptable toxicity, which is defined as unpredictable, irreversible, or grade 4 (excluding myelosuppression).

11.5.3 Non compliance with protocol requirements.
11.5.4 Patient refusal or withdrawal of consent.

11.6 Data and Protocol Management

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

11.6.2 A brief explanation for required but missing data must be recorded.

11.6.3 Dr. Graham will be the final arbiter of responses or toxicity should a difference of opinion exist.

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

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

11.6.6 Patients who are found to be ineligible after enrolling onto the trial will be removed from the study. A letter will be sent to the institution by RTOG Headquarters to acknowledge the ineligible status.

12.0 DATA COLLECTION (3/17/98)

(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 1 week of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td></td>
</tr>
<tr>
<td>Surgical Op Note (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Path Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Study Specific Flowsheet (SF)</td>
<td>(must contain pre tx lab values)</td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
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<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Study Specific Flowsheet (SF)</td>
<td>With First F1 only</td>
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<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
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<tr>
<td>Study Specific Flowsheet (SF)</td>
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<td>Final Dosimetry Information:</td>
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<tr>
<td>Daily Treatment Record (T5)</td>
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<tr>
<td>Isodose Distribution (T6)</td>
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<td>Boost Films (simulation and portal) (T8)</td>
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<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from treatment start for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint will be progression-free survival.
Assess toxicity due to each treatment regimen.

**Sample Size** *(4/17/98)*

13.2.1 The one-year progression-free survival rate for completely resected stage II and IIa non-small-cell lung cancer patients treated with 50.4 Gy radiotherapy is assumed to 70%. The estimated sample size is 46 evaluable patients. Assuming this rate is the lowest one-year progression-free survival rate of interest and assuming any rate above 80% would warrant further investigation. This sample size will ensure 80% power to detect a 10% increase in one-year progression-free survival in relation to standard therapy with a one-sided test of size 0.20. Assuming a 5% ineligibility/inevaluability rate then 49 patients will be required.

13.2.2 Decreasing the one-sided test to 0.10 will increase the required number of evaluable patients to 75 and the total number required for this study to 79 patients.

**Patient Accrual** *(4/17/98)*

13.3.1 The patient accrual is projected at 4 cases per month, based upon the accrual to RTOG 91-05. Therefore, it will take 13 months to complete this study. If the average monthly rate is less than two cases, the study will be re-evaluated with respect to feasibility.

13.3.2 The observed accrual rate has been 6.6 patients per month. The total number of patients should be accrued within the above planned 13 month time period.

**Analyses Plans**

13.4.1 *Interim Analyses*

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

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

b) the quality of submitted data with respect to timeliness, completeness, and accuracy.

c) compliance rate of treatment delivery with respect to the protocol prescription.

d) the frequencies and severity of the toxicities.

Measures of treatment efficacy, such as progression rates and survival, will be reported only to the study chairperson, site chair, group statistician, and chairman of the strategy planning committee. Through examining the above items, the monitoring committee and the statistician can identify problems with the execution of the study. These will be reported to the RTOG committee responsible for this study and, if necessary, the Executive Committee, so that corrective action can be taken.

13.4.2 *Analysis for Reporting the Initial Treatment Results*

This major analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analyses with the reasons for exclusion.

b) institutional accrual.

c) distribution of the important prognostic baseline variables.

d) observed results with respect to the endpoints described in Section 13.1. Further subgroup analysis would not be undertaken because of the small sizes involved in each subgroup.

**Inclusion of Women and Minorities**

In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into inoperable lung trials failed to show any treatment interaction with gender.21 Others have shown gender to be a prognostic factor, but no treatment interactions have occurred.22,23 The RTOG found no difference in survival of non-small cell lung cancer patients by race.24 Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.
REFERENCES


APPENDIX I

RTOG 97-05

PHASE II STUDY OF POSTOPERATIVE ADJUVANT THERAPY IN PATIENTS
WITH COMPLETELY RESECTED STAGE II AND STAGE IIIA
NON-SMALL CELL LUNG CANCER

Sample Patient Consent Form

RESEARCH STUDY

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

PURPOSE OF THE STUDY

It has been explained to me that I have non-small cell lung cancer. I have been invited to participate in this research study. This study involves additional treatment following my surgery with radiation therapy and chemotherapy.

The purpose of this study is to determine if additional treatment after surgery can reduce the incidence of tumor recurrence and thereby prolong survival. To do this, I will receive radiation therapy plus chemotherapy following surgery. At the present time, individuals with completely removed non-small cell lung cancer are usually given no additional treatment or radiation therapy alone.

DESCRIPTION OF PROCEDURES

This study involves the administration of radiation therapy combined with chemotherapy following surgical removal of my lung cancer. The radiation therapy will consist of 28 daily treatments given 5 days per week over a 6-week period. The treatment will begin no later than 8 weeks and no sooner than 2 weeks after my surgery (depending on the type of surgery required to remove the tumor). Radiation treatment is given on an outpatient basis. Chemotherapy will consist of 4 cycles of two anticancer drugs, paclitaxel and carboplatin. Both drugs are administered into a vein. Both drugs are given on day 1 as an outpatient every three weeks. This will occur four times. The first two cycles of chemotherapy are given along with the radiation therapy.

Following completion of treatment, I will be followed on a regular basis by my physician.

RISKS AND DISCOMFORTS

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

Risks from Radiation Therapy

Chest Radiation Therapy may cause: 1) difficulty, pain or a burning sensation on swallowing. This effect usually begins after the second week of radiotherapy and goes away within 1 month of completion of radiotherapy; 2) fatigue - a tiredness without having done anything to make me tired. Also, a temporary effect which resolves within a month of completion of treatment; 3) skin damage within the port of radiation, the skin may develop a sunburn-like appearance which may itch, feel dry or burn slightly. Although skin color and the sunburn-like reaction resolves 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 predispose me to infection. Decreases in platelets may make me bleed or bruise easily; 5) scarring of the lung (i.e., radiation fibrosis) which may result in chronic shortness of breath and a cough.

**Risks from Chemotherapy:**

**Carboplatin (Paraplatin)** can lower the blood counts, which could cause an increased risk of infection, bleeding or tiredness. I might need antibiotics, hospitalization, and/or transfusions if the blood counts are severely lowered. It may cause nausea and vomiting, diarrhea, weight loss, fever, and hair loss. It rarely causes 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 ringing in the ears, numbness of the fingers and toes, cessation of menstrual periods, allergic reactions, and decrease in calcium or magnesium levels may occur.

**Paclitaxel (Taxol)** commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from my vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If I am treated with a high dosage or for a prolonged period, I may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that I would notice. In addition, paclitaxel may increase the severity and frequency of radiation risks, including injury to the esophagus, skin, and lungs.

This study may be harmful to an unborn child. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. The results will be made available to the study participant prior to the initiation of this study.

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.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

**CONTACT PERSONS**

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

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 treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater control of my disease and prolongation of my life but I understand this is not guaranteed.

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

**ALTERNATIVES**

Alternatives which could be considered in my case include radiation therapy performed off-study either alone or with chemotherapy or treatments to make me feel better. An additional alternative is no further therapy. I understand that my doctor can provide detailed information about the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures related to this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

**VOLUNTARY PARTICIPATION**

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

**CONFIDENTIALITY**

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

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

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

KARNOFSKY PERFORMANCE SCALE

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

ANATOMICAL STAGING FOR LUNG CANCER
(IUCC-AJCC, 1988)

TNM CATEGORIES (Note Definitions)

**T-Primary Tumor**

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

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

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

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

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

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

**Definitions**

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

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

**N-NODAL INVOLVEMENT**

**N0** No demonstrable metastasis to regional lymph nodes.

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

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

**N3** Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supradavicular lymph nodes.
**Distant Metastasis**

- **MO**  No (known) distant metastasis
- **M1**  Distant metastasis present - Specify Site(s)

**STAGE GROUPING OF CARCINOMA OF THE LUNG**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>T1S</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIa</strong></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIb</strong></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

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

- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above

- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
APPENDIX VI

AMERICAN THORACIC SOCIETY FOR DEFINITIONS OF REGIONAL NODAL STATIONS
APPENDIX VII

SUGGESTED RADIATION FIELDS OF INITIAL AP:PA PORTALS

Suggested radiation therapy fields for initial AP:PA portals. Treat same volume with obliques of lateral to reach 50.4 Gy.

N1 disease with no extranodal extension.  Boost volume for N1 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.

N2 disease with no extranodal extension.  Boost volume for N2 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.