NCI HIGH PRIORITY STUDY

INT 0139
RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-09

A Phase III Comparison Between Concurrent Chemotherapy
Plus Radiotherapy, and Concurrent Chemotherapy plus Radiotherapy followed by
Surgical Resection for Stage IIIA (N2)
Non-Small Cell Lung Cancer

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ELIGIBILITY SUMMARY

This study will determine if chemoradiotherapy followed by surgical resection is superior to chemoradiotherapy for patients who meet the following eligibility requirements (See Section 3.0 for details):

- Demonstrate single, primary nonsmall cell lung cancer of size T1, T2 or T3 distinct from mediastinal nodes
- Prove ipsilateral mediastinal (N2) node positivity by biopsy using any method
- Document negative N3 nodes (contralateral mediastinum, supraclavicular) by biopsy or CT criteria
- Prove pleural effusion, if present, is non-malignant unless too small to safely tap
- Complete staging tests within specified time periods to document chest disease and rule out distant metastases
- Document acceptable blood work and performance status
- Prove adequate pulmonary function and general medical condition to enable patient to withstand possible surgical resection
- Complete a prestudy evaluation and approval by medical and radiation oncology and thoracic surgery attending physicians

2/1/96

10/15/96
3/7/97
4/20/98
9/8/98
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ELIGIBILITY CHECKLISTS
INT 0139
RADIATION THERAPY ONCOLOGY GROUP

SCHEMA
Biopsy-proven T1-3 N2 NSCLC
See Section 5.3 for stratification

RANDOMIZATION (Step 1)

ARM 1
Induction RT (45 Gy)
+ Concurrent Induction
Chemotherapy (CT)
[Cisplatin 50 mg/m2 IVPB days 1,8,29, 36
VP-16 50 mg/m2 IVPB, days 1-5, 29-33]  ↓
Re-evaluation
2-4 Wks. After Completion of Induction
↓
REGISTRATION 2 (Step 2)
↓
Local or No Evidence of Distant Metastases & No evidence of Local Progression
↓
Surgical Candidate
↓
Off Protocol Treatment ↓ Refuse or medically unfit for surgery
↓ YES
FOLLOW-UP ↓
↓
Option 3 (Surgery & Add’l Chemo)
2 Additional Cycles CT starting 4-6 wks postoperatively 3 weeks after ↓
↓
FOLLOW-UP (per Section 12.0)

ARM 2
Induction RT (45 Gy)
+ Concurrent Induction
Chemotherapy (CT)
[Cisplatin 50 mg/m2 IVPB days 1,8,29,36
VP-16 50 mg/m2 IVPB, days 1-5, 29-33]  ↓
Re-evaluation
7 days before Completion of Induction
↓
REGISTRATION 2 (Step 2)
↓
Local or No evidence of Distant Metastases, and No Evidence of Local Progression ↓
↓
Surgical Candidate
↓
Off Protocol Treatment ↓ Refuse or medically unfit for surgery
↓ YES
FOLLOW-UP ↓
↓
Option 4 (Add’l Chemo)
2 additional cycles CT at least 3 weeks after Cycle 2, Day 8;
cycle 2, day 8 ↓
↓
Option 5 (Add’l Chemo + XRT)
Continue RT with No Break; Begin 2 Additional Cycles
RT Boost Field Planned by CT scan.
↓
↓
FOLLOW-UP

Eligibility: See Section 3.0
Required Sample Size: 510

7/14/95  10/15/96
2/1/96  3/7/97
Has the patient a diagnosis of lung cancer, Stage Group IIIa (N2) (International Lung Cancer Staging System)?

Report the T-N classification.

Has the histology been confirmed as non-small cell type (adenocarcinoma, non-lobar, non-diffuse bronchio-alveolar carcinoma, large cell carcinoma or squamous cell carcinoma)?

Was the cytologic or histologic diagnosis based on examination of material obtained from the primary tumor site?

If no, was the pathologic proof based only on material from the mediastinal nodes?

Is there radiographic, bronchoscopic, or surgical evidence of a separate, distinct lung lesion?

Is there evidence of more than one parenchymal lung lesion, i.e., a second lesion either in the same lung or in the contralateral lung?

Has the patient undergone mediastinal biopsy or aspiration to establish pathologic proof (histology or cytology) of ipsilateral (N2) nodal positivity?

Has every attempt been made to sample contralateral nodes?

If no, were there no nodes or were there nodes ≤ 1 cm visible on the contrast CT?

From the Operative and Pathology reports, can all mediastinal nodes shown to be both positive and negative be designated on the I1 form according to the Lymph Node Map in Appendix III?

Is the patient being enrolled because of ipsilateral N2 disease confined to the AP window (Level 5)? (If no, skip to Q 12)

a. If yes, specify the basis for establishing the AP window (Level 5) nodal status (select one):
   1- direct biopsy of AP window nodes
   2- vocal cord paralysis established by indirect laryngoscopy
b. Has direct invasion of the AP window region by the primary tumor (T4 lesion) been ruled out?

12. Were nodes palpable in supraclavicular fossae or neck?
   (Y) If yes, were they excised and histologically negative?

13. Is there evidence of pleural effusion?
   (Y) If yes, was a thoracentesis performed with negative cytology or was pleural fluid present only on CT scan (and not the chest x-ray) and deemed too small to tap?

14. Is there any evidence of pericardial effusion or superior vena cava syndrome?

15. Has the patient undergone the complete prestudy evaluation specified in Section 3.5 with distant metastasis ruled out?

16. Have all the required tests and biopsies been performed within the time frame specified in Section 3.8?

17. Is the patient's tumor mass measurable or evaluable on chest Xray or CT as specified in Section 3.1.2.

18. Is the status of the mediastinum, lung parenchyma, entire liver and adrenal glands documented on the CT report or documented in writing by the surgeon and/or medical oncologist.

19. Has the patient received chemotherapy, radiotherapy or surgery (excluding diagnostic procedures for current disease) for lung cancer?

20. Is the current white blood count ≥ 4000?
   (Y) If yes, report the current WBC (skip to Q 21)
   (Y) If no, is the absolute granulocyte count (AGC) ≥ 2000?
      (Y) If yes, report the current AGC
      (Y) Report the current WBC
(Y/N) 21. Is the Hgb level $\geq 10$? (If yes, skip to Q22)

(Y) If the hemoglobin is less than 10.0 will the patient receive transfusion according to Section 3.7.2.2 and if hemoglobin is $< 8.5$ has a bone marrow been done to rule out metastatic disease?

(Y) 22. Is the platelet count $\geq$ institutional lower limit of normal?

Report platelet count ($x 1000$)

(Y/N) 23. Are the serum bilirubin and SGOT $\leq 1.5$ times the institutional upper limit of normal?

(Y) If no, are the abnormal results due to documented benign disease?

24. Report the SGOT result.

25. Report the serum bilirubin result.

($\geq 50$) 26. Report the measured or calculated creatinine clearance ($ml/min$) result (if not measured, protocol formula in Section 3.7.3.2 must be used to calculate result).

(Y) 27. Are the results of the preregistration pulmonary function tests in compliance with Section 3.7.4 of the protocol?

(N) 28. As determined by the attending thoracic surgeon, are there any medical contraindications to potential pulmonary resection?

(N) 29. Is there any medical condition which in the investigators opinion is not controlled or cannot be adequately controlled with appropriate therapy (see Section 3.11.11)?

($\geq 70$) 30. Report the Karnofsky Performance Status. (If 90 or 100, skip to Q 31).

(N) If 70 or 80, is there $> 10\%$ weight loss due to tumor?

(Y) Is the patient's albumin level $\geq 0.85$ times the institutional lower limit of normal?

Report the albumin (G/DL)

(Y) 31. Is the patient willing to accept potential hearing loss that may result from treatment?
32. Any evidence of symptomatic peripheral neuropathy?

33. If female, is the patient pregnant or lactating?

34. If the patient has reproductive capability, has the patient agreed to use effective contraception? (if no reproductive capability, code n/a)

35. Other than adequately treated basal/squamous skin cancer, in situ breast or cervix cancer, is there history of a prior malignancy from which the patient has not been disease free for a minimum of 5 years?

36. Has each of the attending physicians (medical oncologist, thoracic surgeon, radiation oncologist) approved and co-signed the staging designations reported at registration of this case?

37. Has the radiotherapy facility including the participating radiotherapists, surgeons and medical oncologists received pre-approval by the study coordinators as specified in Sections 3.9?

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

39. Will treatment start within 5 working days of registration?

40. Will the patient participate in the Tobacco, Alcohol and Diet Component?
   - If no, reason not participating
     0. Not applicable (participating)
     1. Patient refusal
     2. Non-English language or illiterate
     3. Physical barrier (blind, etc.)
     4. Investigator refusal
     5. Other reason (specify) ________________

The following questions will be asked at randomization:

41. Was the Eligibility Checklist (above) completed?

42. Is the patient eligible for this study?

43. Patient's Name

44. Verifying Physician
RTOG Institution # ____________

ECOG R9309/NCI Navy 9317
SWOG 9336/CALGB 9592/NCCTG R9309

ECOG R9309/NCI Navy 9317
SWOG 9336/CALGB 9592/NCCTG R9309

NCIC CTG BR.13
(circle one)
RTOG 93-09 Case # __________
Group Seq # ____________

45. Patient ID #
46. Referring Institution # (if different)
47. T-Classification (T1 vs. T2 vs. T3)
48. Karnofsky (70-80 vs. 90-100)
49. Name of the treating medical oncologist.
50. Name of the radiotherapy facility.
51. Name of the treating radiotherapist.
52. Name of the attending thoracic surgeon.
53. Patient's Birthdate
54. Sex
55. Race
56. Social Security Number
57. Zip Code (9 digit if available)
58. Method of Payment
59. Will any component of the patient’s care by at a military or VA facility?
60. Treatment Start Date (must be within 5 working days of randomization)
61. Treatment Assignment

Completed by ___________________________ Date ____________________
Telephone ____________________________
RTOG Institution #  INT 0139

ECOG R9309/NCI Navy 9317  ELIGIBILITY CHECK/SECOND STEP (7/14/95, 2/1/96, 10/15/96)
SWOG 9336/CALGB 9592/NCTG R9309  (for patients previously randomized to treatment Arm 1)
NCIC CTG  BR.13
(circle one)
RTOG  93-09  Case #

Group Seq #

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ELIGIBILITY B

______(Y/N)  1. Based on the evaluation procedures and criteria specified by the protocol, is there any evidence of tumor progression or distant metastasis?  *(If no, skip to Q 2)*

If yes, ask the registrar to "discontinue case".

______(Y/N)  2. Based on evaluation by the thoracic surgeon, treating medical oncologist and patient agreement, will this patient undergo the assigned surgery?  *(If yes, skip to Q4)*

______

3. If no surgery, specify reason for non-surgical option *(choose one)*

1. medical contraindication
2. patient refusal
3. physician refusal
4. other reason
   specify __________________________

__________________________  4. Patient's Name
__________________________  5. Verifying Physician
__________________________  6. Patient ID#
__________________________  7. Referring Physician
__________________________  8. Treatment Arm
__________________________  9. Progression *(No vs. Yes)*
__________________________ 10. Surgery *(No vs. Yes)*
__________________________ 11. If yes, date of surgery
__________________________ 12. Date of re-registration if no surgery.

Completed by  ________________________  Date  ________________________
Telephone  __________________________
ELIGIBILITY C

______ (Y/N) 1. Based on the evaluation procedures and criteria specified by the protocol, is there any evidence of tumor progression or distant metastasis?  (If no, XRT is to continue without a break according to protocol)

   If yes, ask the registrar to "discontinue case".

2. Patient's Name
3. Verifying Physician
4. Patient ID#
5. Referring Physician
6. Treatment Arm
7. Progression (No vs. Yes)
8. Surgery (No vs. Yes)
9. As applicable, date of surgery, or RT start.

Completed by ____________________________ Date ____________________________
Telephone ____________________________
1.0 INTRODUCTION

Few patients with regionally advanced non-small cell lung cancer (stage III as defined by the New International Staging System) present with disease amenable to upfront surgical resection for potential cure. Of the stage IIIa subset with positive N2 nodes (ipsilateral mediastinal nodes), only 10-20% of patients present with "favorable" disease, that is, a normal mediastinum on the preoperative chest X-ray and a single positive mediastinal node or nodal area found at mediastinoscopy or thoracotomy. These patients have a 40-50% 2-year survival and a 20-30% 5-year survival following complete surgical resection, with or without adjuvant radiotherapy. The remainder of patients with stage IIIa disease have bulky extranodal mediastinal tumor or multiple levels of involved N2 nodes, and are not currently considered candidates for surgical resection. Traditionally, these patients were treated with chest radiotherapy (RT). Although RT is very effective in achieving tumor shrinkage and in palliating symptoms, 5-year survival usually does not exceed 5-10%. For example, RTOG trial 73-01 which tested four different doses of continuous and split course RT, found an overall 5 year survival of less than 10% with no difference among the four RT arms. Two standard RT arms of the recent Southeast Group trial each achieved less than a 5% 5-year survival. In a CALGB trial, the "standard" RT arm only resulted in a 13% 2-year survival. Using higher dose hyperfractionated RT, the RTOG reported an improvement in 2-year survival in trial 83-11, but only to 20%.

The poor survival rate of patients with stage IIIa bulky N2 disease is related both to the failure of RT to control bulky primary tumor and to the rapid development of distant metastases. Thus, there has been great interest in exploring combined modality approaches, with "induction therapy" (a cytoreductive therapy) administered prior to a definitive locoregional treatment. Although an early goal was to "convert" unresectable disease to resectable, the current intent in all combined modality trials is to eliminate distant micrometastases in addition to improving local control. All possible permutations of the three modalities of RT, chemotherapy (CT) and thoracic surgery have been tested in phase II pilot studies, and in a few randomized trials. The induction therapy has been RT, CT, RT then CT, or RT + CT, with the definitive local treatment either surgery or RT, sometimes then followed by more CT. It should be noted throughout the discussion to follow that only in a few trials have the terms "unresectable", "locally advanced", or "marginally resectable" been clearly defined. In addition, the use of several staging systems over time (RTOG III, III MO, or more recently IIIa subsets and IIIb), has further confused the interpretation of various trials' findings.

The first type of induction therapy tested was preoperative RT in the 1950's and 1960's. A comprehensive review of this topic has been published. The collective literature supports the following conclusions: preoperative RT regimens result in pathologic complete responses in 15% to 45% of patients, but operative complications increase substantially with high-dose RT (doses above 45 Gy). Randomized trials failed to show a survival benefit when preoperative RT was compared to surgical resection alone, but modern non-invasive and intraoperative staging techniques were not used in these trials. The concept of preoperative RT was recently re-examined as one arm of a randomized phase II trial by the Lung Cancer Study Group (LCSG 881). A preoperative dose of 44 Gy was administered to patients with pathologically proven stage IIIa disease. The median survival was just 12 months, and only one of 33 patients had a pathologic complete response. Thus, preoperative RT does not appear to improve long-term survival in unresectable stage IIIa NSCLC, despite rigorous staging, excellent quality control and modern radiotherapy techniques.

During the past 10 years, the recognition that systemic disease was the most common form of relapse in patients with stage III tumors led to a series of trials using CT in addition to RT. The CT was given either prior to definitive RT, closely sequenced with RT, or concurrently with RT. These trials did not include surgery but instead used the RT for local control. They were based on the important response differential observed between the same CT regimen given to patients with locally advanced tumor, versus the lower response seen in metastatic disease. Higher-dose cisplatin-based regimens were generally more effective in both stage IV as well as stage III NSCLC, compared with lower-dose cisplatin programs such
as CAP, or non-cisplatin-containing regimens, and were associated with improved survival.\textsuperscript{17,19,21-23} Thus, the earliest trials with induction CT followed by or sequenced with RT employed CAP-like regimens, which yielded lower response rates than more recently reported trials. However, these early trials with induction CT plus RT represented an improvement over the historical experience with RT alone, with 2- and 3-year survivals of approximately 20%.\textsuperscript{16,24,25} Since then, there were numerous small phase II pilot studies which tested higher-dose cisplatin in combination with drugs such as mitomycin C, vinblastine, vindesine, etoposide, with or without sequential or concurrent RT, in various subsets of stage III “unresectable” disease.\textsuperscript{16-18,20,26,27} Response rates were usually higher than with CAP/RT combinations, (from 50-80%), but the median and 2-year survivals were variable. Freiss et al. reported one particularly promising trial that used 4 monthly cycles of cisplatin and etoposide together with concurrent, continuous RT to approximately 60 Gy, beginning on day 1.\textsuperscript{27,28} In 20 patients treated in this manner, the response rate was 80% and the median and 2-year survivals were 16 months and 30%, respectively.\textsuperscript{28} This study was based on extensive and positive experience with this regimen in a group-wide trial for limited stage small cell lung cancer in the Southwest Oncology Group.

Based upon these encouraging phase II pilots, there was impetus to design randomized trials that compared CT with RT to RT alone. At least 8 major trials were performed, 5 of which employed no cisplatin or low-dose cisplatin CT\textsuperscript{8,29-32}, and three of which used high-dose cisplatin.\textsuperscript{9,33,34} In a 3-arm trial, the Southeast Group found no difference in survival (median and 3-year) among single agent vindesine, RT, and combined vindesine and RT.\textsuperscript{8} A Finnish trial showed no benefit to two cycles of CAP, followed by CAP alternating with split course RT compared to RT alone.\textsuperscript{29} The Southwest Oncology Group compared RT to FOMi/CAP for two cycles followed by RT and noted no improvement.\textsuperscript{31} The NCCTG reported no survival advantage to the non-cisplatin-containing MACC program followed by RT compared to RT alone, although there was a non-significant but intriguing doubling of 2-year survival in the combined modality arm.\textsuperscript{30} The EORTC compared RT alone, RT with weekly cisplatin (30 mg/m\textsuperscript{2}), and RT with daily cisplatin (6 mg/m\textsuperscript{2}).\textsuperscript{32} Median and 2-year survival was significantly better in the daily cisplatin arm compared to RT alone (p < .02). The CALGB tested cisplatin plus vinblastine for two cycles prior to RT, versus RT alone.\textsuperscript{9} Median and 3-year survival rates were significantly better in the combined modality arm. The Hoosier Oncology Group reported preliminary results of a trial which compared continuous RT (60 Gy) to the same RT with cisplatin, 70 mg/m\textsuperscript{2}, every three weeks for three doses.\textsuperscript{33} There was no difference in median survival, but the two-year survival was 15% for CT/RT, versus 6% for RT alone. Finally, the French have updated the survival analysis for the comparison of RT (65 Gy) to three cycles of vindesine, cyclophosphamide, cisplatin, and CCNU before and after the same RT\textsuperscript{34}. Disease-free and long-term survival were significantly better for the combined modality arm (3-year survival 4% vs. 12%). When considered together, these trials underscore the poor 2- to 3-year survival achieved with RT alone using modern techniques, and suggest that combined CT and RT in general doubles the 2-year survival rate achieved with RT alone. Five-year survival data regarding the emergence of plateaus is not yet available.

The other combined modality approach tested during the last decade was CT, with or without RT, followed by surgical resection. The hope was that this approach would offer "definitive" local control by resecting all residual tumor. Many phase II pilot trials were reported, but no randomized trials tested the contribution of surgical resection.\textsuperscript{15,17,35-42} It is hard to determine what form of induction therapy is optimal because heterogeneous groups of patients were entered in these trials.\textsuperscript{42} For example, although most studies emphasized the treatment of patients with bulky N2 disease, some trials included stage IIIb tumors (T4 disease) while others included T3N0-1 tumors. Not all trials required rigorous staging by mediastinoscopy and lymph node dissection at thoracotomy. Collectively, these studies showed response rates to induction therapy of 53-87%, resectability rates of 15-85% (most were 50-60%), and pathologic complete response rates of 15-20%. Median survival rates varied from less than a year to nearly 2 years, with most trials reporting medians of 15-22 months. The toxicities of the various programs were also highly variable, both across regimens, and with the same regimen but among different institutions. Using the MVP induction regimen as an example, the excellent surgical results reported by the Memorial group\textsuperscript{38,41} were not duplicated by either the LCSG or the Toronto group\textsuperscript{15,39}. The median survival in the
LCSG trial was less than 1 year and the post-operative mortality was 17%. The Toronto group recently updated their results, with an overall treatment-related mortality of 15%.

In late 1988, the Southwest Oncology Group opened trial SWOG 8805 for patients with bulky stage IIIa (N2) and selected stage IIIb (T4 or N3, but not pleural effusion) disease, using rigorous staging criteria. The objectives were to (1) assess the feasibility of the Friess regimen (cisplatin, VP-16, and concurrent RT), followed by surgical resection in a cooperative group setting, and (2) determine response and resectability rates, progression-free and overall survival for both the stage IIIa and IIIb subsets. Pathologic proof of T4, N2 or N3 disease by mediastinoscopy, fine needle aspiration, or thoracotomy was required. This trial was unique because a wide variety of stage IIIb presentations were included. Induction therapy was 2 cycles of cisplatin and VP-16 given concurrently with continuous radiation to a total dose of 45 Gy. Restaging was performed 2-4 weeks after completion of chemoradiotherapy. Patients with no evidence of local or distant progression underwent thoracotomy, attempted resection and complete nodal sampling. If the resection was complete and mediastinal nodes were negative, no further therapy was given. If the patient had unresectable disease, an incomplete resection, or positive mediastinal nodes, a boost consisting of 2 cycles of CT and completion of the RT to 59.4 Gy was given.

An interim analysis based on complete data from the first 75 patients enrolled in SWOG 8805 was presented at ASCO in May 1991, and the surgical results were recently reported. The objective response rate was 69% (n=52); an additional 16 patients had stable disease, so 68 (91%) were eligible for surgery. Sixty-three patients underwent thoracotomy, and 55 patients had complete resection (73% of the original 75). By stage, 74% IIIa and 71% IIIb had a complete resection. Of note, 12 of the 16 patients with stable disease after induction therapy were resected. Twenty-one percent of patients had no evidence of tumor in the specimen, and 38% had only a rare microscopic focus. Induction treatment was well tolerated: only 6 patients had a grade 4 toxicity (diarrhea, esophagitis, vomiting, or granulocytopenia). The operative mortality was 6%, and the postoperative morbidity was similar to that previously reported in surgical series. Preliminary estimates of survival for the first 75 eligible patients, with a median followup of 18 months, indicate a median survival of 17 months, with no difference as yet apparent between the IIIa and IIIb subsets. It is too early for long-term results, but the projected survival at 2 years is 40%. These data represent a near-doubling of survival compared to that expected for this population, and clearly demonstrate the feasibility of this treatment regimen in a multi-institutional setting.

Thus, combined modality programs which include CT in the induction regimen appear to confer a survival advantage over RT alone. Although surgical resection theoretically might provide the definitive approach to local control, it is unclear from the pilot studies performed to date whether combined modality regimens that include surgical resection are associated with a better long-term survival rate than those using CT plus RT alone.

Therefore, during the past two years several phase III randomized trials were developed by the cooperative groups to determine the optimal combined modality approach to stage III NSCLC. Because of a concern about multiple overlapping trials, CTEP held two successive Lung Cancer Strategy meetings during the fall of 1992. The consensus from those meetings was that defining the role of surgery as a local control modality following CT +/- RT induction therapy was the next critical question to be answered in the management of stage IIIa (N2) NSCLC. An Intergroup effort was felt to be necessary in order to answer this question in a timely manner, due to the large numbers of patients required for such a randomized trial. The feasibility of the SWOG 8805 program in a multi-institutional setting, and the preliminary resectability and survival rates observed to date for the stage IIIa subset were felt to be compelling reasons to choose this approach as the "trimodality" arm. However, the early survival data for the stage IIIb subset were thought to be too immature to allow the inclusion of such patients in an intergroup phase III trial. Other minor modifications to the SWOG 8805 regimen were proposed to allow for a "cleaner" trial design. These included uniform RT ports in both arms, deletion of the small dose of postoperative RT, for which
there was not felt to be a strong therapeutic rationale; and the use of 2 cycles of postoperative chemotherapy for all patients because of the high risk of distant metastases in this group of patients.

This Intergroup phase III trial will compare the modified SWOG 8805 program to a non-surgical arm of concurrent cisplatin, VP-16, and continuous RT to 60 Gy, in patients with stage IIIa (N2) NSCLC. The non-surgical arm will thus provide "standard" RT, with 4 uninterrupted monthly cycles of CT. This will duplicate the Friess regimen, with the third cycle of CT beginning approximately when the RT ends.27,28 In both arms, after completion of induction chemoradiotherapy, a simple determination of progression or not will be made, rather than a detailed ascertainment of response (CR, PR or stable disease). It is not necessary to duplicate these response determinations already established in SWOG 8805 in this type of trial; furthermore, it is important not to break the continuity of the RT in the non-surgery arm.

Therefore, the aim of this trial is to determine if surgical resection is a necessary part of combined modality treatment for stage IIIa NSCLC in an Intergroup setting. The major endpoints will be median, 2-year and 5-year progression-free and overall survival. Evaluation of patterns of relapse is a secondary endpoint.

As part of the project sponsored by the NIH Office of Research on Women's Health and the NCI, an additional short "Tobacco use, Alcohol use, and Diet Assessment" questionnaire will be completed by all patients. This aspect of the study is exploratory, in order to describe the impact of smoking and diet behaviors on toxicity, survival and second cancers. There is growing evidence that smoking cessation at diagnosis may prolong survival, either directly or by reducing secondary malignancies.45-46 Furthermore it has been hypothesized that low fruit and vegetable consumption and high alcohol intake may increase the risk of developing lung cancer. However, the relationship of these behaviors to toxicity or disease outcome remains unstudied. The lifestyle module developed for the trial will explore and describe lifestyle differences at diagnosis, through treatment, and during follow-up with the goal of studying male/female differences and outcome effects of these behaviors.

2.0 OBJECTIVES

2.1 Assess whether concurrent chemotherapy and radiotherapy followed by surgical resection results in a significant improvement in progression-free, median, and long-term (2-year, 5-year) survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIa (N2-positive) non-small cell lung cancer.

2.2 Evaluate the patterns of local and distant failure for patients enrolled in each arm of the study, in order to assess the impact of the therapy on local control and distant metastases.

2.3 To obtain exploratory descriptive information on the relationship of tobacco use, alcohol use and dietary patterns on toxicity and outcomes in males and females.

3.0 ELIGIBILITY CRITERIA (2/1/96)

All queries about eligibility should be directed to RTOG Data Management (215) 574-3214 with Dr. Albain (708) 327-3102 as final arbiter.

3.1 General Requirements

3.1.1 Single, newly diagnosed, primary lung parenchymal lesion of stage IIIA (T1, 2 or 3) with ipsilateral positive mediastinal nodes (N2)

3.1.2 Either measurable or evaluable disease by chest xray and/or contrast CT scan is allowed

3.1.3 A contrast CT scan of the thorax is required to complete the T and N staging

3.1.4 Histologic (biopsy) or cytologic (needle aspiration or sputum) proof of non-small cell histology must be obtained and satisfy both of the following:

3.1.4.1 Adenocarcinoma, large cell carcinoma, squamous carcinoma or non-lobar and non-diffuse bronchoalveolar cell carcinoma

3.1.4.2 Documentation of non-small cell carcinoma may originate from the mediastinal node biopsy or needle aspiration only if a distinct lung primary separate from the nodes is clearly evident on the CT scan.
3.2 Primary Tumor Stage (T Stage) Requirements

3.2.1 T1, T2, or T3 only according to International Lung Cancer Staging System in Appendix II

3.2.2 Lesion must clearly arise from the bronchus

3.2.3 If a pleural effusion is present, 1 of the 2 following criteria must also be met to exclude T4 disease:

3.2.3.1 When the pleural fluid is present either before or after prestudy mediastinoscopy or exploratory thoracotomy, a thoracentesis with negative cytology must be performed, OR,

3.2.3.2 When pleural fluid is present only on the CT scan and not the chest xray, but is deemed too small to tap safely under either CT or ultrasound guidance, the patient is eligible and this must be clearly documented on the I1 form.

3.3 Nodal Stage (N stage) Requirements on the Ipsilateral (same as primary) Side

3.3.1 Positive ipsilateral mediastinal node or nodes (nodal stage N2), with or without positive ipsilateral hilar (N1) nodes

3.3.2 N2 nodes must be separate from primary tumor by either CT scan or surgical exploration

3.3.3 Proof of N2 disease may be either histologic (biopsy) or cytologic (needle aspiration)

3.3.4 Diagnostic methods acceptable for N2 documentation include: thoracotomy, mediastinoscopy, mediastinotomy, Chamberlain procedure, Wang needle or fine needle aspiration under bronchoscopic or CT guidance

3.3.5 The only exception to 3.3.4 is a special circumstance in which if all of the following are true, a nodal biopsy or aspiration can be omitted:

3.3.5.1 Paralyzed left true vocal cord documented by bronchoscopy or indirect laryngoscopy

3.3.5.2 Nodes visible in the AP (Level 5) region on CT scan

3.3.5.3 Distinct primary separate from the nodes is visible on CT scan

3.3.6 Regardless of method of documentation of N2 disease, the following must be true:

3.3.6.1 From the Operative and Pathology reports, all mediastinal nodes shown to be both positive and negative must be designated on the I1 form according to the Lymph Node Map in Appendix III

3.3.6.2 If the procedures to document N2 eligibility were done at a non-member facility, the patient is still eligible if the study institution PI reviews the outside pathology slides and report with the study institution's pathologist in conjunction with the outside operative report, and generates a report that verifies the original diagnosis and lymph node mapping, as consistent with the staging requirements of the protocol

3.4 Nodal Status in the Contralateral (opposite) Mediastinum and Neck must be Negative

3.4.1 Nodes may not be present in the supraclavicular areas or higher in the neck unless they are proven to be benign on excisional biopsy

3.4.2 The negative status of the contralateral mediastinal nodes must be established by any one of the following ways:

3.4.2.1 Mediastinoscopy, mediastinotomy, Chamberlain procedure, or thoracotomy must be done if lymph nodes larger than 1 cm are visible on the contrast CT scan of the chest on the side opposite the primary.

3.4.2.2 If there are either no nodes or if nodes less than or equal to 1.0 cm are visible on the contrast CT scan of the chest on the side opposite the primary tumor, a surgical procedure as in 3.4.2.1 is not required

3.4.3 If criteria in 3.4.2.1 are met, using the Pathology and Operative reports, the lymph node station (level) designations should be used to label the negative contralateral nodes according to Appendix III on the I1 form.

3.5 Evaluation to Exclude Distant Metastases (M stage M0)

3.5.1 Lymphadenopathy may be present on physical examination only if there is biopsy-proof of a benign cause

3.5.2 The serum SGOT or SGPT and bilirubin must be less than or equal to 1.5 times the upper institutional limit of normal unless benign cause is documented
3.5.3 Hepatomegaly or splenomegaly on physical examination or CT scan of the upper abdomen must have a benign cause documented.

3.5.4 No evidence of distant metastases on contrast CT or MRI of the brain, bone scan, CT of the lungs to exclude other ipsilateral or contralateral parenchymal lesions, and on contrast CT of the upper abdomen including ENTIRE liver and adrenals.

3.5.5 Abnormal findings in the abdomen should be further assessed by MRI or ultrasound.

3.5.5.1 If clearly benign on further imaging, invasive assessment by biopsy is not required.

3.5.5.2 If indeterminate on further assessment, biopsy is required unless in clinical judgement area is inaccessible.

3.5.6 Bone scan abnormalities with normal plain radiographs are considered metastatic unless they are either:

3.5.6.1 Clearly caused by degenerative joint disease, traumatic fracture or other benign entity, OR

3.5.6.2 Are proven to be benign by additional tests such as MRI, CT or biopsy.

3.6 Multidisciplinary Pretreatment Assessment

3.6.1 The surgeon who would potentially perform the thoracotomy, the treating medical oncologist and the treating radiation oncologist must all assess patient before registration and their names provided on the on-study (11) form.

3.6.1.1 They must agree on the staging designations in 3.2, 3.3, 3.4 and 3.5 above.

3.6.1.2 They must agree that the patient is potentially operable and resectable after induction chemotherapy and radiation.

3.7 Other Laboratory and Function Studies Requirements

3.7.1 Performance Status Evaluation

3.7.1.1 Apply Karnofsky (KPS) system found in Section 11.4 during pretreatment history and physical examination.

3.7.1.2 Eligible if 90 or 100%, OR,

3.7.1.3 If 70 or 80%, the albumin must be at least .85 x lower institutional normal and weight loss within 3 months prior to diagnosis must be less than or equal to 10%.

3.7.2 Hematology Requirements

3.7.2.1 Hemoglobin less than 8.5 must be investigated by bone marrow to rule out metastatic tumor; if marrow is negative, patient is eligible.

3.7.2.2 Hemoglobin levels of 10.0 or greater are strongly recommended just prior to treatment via transfusion, if necessary, to insure better tolerance of chemorT.

3.7.2.3 White blood cell count at least 4000; if less, granulocytes at least 2000.

3.7.2.4 Platelets at least institution lower limit of normal.

3.7.3 Renal Requirements

3.7.3.1 The creatinine clearance must be at least 50 ml/min.

3.7.3.2 This may be measured or calculated according to the following formula:

\[
\frac{(140-\text{age}) \times (\text{body weight in kg})}{72 \times \text{serum creatinine}}
\]

Multiply this number by 0.85 if the patient is female.

3.7.4 Pulmonary Function Requirements (4/20/98)

3.7.4.1 FEV1 greater than or equal to 2.0 liters; if less than 2.0 liters, the predicted postresection FEV1 must be at least 800cc based on the following formula using the quantitative V/Q scan:

\[
\text{If a pneumonectomy will be necessary or is a strong possibility, predicted post-resection FEV1} = \text{FEV1} \times \text{% perfusion to uninvolved lung from quantitative lung V/Q scan report. If only a lobectomy will be required, predicted post-resection FEV1 = FEV1} \times \text{% perfusion to uninvolved lung plus the FEV1} \times \text{estimated % perfusion to uninvolved ipsilateral lobe(s).}
\]

3.7.4.2 A diffusion capacity should be measured. If a pneumonectomy is planned or is a strong possibility after induction therapy, the diffusion capacity (as corrected for hemoglobin) should be $\geq$ 50% predicted.
3.8 **Required Timing of Tests and Treatment** *(4/28/97)*

3.8.1 The prestudy history and physical, blood tests, creatinine clearance, and chest Xray must be completed within **28 days (four weeks) prior to registration**.

3.8.2 All other prestudy requirements on the study calendar including CT scan of the chest *(except method of diagnosis and documentation of N2 disease)* must be done within **42 days (six weeks) prior to registration**.

3.8.3 The method of diagnosis and documentation of N2 disease must be done within **56 days (eight weeks) prior to registration**.

3.8.4 The timing clock starts from the date the first test or measurement is performed.

3.8.5 The above four conditions must allow the treatment to commence within 5 working days of registration in order to satisfy both of the following:

3.8.4.1 The radiotherapy must begin no later than Wednesday.

3.8.4.2 The chemotherapy must start within 24 hours of the radiation.

3.8.5 Special exceptions to all of the above due to holiday or weekend day or time zone differences must be pre approved jointly by Dr. Albain and the RTOG headquarters on a **case by case basis**.

3.9 **New Institution Approval Requirements** *(Appendix VI-A, B, C)*

3.9.1 The medical oncology questionnaire should be completed by a minimum of one medical oncologist at each site.

3.9.2 All participating radiation oncologists and surgeons at each site must complete the questionnaire.

3.9.3 Each cooperative group will process their institutions’ questionnaires. **COMPLETED QUESTIONNAIRES MUST BE SUBMITTED TO THE APPROPRIATE GROUP OFFICE ALLOWING AT LEAST THREE BUSINESS DAYS FOR PROCESSING**.

3.10 **Informed Consent Process**

3.10.1 All patients must be informed of the investigational nature of the study.

3.10.2 All patients must sign a written, study-specific informed consent that conforms to institutional and federal guidelines.

3.11 **Ineligibility Criteria**

3.11.1 Small cell carcinoma and lobar or diffuse bronchoalveolar cell carcinoma.

3.11.2 Two or more parenchymal lung lesions.

3.11.3 Previous diagnosis of lung cancer.

3.11.4 Previous surgical resection of the current primary lesion.

3.11.5 Prior radiotherapy or chemotherapy for lung cancer.

3.11.6 Pericardial effusion.

3.11.7 Superior vena cava syndrome.

3.11.8 Significant hearing loss and patient unwilling to accept potential for further hearing loss.

3.11.9 Symptomatic peripheral neuropathy.

3.11.10 Currently receiving chemotherapy for another condition *(such as arthritis)*.

3.11.11 Medical illness not controllable by appropriate medical therapy including but not limited to myocardial infarction within previous 3 months, active angina, unstable heart rhythms, congestive heart failure and peptic ulcer disease under active treatment.

3.11.12 Pregnant or lactating women may not participate. Women/men of reproductive age or potential may not participate unless they use effective contraception.

3.11.13 Prior or concurrent malignancy other than adequately treated basal or squamous cell skin cancer, in situ cervical cancer, and either ductal or lobular carcinoma in situ of the breast. Any other prior malignancy EXCEPT lung cancer is allowed if a 5-year disease-free interval has elapsed since last treatment.

3.12 For questions regarding eligibility discuss with Dr. Albain if they cannot first be resolved at RTOG Headquarters.

4.0 **PRETREATMENT EVALUATIONS**

Per Section 3.0

5.0 **REGISTRATION PROCEDURES**

5.1 **Randomization** *(7/1/94, 7/14/95, 2/1/96, 10/15/96, 4/20/98)*

Physicians must complete Appendix VI prior to entering any patients *(Section 3.9)*.
RTOG members and NCI Navy will send a completed set of questionnaires to RTOG Headquarters. ECOG, NCCTG, NCIC CTG and SWOG members will submit the questionnaire sets to their respective Groups for verification and approval by the Principal Study Chairs. SWOG questionnaires should be submitted to the SWOG Operations office. This pertains only to those institutions who are not currently listed as participants. CALGB institutions will submit completed questionnaires to the CALGB Registrar at the CALGB Data Management Center for verification and approval.

Patients will be randomized only after pretreatment evaluation is completed and eligibility criteria are met. Patients are randomized prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. (Non-RTOG Institutions will call their own Cooperative Groups. See Section 5.4). The patient will be randomized to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & RTOG Number
- Patient's Name & ID
- Verifying Physician's Name
- Oncologists' Names (per Section 3.18)
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date (must be within five working days of randomization)

5.1.1 All patients will be initially randomized according to the eligibility requirements of Section 3.0. All randomized patients will undergo a second registration as described in Section 5.2.

5.1.2 At the time of randomization, the caller must be prepared to answer every question on the Eligibility Checklist and provide stratification and descriptive factors.

5.1.3 Exceptions to the registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible AND/OR cancellations will not be allowed.

5.2 Registration 2 Eligibility:
The second registration process requires a second phone call to the RTOG Group Office for all patients (see Section 5.1) at which time the following information must be provided:

- Institution Name and RTOG number
- Patient Name and the RTOG Assigned Case Number
- Randomized Assignment (Arm 1 or 2)
- Tumor Status (progression information: yes vs. no)
- Eligibility Information for Second Registration

Patients whose tumor has not progressed will be assigned an option number reflecting their subsequent treatment plan (see Section 6.0). A confirmation of second registration and a new data collection calendar will be mailed for patients assigned options 3, 4, or 5 (see Sections 5.2.1 and 5.2.2).

Patients reported to have tumor progression at the second registration call will not be assigned a new option number and will be designated as "discontinued". The original data collection calendar will be followed.

5.2.1 Re-registration of Patients Randomized to Arm 1: The re-registration call on all patients assigned Arm 1 must be made after completion of the 2-4 week restaging tests but prior to surgery. If tumor progression has occurred prior to completion of induction treatment, the second registration call may be made earlier than the 4 week period, i.e. upon diagnosis of progression. Arm 1 patients without progression who will undergo surgery will be assigned option 3 (surgery followed by additional chemo. See Sections 4.4.4 and 6.5.1). Arm 1 patients who have not had tumor progression but who are not surgical candidates or who have refused surgery (see Section 6.4.2) will be assigned option 4 (two cycles of additional chemo). Arm 1 patients who have had...
tumor progression during the induction phase of treatment will not be assigned a new option number however the second registration phone call is still required.

5.2.2 Re-registration of Patients Randomized to Arm 2: The re-registration call on all patients assigned Arm 2 must be made within the 7 days following the registration re-evaluation (see Section 6.3.2). If progression has occurred prior to completion of the induction RT and chemotherapy, the second registration call may be made prior to the specified post-evaluation time period, i.e., upon diagnosis of progression. Arm 2 patients without progression will be assigned option 5 (additional chemo and XRT, see Sections 6.5.2 and 6.5.1). Arm 2 patients who have progressed during the induction therapy treatment will not be assigned a new option number however the second registration call is still required.

5.3 Stratification/Descriptive Factors (2/1/96)
5.3.1 At the time of initial registration, patients will be stratified according to:
5.3.1.1 Contralateral mediastinum sampling or biopsy, yes or no.
5.3.1.2 T1 vs. T2 vs. T3 (Appendix II)
5.3.1.3 Karnofsky performance status 70 or 80% vs. 90 or 100% (Section 11.4)

5.4 Non-RTOG Institutions (7/1/94, 7/14/95, 2/1/96, 10/15/96)
Each participating Cooperative Group must ensure that the physician questionnaires in Appendix VI were approved by the Principal Study Chairs and that IRB approval was obtained prior to accession of cases. Patients who meet the eligibility criteria in Section 3.0, sign the consent form, and pass the pretreatment evaluations, may be randomized into the study prior to any protocol therapy. Member institutions will phone their respective Cooperative Group Headquarters. The following information will be required at the time of patient entry:

- Institution's Name and RTOG Institution Identification Number (when calling RTOG)
- Patient's name and ID number
- Verifying Physician's Name
- Names of Medical, Radiation, and Surgical Oncologists
- Eligibility Criteria Information
- Stratification Information
- IRB Approval Date
- Demographic Data
- Treatment Start Date (must be within three working days of randomization)

5.4.1 ECOG (617) 632-2022, 8:30 am-4:30 pm, Eastern Time
NCI Navy will call RTOG directly per Sections 5.1 and 5.2.
SWOG (206) 667-4623, 6:30 a.m.-1:30 p.m. Pacific Time
CALGB (919) 286-4704, 9:00 a.m. - 5:00 p.m. Eastern Time
(Nregistrants will be accepted through the Main Institution only).
NCCTG (507) 284-4130, 8:00 a.m. - 3:30 p.m. Central Time
NCIC CTG (613) 545-6430, 8:00 a.m. - 5:00 p.m. Eastern Time

5.4.2 The Cooperative Group will obtain and verify all eligibility and information and then phone RTOG Headquarters, Monday-Friday, between 8:30 am to 5:00 pm ET and RTOG will assign the treatment option and RTOG case number.

5.4.3 After receiving the case number and the treatment assignment, the Cooperative Group will phone their registering institution and relay this information.

5.4.4 The case number and treatment option will be confirmed by mail. RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case. The participating Group should then forward a copy of the calendar and the confirmation to the participating institution.
5.4.5 **Registration 2:** A second phone call is required for the second registration. Non-RTOG institutions will contact their own cooperative groups (see Section 5.4.1); refer to Section 5.2 for applicable information.

6.0 **TREATMENT PLAN** (2/1/96)

* All questions about chemotherapy and the overall treatment program should be directed to Dr. Albain at (708) 327-3102.

* All questions about radiation therapy delivery should be directed to Dr. Turrisi at (803) 792-3271.

* Please call Dr. Rusch at (212) 639-5873 with questions about protocol surgery.

6.1 **Induction chemotherapy, Arms 1 and 2:** Chemotherapy and radiotherapy are to begin within 24 hours of each other. Day 1 of radiotherapy must be Monday, Tuesday, or Wednesday, but no later in the week. Treatment must begin within five working days after registration. (4/28/97)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
<th>RETX NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>50 mg/M²</td>
<td>IV</td>
<td>1.8</td>
<td>days 29,36 In 250 ml normal saline over 60 minutes. *</td>
</tr>
<tr>
<td>VP-16</td>
<td>50 mg/M²</td>
<td>IV</td>
<td>1-5</td>
<td>days 29-33 In 250 ml normal saline over 60 minutes.</td>
</tr>
</tbody>
</table>

* The patients must receive IL of NS with potassium and magnesium added, along with mannitol and polyantiemetics on day 1 and day 8. The following is strongly recommended: Prior to cisplatin, begin intravenous hydration with 1,000 ml NS + 20 meq KCL + 4 gms MgSO4 at 250 cc/hr over two hours. The cisplatin is then preceded and followed by 12.5 grams of mannitol, IV push. Appropriate polyantiemetic regimens must be used prior to and following the administration of cisplatin (e.g., phenothiazine, antihistamine, benzodiazipine plus dexamethasone - OR - ondansetron or 5HT3 antagonist with or without dexamethasone and PRN benzodiazipines). After cisplatin infusion, complete the remaining 500 cc of hydration fluid over two hours. The patient should be encouraged to drink as much liquid as possible overnight if an outpatient; otherwise, an additional two liters of fluid should be given IV over the next 12 hours if the patient is an inpatient.

6.2 **Induction Radiotherapy, Arms 1 and 2:**

6.2.1 **Equipment** (4/20/98)

6.2.1.1 All fields must be simulated by a standard radiotherapy approved-use simulator.

6.2.1.2 Only linear accelerators generating photons with peak energy between 4-18 MeV will be used.

6.2.1.3 All equipment must be isocentrically rotational with minimum source axis distance of 80 cm.

6.2.2 **Dose Uniformity**

6.2.2.1 All doses are to be prescribed and calculated assuming a homogenous patient. There will be no heterogeneity corrections used in definitions of these doses.

6.2.2.2 Prescription At the mid separation of the central ray for two opposed coaxial equally weighted beams.

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

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

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

6.2.2.3 Uniformity requirement - Using a sagittal plane through the spinal cord, the dose from top to bottom cannot exceed 10%. Separations 1 cm from top and 1 cm from bottom of field must be obtained to provide off-axis spinal cord dose, record max-cord dose daily.
6.2.2.4 Compensators or sagittal plane wedges may be used. If for some reason these are not available, all critical organs must be blocked at appropriate normal tissue dose.

6.2.3 Normal tissue tolerances

6.2.3.1 Maximum spinal cord dose is 50 Gy to any point during the initial 45 Gy induction irradiation. Subsequently (during boost, see Section 6.5), the spinal cord must be shielded from direct radiation.

6.2.3.2 The entire heart may not receive more than 40 Gy. Up to 50% of the cardiac silhouette may receive up to 60 Gy.

6.2.3.3 The ipsilateral normal appearing lung tissue may receive a dose up to 25 Gy. The lung contralateral to the tumor-bearing lung should be spared traversing radiation whenever possible, but the entire lung may receive up to 5 Gy, and any portion irradiated should be minimized and restricted to 15 Gy.

6.2.4 Dose-time factors

6.2.4.1 1.8 Gy per day; five days per week, except holidays. Begin the RT within 24 hours of the first day of chemotherapy. RT should not begin any later than Wednesday to insure simultaneous therapy for the majority of each chemotherapy cycle (See Section 6.1).

6.2.4.2 The first 45 Gy will be delivered in 5 weeks for both Arm 1 and for Arm 2. For subsequent boost RT (to 61 Gy, continuing without a break in Arm 2), see Section 6.5

6.2.4.3 TREATMENT INTERRUPTIONS ARE STRONGLY DISCOURAGED. Two circumstances in which a break may be appropriate are hospital admission for severe esophagitis requiring parenteral alimentation and/or Grade 4 neutropenia with fever. Regardless of cause, if an interruption greater than 3 consecutive days is planned, the Primary Study Coordinator for Radiation Oncology, Dr. Turrisi, or, in his absence, the Primary Medical Oncology Coordinator, Dr. Albain, must be notified. If neither is available, contact other Intergroup Radiation Oncology Coordinators, as listed. If not done, this will constitute a major protocol violation. Regarding esophagitis, provide patients with all possible symptomatic measures. Carafate, antacids, viscous xylocaine, and dyclonine are all allowed and encouraged, as well as dietary supplements.

6.2.5 Target Volume: Both Arms

The target will be defined by CT scan and clinical evaluation prior to therapy. This volume includes ipsilateral hilar and subcarinal lymph nodes; and nodes to at least 2 cm above or below known mediastinal disease, and any lymph node ≥1 cm on CT scan. If no nodes are visible, the tumor and hilar nodes surrounded by 1.5-2.0 cm plus the mediastinum from the inferior head of the clavicle through 5.0 cm below the carina define the target. For patients with lower lobe lesions, cover the mediastinum to include paraesophageal and inferior pulmonary ligament nodes. This target volume must receive the 45 Gy tumor dose.

DO NOT TREAT SUPRACLAVICULAR NODES.

Field margins of 1.5-2.0 cm are required around the radiographically-visible primary tumor volume. In cases with extensive atelectasis and/or pneumonia where tumor margins are obscure, field boundaries are left to the judgement of the participating radiation oncologist. In these instances, fields may be reduced as radiographic clearing occurs. The contralateral hilar nodes are not to be treated, but a 1 cm margin on the contralateral mediastinal shadow is required.

6.3 Re-evaluation following induction, ARMS 1 and 2: (refer to either 6.3.1 or 6.3.2 depending on arm assigned). The Post Induction Evaluation Form must be submitted at this time.

6.3.1 ARM 1: Re-evaluation

Two to four weeks after completion of initial induction chemoradiotherapy outlined in 6.1 and 6.2, all patients will be reassessed according to the following: history and physical by medical oncologist and evaluation by thoracic surgeon, EKG, blood gases, repeat PFTs with diffusion capacity (quantitative V/Q scan or split functions need not be repeated unless FEV1 worse than prestudy), full laboratory screen as per prestudy (except creatinine clearance not necessary to repeat here), chest X-ray, and chest and upper abdominal CT scan to include entire liver. A contrast brain CT or MRI is not required unless the patient has new symptoms. A bone scan is not required unless there is new bone pain or new elevation of the alkaline phosphatase or LDH.
Repeat the bronchoscopy if the initial bronchoscopy results impact on resectability; otherwise it does not need to be repeated.

6.3.2 **ARM 2: Re-evaluation (2/1/96)**
Within 7 days before anticipated completion of the 45 Gy induction RT (*approximately time of second chemotherapy cycle*), the patient should return to the medical oncologist for re-evaluation: history and physical, full laboratory screen as prestudy, repeat PFTs with diffusion capacity, chest X-ray, and chest and upper abdominal CT scan to include liver and adrenals. Do a bone scan only if there is a new elevation of LDH or alkaline phosphatase or new bone pain. A repeat brain scan by contrast CT or MRI is not required unless clinical symptoms are present.

6.3.3 **ARMS 1 and 2**
All patients after evaluation in Section 6.3.1 or 6.3.2 will proceed to Registration 2. If there is no evidence of local progression or distant metastases patients will be assigned options 3 or 4 (*Arm 1*) or option 5 (*Arm 2*) as described in Sections 6.4, 6.5.1 and 6.5.2. Response determinations (*CR, PR, SD*) will not be required for this study, but may be documented if done. If criteria for local and/or distant progressive measurable or evaluable disease (*below, and Section 11.3*) are met, the patient will then go off treatment and receive follow-up according to the schedule in Sections 11.1 and 11.2. All sites of progression that occur during induction therapy or found at post-induction re-evaluation must be documented on the Post Induction Evaluation Form. Refer to Schema page for required re-registrations. Specifically, the criteria for local progression are:

6.3.3.1 A 50% or greater increase in the size of the measurable primary lesion and/or initial nodal disease as measured by the product of the perpendicular diameters of the lesion on chest CT scan...OR....

6.3.3.2 A progression of evaluable disease as defined in Section 11.3.4.5...OR...

6.3.3.3 The new development of local thoracic spine invasion or other direct mediastinal involvement during treatment...OR...

6.3.3.4 The new development during treatment of mediastinal or supraclavicular nodal involvement.

6.4 **Post-induction surgery, (option 3) ARM 1 only:** (if ARM 2, proceed to Section 6.5 for continuation of therapy)

6.4.1 As per Section 6.3.3 all patients who fit the criteria for no progression in the chest or elsewhere, including all patients who have stable disease on reevaluation, will undergo Registration 2 and proceed to surgery (option 3).

6.4.2 If there is a local or distant progression, the patient will go off protocol treatment. Submit Post Induction Evaluation Form. If it is the opinion of the attending thoracic surgeon that the patient has developed a problem which makes surgery medically or technically unsafe, or if the patient refuses surgery, the Primary Study Coordinator for surgery, Dr. Rusch, or, in her absence, Dr. Albain, should be notified and this information will be reported at registration 2. Patients will then proceed with 2 additional cycles of chemotherapy (option 4).

6.4.3 Surgery will be performed 3-5 weeks after completion of chemo/radiotherapy. Occasionally an extra week will be required to recover from toxicity of induction therapy. If longer than a week is deemed necessary, Dr. Rusch or Dr. Albain should be notified. Document the reason(s) for delay on the Post Induction Evaluation Form.

6.4.4 **Surgical guidelines/extent of resection**

6.4.4.1 At thoracotomy, a lobectomy or pneumonectomy will be performed at the discretion of the Attending thoracic surgeon. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins. Documentation of margins by frozen section at surgery is strongly recommended.

6.4.4.2 Lesions with direct extension into parietal pleura or chest wall should be resected with an *en bloc* chest wall resection. Lesions with direct extension into pericardium or diaphragm should have *en bloc* resection of those structures with an attempt made to achieve a minimum of 2 cm gross, or 1 cm microscopic, margins.

6.4.4.3 All visible and technically accessible bronchopulmonary, hilar and mediastinal lymph nodes should be removed and submitted appropriately labeled to the pathologist. Numbering and/or nomenclature outlined in the Lymph Node Map will be used (see Appendix III). Mediastinal lymph nodes removed at thoracotomy should include nodes from the following regions:
6.4.4.3.1 For right sided lesions: 4R, 7, 8, 9, 10R; and if accessible, 2R.
6.4.4.3.2 For left sided lesions: 5, 6, 7, 8, 9, 10L; and if accessible, 4L.
6.4.4.4 The attending thoracic surgeon and medical oncologist must review and sign all post-surgical forms.

6.5 Additional Therapy (2/1/96)

6.5.1 Additional Chemotherapy, Arms 1 and 2, all patients (including unresectable, refused or medically unfit for surgery).
Two additional cycles of chemotherapy will be given as outlined in Section 7.1.
For patients in ARM 1, (option 3) chemotherapy will be given without additional radiotherapy, starting no sooner than 4 weeks and no later than 6 weeks from the date of operation. If additional delay is necessary, contact Dr. Albain, or in her absence, an appropriate group medical oncologist.
For patients in ARM 2, (option 5) and for patients in Arm 1 who did not undergo surgery (option 4), additional chemotherapy will be started no sooner than 3 weeks after cycle 2, day 8. A one week delay is permitted for recovery from toxicity of cycle 2, according to criteria in Section 7.3 and documented on flowsheet; if any additional delay is required, notify Dr. Albain or in her absence, appropriate group medical oncologist and document reason. Cycle 4 will begin 3 weeks after cycle 3, day 8, unless toxicity develops (Section 7.3).

6.5.2 Additional Radiotherapy: Arm 2 only (option 5)
6.5.2.1 RT will be continued (if there is no local or distant progression) with an additional 16 Gy with 2 Gy fractions, daily except weekends. There will be no break following completion of the induction RT. The CT scan done during the reevaluation may NOT be used for planning portals. Use the original tumor size, any node measuring ≥ 1.0 cm, plus 1-1.5 cm margins (for set-up, variation, motion, and dose build-up) to define the field for the additional radiotherapy.

6.5.2.2 The target volume includes the tumor, any node measuring 1.0 cm or more on CT scan or clinical examination. Angled oblique or lateral fields, or a combination of fields must exclude spinal cord, but provide coverage of the target volume. Minimize lung volume and dose whenever possible.

6.5.2.3 Off-axis points will be recorded 1 cm from the top and bottom of the fields, at points to determine spinal cord maximums and minimums, and target volume minimums. The same criteria for radiation interruption will be employed as per Section 6.2.4.3. Spinal cord to be excluded as per Section 6.2.3.1.

6.6 Upon completion of all treatment, patients in both arms of the study will be followed according to the schedule in Section 11.0.

6.7 Criteria for Removal from Protocol Treatment:
6.7.1 Disease progression (as outlined in Section 11.3.4.5) at any time during therapy or the follow-up period. The patient should be restaged and sites of recurrence and/or progression documented. Rebiopsy is strongly encouraged.
6.7.2 Unacceptable toxicity.
6.7.3 The patient may elect to withdraw from study treatment at any time for any reason.
6.7.4 Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up.
6.8 All reasons for discontinuation of treatment must be documented.
6.9 All patients will be followed until death.
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 Cisplatin (CDDP)(NSC-119875)

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

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

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

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

7.1.5 Administration: Cisplatin should be given immediately after preparation as a slow intravenous infusion as per Section 6.1.

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

7.2 VP-16 (NSC-141540) (Etoposide)(Vepesid)(Ethylidene-Lignan P.)

7.2.1 Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum peltatum, and has antineoplastic properties in experimental animals and in man. The empiric formula C_{29}H_{32}O_{13} has a molecular weight of 588.

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

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

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

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

7.2.6 Pharmaceutical Data: Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in clear ampules for injection. Each ampule also contains anhydrous citric acid 10 mg, benzyl alcohol 150 mg polysorbate 80 purified 400 mg, polyethylene glycol, and absolute alcohol. The manufacturer recommends etoposide dilution to a concentration of 0.2 or 0.4 mg/ml with either 0.9% Normal Saline, USP or 5% Dextrose Injection, USP. Diluted to these concentrations, it yields a product that is stable for 96 and 48 hours respectively, at room temperature (25 °C), and under normal room fluorescent light in both glass and plastic containers.

7.2.7 Administration: VP-16 should be given as a slow intravenous infusion as per Section 6.1 (7/1/94).

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

7.3 Toxicities to be Monitored and Dosage Modifications

* Questions about chemotherapy administration should be directed to Dr. Albain at (708) 327-3102.

7.3.1 Dosage modifications for day 1 of each chemotherapy cycle:

7.3.1.1 Myelotoxicity Adjustment

<table>
<thead>
<tr>
<th>If, on Day 1 of Cycle</th>
<th>ANC ≥ 2,000 and Platelets ≥ 100,000/ l</th>
<th>Give full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>If, on Day 1 of Cycle</td>
<td>ANC &lt; 2,000 or Platelets &lt; 100,000/ l</td>
<td>Delay 1 week</td>
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<tr>
<td>If, after 1 week delay</td>
<td>ANC &lt; 2,000 or Platelets &lt; 100,000/ l</td>
<td>Notify Study Coordinator</td>
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<tr>
<td>If febrile neutropenia during previous course</td>
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<td>Reduce VP-16 1 level</td>
</tr>
</tbody>
</table>

7.3.1.2 Renal Toxicity Adjustment for Day 1 of Each Chemotherapy Cycle

<table>
<thead>
<tr>
<th>If, on Day 1 of Cycle</th>
<th>Calc. creatinine clearance &lt; 50 ml/minute</th>
<th>Delay cisplatin 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>If, after 1 week delay</td>
<td>Calc. creatinine clearance ≥ 50 ml/min</td>
<td>Give full dose but increase pre- and post-cisplatin hydration</td>
</tr>
</tbody>
</table>

| If, after 1 week delay | Serum creatinine ≥ 1.7 mg% but ≤ 2.0 mg% and Calc. creatinine clearance ≥ 45 ml/min | Reduce cisplatin 1 level and increase pre- and post-cisplatin hydration |
If, after 1 week delay Serum creatinine ≥ 1.7 mg% and Calc. Creatinine clearance < 45 ml/min Omit cisplatin on day 1 and 8 and re-evaluate at next cycle

7.3.1.3 There will be no dose escalations.
7.3.1.4 The use of CSFs **WILL BE PROHIBITED** during the entire treatment due to potential interaction with concurrent or previous RT.

7.3.2 *Dose levels for day 1 chemotherapy modification*

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<tr>
<th>DRUG</th>
<th>DOSE LEVEL</th>
<th>DOSE</th>
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<tr>
<td>Cisplatin</td>
<td>Full Dose</td>
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<td></td>
<td>-1 Level</td>
<td>25 mg/m², d1,8</td>
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<td>VP-16</td>
<td>Full Dose</td>
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<td></td>
<td>-1 Level</td>
<td>50 mg/m²/d x 4 days</td>
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<td></td>
<td>-2 Level</td>
<td>50 mg/m²/d x 3 days</td>
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<td></td>
<td>-3 Level</td>
<td>50 mg/m²/d x 2 days</td>
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</table>

7.3.3 *Day 8 cisplatin modifications*
7.3.3.1 Cisplatin will be omitted on day 8 if day 1 dose was omitted.
7.3.3.2 Cisplatin will be omitted if there is Grade 4 neutropenia on day 8. There will be no modification for grades 1-3 myelotoxicity.
7.3.3.3 Cisplatin will also be omitted if patient develops ≥ Grade 2 renal toxicity, Grade 4 esophagitis, or febrile neutropenia.
7.3.3.4 Contact Study Coordinator if in the opinion of the investigators, there is any other reason to omit day 8 cisplatin.
7.3.3.5 If cisplatin omitted on day 8, it should not be given again until day 1 of next cycle.

7.3.4 *Radiotherapy interruptions/delays (see Section 6.2.4.3):*
7.3.4.1 Will be permitted only for febrile neutropenia or grade ≥ 3 esophagitis/mucositis requiring parenteral alimentation; other reasons to be discussed with Study Coordinator for Radiation Oncology, Dr. Turrisi, *or in his absence*, Dr. Albain or appropriate group radiation oncologist.
7.3.4.2 Interruptions of longer than 3 days during induction are to be discussed with Dr. Turrisi (*or in his absence, Dr. Albain*), and documented. Interruptions during induction of longer than three consecutive days are to be discussed with Dr. Turrisi, *or in his absence*, Dr. Albain or appropriate group radiation oncologist.
7.3.4.3 The development of documented or suspected radiation pneumonitis during or following completion of RT (*either during or after induction or during or after additional RT*) should be reported immediately to Dr. Turrisi, *or in his absence*, Dr. Albain.
7.3.5 Development of severe dysphagia, dehydration and/or orthostasis refractory to intensive parenteral support or other unusual toxicity may be grounds for treatment removal and should be discussed with Dr. Albain if treatment delay must extend beyond one week.
7.3.6 For chemotherapy dose modification, contact Dr. Albain at (708) 327-3102, *or in her absence* appropriate group medical oncologist. For radiotherapy related questions, call Dr. Turrisi at (803) 792-3271, *or in his absence*, or appropriate group radiation oncologist. (2/14/95)
7.3.7 Unexpected (*nonhemotology, grade 4*) or fatal toxicities (*including suspected reactions*) must be reported to the RTOG Operations Office, Dr. Albain, the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 15.1.4. (2/1/96)
7.3.8 Any treatment or surgical mortality should be reported by fax both to Dr. Albain and to RTOG Headquarters. This is defined as any death not due to tumor progression during, or within 3 months of completion of therapy on Arm 2, or, within 30 days of surgery on Arm 1, or during or within 3 months of completion of post-surgery chemotherapy on Arm 1. Dr. Rusch, Surgical Coordinator, and the RTOG Operations Office (215/928-0153) should also be notified by fax of any surgical mortality or severe morbidity. Interval review of these events will be expedited (see Section 14.4). (2/1/96)
### 8.0 SURGERY

Per Section 6.4

### 9.0 OTHER THERAPY

Not applicable to this study.

### 10.0 PATHOLOGY

There will be no pathology review for this trial.

### 11.0 PATIENT ASSESSMENTS

See the following two pages for Sections 11.1 and 11.2.

#### 11.0 STUDY PARAMETERS

**11.1 STUDY CALENDAR ARM 1 (7/1/94, 2/1/96)**

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<td>Ancillary</td>
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<td>Tobacco ques.</td>
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</table>

**Note:** Forms to be used in this study are listed in the Forms Submission Guidelines in Section 12.0.

- # Repeat bone scan only if new bone pain, and/or new elevation of alkaline phosphatase or LDH; repeat brain scan only if new symptoms.
- † See Section 3.5
- ‡ Quantitative Lung V/Q Scan is only required if FEV1 is < 2.0 liters.
- ** Repeat at restage only if FEV1 is worse than prestudy and quantitative V/Q was required for eligibility.
- ¶ Daily, Monday-Friday x 5 weeks.
§ All patients will be restaged 2-4 weeks after completion of chemo/radiotherapy as per Section 6.3.1. Patients who demonstrate progressive local disease or distant metastases will be removed from protocol treatment. Patients who refuse surgery, or patients for whom surgery is medically contraindicated will proceed to Option 4 to get 2 additional cycles of chemotherapy. All other patients will proceed to Option 3 and will undergo exploratory thoracotomy with mediastinal sampling within one week of restaging as per Section 6.4.

Σ All patients receive 2 additional cycles of chemotherapy and continue the entire physical, lab and X-ray test schedule as per weeks 1-8 and Section 6.5.1. Cycle 3 day 1 begins no sooner than 4 weeks after surgery, and cycle 4 day 1 begins 4 weeks after cycle 3 day 1. Patients who refuse surgery or for whom it is contraindicated will begin cycle 3 day 1 no sooner than 3 weeks after cycle 2 day 8.

Δ Initial follow-up after completion of all therapy: 4-6 weeks after either completion of 2 additional cycles of chemotherapy.

£ Subsequent follow-up: Every 2 months x 1 year; then every 3 months x 2 years, then every 6 months indefinitely. CT scans of the chest/upper abdomen and CT or MRI of the brain to be done only at 12, 18, and 24 months, and yearly thereafter.

◊ If the patient developed a new lung primary, any other new malignancy or myelodysplastic syndrome since last follow-up, submit notice of second malignancy on the appropriate place on the Follow-up Form within 14 days of diagnosis.

x Must be offered to all patients; patients may refuse to answer any or all questions.

° Use baseline form prestudy and the followup form for all subsequent visits.

∞ Complete at first subsequent followup visit, then at 12, 18, 24 months and yearly thereafter.

### 11.2 STUDY CALENDAR ARM 2 (2/1/96)

<table>
<thead>
<tr>
<th>Required Studies</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>§ Continue chemo/XRT</th>
<th>Δ</th>
<th>£</th>
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<tbody>
<tr>
<td>Physical</td>
<td>Pre</td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 3</td>
<td>Wk 4</td>
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<td>Laboratory</td>
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</tr>
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<td>CBC/Differential/Platelet</td>
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<td>Serum Creat/Na,K,CO2,CL</td>
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<td>SGOT or SGPT/Alk Phos</td>
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<td>Pregnancy Test</td>
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<tr>
<td>X-Rays &amp; Scans</td>
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<td>Chest X-ray</td>
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<td>PFTs/DLCO/ABG</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Treatment</td>
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<td></td>
</tr>
<tr>
<td>Cisplatin x 1 Dose</td>
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<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>VP-16 x 5 Daily Doses</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>RT/Chest</td>
<td>X‡</td>
<td>X‡</td>
<td>X‡</td>
<td>X‡</td>
<td>X‡</td>
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<tr>
<td>Second prim/other malig.</td>
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<tr>
<td>Ancillary</td>
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<tr>
<td>Tobacco ques. x°</td>
<td>X°</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*NOTE: All forms to be used in this study are listed in the Forms Submission Guidelines in Section 12.0.

# Repeat bone scan only if new bone pain, and/or new elevation of alkaline phosphatase or LDH.

Ω Repeat brain scan only if new symptoms.

‡ See Section 3.5

∞ Complete at first subsequent followup visit, then at 12, 18, 24 months and yearly thereafter.
Quantitative Lung V/Q Scan is only required if FEV1 is < 2.0 liters.

Daily, Monday-Friday x 5 weeks, then continue boost dose without a break.

All patients will be restaged according to Section 6.3.2 within 7 days before anticipated completion of 45 gy RT. Patients who demonstrate progressive local disease or distant metastases will be removed from protocol treatment. All other patients will continue with additional RT WITHOUT interruption.

Additional RT: In direct continuity with induction, patients will continue with additional XRT (Option 5) and 2 additional chemotherapy cycles as per Section 6.5. Cycle 3 day 1 begins 3 weeks after cycle 2 day 8. Cycle 4 day 1 begins 3 weeks after cycle 3 day 8. Perform history and physical, lab tests, and chest x-ray during boost RT, and chemotherapy on same schedule as weeks 1-8.

Subsequent follow-up after completion of all therapy: 4-6 weeks after completion of boost.

If the patient developed a new lung primary, any other new malignancy or myelodysplastic syndrome since last follow-up, submit notice of second malignancy form and document on appropriate place on the Follow-up Form within 14 days of diagnosis.

Must be offered to all patients; patients may refuse to answer any or all questions.

Use baseline form prestudy and the followup form for all subsequent visits.

Complete at first subsequent followup visit, then at 12, 18, 24 months and yearly thereafter.

11.3 Criteria for Evaluation and Endpoint Definitions

11.3.1 Measurable Disease: Either: 1) bidimensionally measurable lesion with clearly defined margins by medical photograph (skin lesion), or by x-ray or scan, with at least one diameter greater than .5 cm (bone lesions are not included) or 2) palpable lesion with both diameters 2 cm or greater.

11.3.2 Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined, palpable lesions with either diameter less than 2 cm, any lesion with both diameters less than .5 cm, bone disease.

11.3.3 Non-Evaluable Disease: Pleural effusions, ascites, disease documented by indirect evidence only (e.g., by lab values).

11.3.4 Objective Status, To Be Recorded at Each Evaluation: If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

11.3.4.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease related symptoms. No evidence of non-evaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable and non-evaluable lesions and sites must be assessed. Refers to clinical CR. When restaging surgery is required, a separate pathologic response variable is coded.

11.3.4.2 Partial Response (PR): Applies only to patients with at least one measurable lesion: Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed.

11.3.4.3 Partial Response, Non-Measurable (PRNM): Greater than 50% decrease in estimated area of evaluable, but non-measurable, tumor mass, as agreed upon by two independent observers, not to include pleural effusions. (Note: Response in patients with these specific types of evaluable disease and no measurable disease will be reported separately. Patients with both measurable and evaluable disease will be assessed for response according to Section 11.3.4.2).

11.3.4.4 Stable/No Response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites and lesions must be assessed.

11.3.4.5 Progression: 50% increase or an increase of 10 sq. cm (whichever is smaller) in the sum of products of measurable lesions over smallest sum observed (over baseline if no decrease), OR reappearance of any lesion which had disappeared, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to deteriorating condition (unless deterioration is clearly unrelated to this cancer). For scan only bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease does not constitute progression.

Exceptions: (1) In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond four
weeks or there must be additional evidence of progression. (2) Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

11.3.6 **Unknown**: Progression has not been documented and one or more measurable or evaluable lesions or sites have not been assessed.

11.3.5 **Note that non-evaluable disease** does not affect objective status except in determination of CR (must be absent), and in determination of progression (if NEW sites of non-evaluable disease develop).

11.3.6 **Best Response**: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every three to six weeks, two objective statuses or CR are required for a best response of CR; two of PR or better, but not qualifying for CR, are required for PR; two of PRNM or better but no qualifying for CR, are required for PRNM; two of stable/no response or better, but not qualifying as PR, or CR, are required for stable/no response; patients with objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease.

For patients with disease scheduled to be assessed only at greater than six week intervals, only one objective status of stable/no response will be required for a best response of stable/no response, but for a best response of CR, PR or PRNM there must be confirmation. A second assessment should be scheduled for four weeks after the first documentation of response.

11.4 **Performance Status**: Patients will be graded according to the Karnofsky scale:

<table>
<thead>
<tr>
<th>KARNOFSKY SCALE (KPS)</th>
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<tbody>
<tr>
<td>Able to carry on normal activity; no special care is needed</td>
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<tr>
<td>Unable to work, able to live at home, cares for most personal needs; varying amount of assistance is needed</td>
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<tr>
<td>Unable to care for self, requires equivalent of institutional or hospital care; disease may be progressing rapidly</td>
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</table>

11.5 **Time to Treatment Failure**: From date of registration to date of progressive disease (as defined in Section 11.3.4.5), or to date off treatment due to toxicity, refusal or death.

11.6 **Time to Death**: From date of registration to date of death.

12.0 **DATA COLLECTION** (4/20/98)

12.1 Data must be submitted according to the protocol requirements for ALL patients randomized, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
12.2 Within one week of Randomization (4/20/98)

Submit the following directly to RTOG:

12.2.1 Simulator films (with drawn target volume) included under T3.
12.2.2 Port films (double or triple exposure) to verify simulation (T3)
12.2.3 Pre-RX CT scan films (target and nodes identified on CT panels by marking pencils and crayons) (C1)
12.2.4 RT calculation form (T4)
12.2.5 Protocol treatment form (T2)
12.2.6 Medical Oncology Treatment Planning Form (M2) (discontinued)
12.2.7 Demographic Form (A5)

12.3 Within 14 days of Initial Registration:

Submit copies of the following:

12.3.1 Combined Modality Lung Initial Evaluation Form (I1)
12.3.2 Institution Operative Report for each prestudy procedure (bronchoscopy, mediastinoscopy, exploratory thoracotomy, etc.)
12.3.3 Institution Pathology Report and/or cytology reports (P1)
12.3.4 Institution Chest X-ray Report
12.3.5 Institution Pre-Rx CT Scan of Chest and Upper Abdomen Report (C3)
12.3.6 Study-Specific Flow Sheet documenting prestudy labs (SF)
12.3.7 Pretreatment Tobacco, Alcohol, and Diet Questionnaire (PQ)

12.4 Arms 1 and 2 - At the time of Re-evaluation per Section 6.3:

Submit copies of the following:

12.4.1 Study-Specific Flow Sheet (SF) documenting treatment, laboratory work, and toxicity, since initial submission through completion of induction treatment (Section 12.3.6)
12.4.2 Post Induction Evaluation Form (F0)
12.4.3 Institution Chest X-ray and CT Chest Reports (C3)
12.4.4 Follow-up Tobacco, Alcohol, and Diet Questionnaire (PF)
12.4.5 Arm 1 only, submit Radiation Therapy Form (T1)
12.4.6 Arm 2 only, submit Radiation Therapy Form (T1), within two weeks of completion or termination of radiation therapy boost. Option 5, only submit a Study-Specific Flowsheet (SF) documenting combined modality toxicity, treatment, and relevant laboratory data within 30 days of completion of post XRT chemotherapy.

12.5 Arm 1 only - Within 30 days of Surgery (Protocol Option 3): (2/1/96)

Submit copies of the following:

12.5.1 Surgery Form documenting surgery and post-surgical treatment (S1)
12.5.2 Operative Report from Surgery (S2)
12.5.3 Pathology Report from Surgery (should include nodal mapping results) (S5)

12.6 Arms 1 and 2 - Within 30 Days of 1st Post-Therapy Follow-up Evaluation (See Study Calendar under 1st Follow-up for definition):

Submit copies of the following:

12.6.1 Materials from additional RT, Arm 2
   1. Central axis, isodose distribution (T6) off axis calculation 1 cm from cephalad and caudad margin on the sagittal plane of spinal cord
   2. Boost field portal and simulation films (T8) (Arm 2, Option 5 only)
   3. Treatment record (T5)
12.6.2 Study-Specific Flowsheet (SF) documenting rest of treatment including additional chemotherapy requirements on Study Calendar, Arms 1 and 2.
12.6.3 Institution CXR and CT scan reports (C3)

12.7 Arms 1 and 2 - During Follow-up (See Section 11.0):

Submit copies of the following:

12.7.1 Follow-up Form (F1) documenting required parameters as specified on the Study Calendar.
12.7.2 Institution CXR and CT scan reports (C3) (when done) to be sent also.
12.7.3 Follow-up Tobacco, Alcohol, and Diet Questionnaire (PF)
12.8  **Arms 1 and 2 - Within 14 days of Progression/Relapse or other Reason for Removal from Protocol Therapy:**

Submit copies of the following:

12.8.1 Follow-up Form (F1) documenting the date of progression/relapse/other reason, and summarizing inclusive dates of treatment, and patient status. Provide details of restaging at time of relapse, and all appropriate pathology and radiology reports documenting all sites of relapse. Submit until death.

12.9  **Within 4 weeks of Knowledge of Death:**

Submit copies of the following:

12.9.1 Follow-up Form (F1) documenting death information and events since last submission. If the patient developed a new lung primary, any other new malignancy, or myelodysplastic syndrome since the last follow-up, document on appropriate place on the Follow-up Form. Include pathology reports when histologic confirmation has been made.

12.10  **Data Submission-Non RTOG Institutions (7/1/94, 7/14/95, 2/1/96, 10/15/96)**

12.10.1  **Data**

The RTOG assigned case and study number must be recorded on all data items submitted. **CALGB, ECOG, NCCTG, NCIC CTG, and SWOG institutions will send all RT materials (both initial and final) directly to RTOG at the following address:**

RTOG Operations Office
American College of Radiology
1101 Market Street, 14th Floor
Philadelphia, PA  19107

All other data will be submitted to the participating Cooperative Group Offices. **Both the CALGB or ECOG or SWOG, NCCTG, NCIC CTG, or NCI Navy and RTOG assigned case and study numbers must be recorded on all items submitted. Unidentified data will be returned.**

**SWOG** - Non-RT data is sent to the SWOG Statistical Center at:

Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA  98104-2092

**CALGB** participants should submit all other data forms to the CALGB Data Management Center. Forms will then be forwarded to the RTOG Headquarters. The CALGB Data Management Center address is:

CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC  27705

**NCIC CTG** - All other data forms must be submitted, for forwarding to RTOG, to the NCIC CTG Central Office:

82-84 Barrie Street
Queen's University
Kingston, Ontario, K7L 3N6

12.10.2  **Time Critical Data (fax #215/928-0153, as applicable)**

Time critical data which require rapid submission are:

C1- Pretreatment CT Scan
M2- Medical Oncology Treatment Planning Form
T2- Protocol Treatment Form
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is progression-free and overall survival.

13.1.2 This study will examine patterns of failure for the two treatment regimens.

13.2 Sample Size (3/7/97)

13.2.1 The sample size is based upon the survival from the time of randomization. Patients will be randomized to either induction concurrent chemo-radiotherapy followed by surgery followed by chemotherapy (S+CT, Arm 1) or induction chemo-radiotherapy followed by boost radiotherapy plus chemotherapy (BRT+CT, Arm 2). The S+CT arm is based upon SWOG trial 8805 which has a reported one-year survival of 61%, 43, 44 median survival of 17 months, and two year survival of 40% for stage IIIa patients. Friess, et al. conducted a phase II trial on the regimen used in the BRT+CT arm. The estimates of the one-year and median survival is 65% and 15 months.27,28 These survival estimates incorporate treatment noncompliers; therefore, the sample size will not be adjusted.

13.2.2 According to the phase II data available the projected one-year survival on the S+CT will be 61% compared to 65% for the BRT+CT arm, but the median and two-year survival are 17 versus 15 months and 40% versus 25%, respectively. This indicates a possible crossing in the survival curves with clinically significant difference occurring beyond 2 years. Two methodologies were used to compute the estimated sample size to detect this difference. Using a conservative approach, assuming a two-year survival rate of 35% on the S+CT arm, and that the two-year rates are binomially distributed then 278 evaluable patients per arm will be required. This sample size will ensure a 80% (b=0.20, type II error) probability of detecting at least a 10% absolute difference in two-year survival (25% vs. 35%). In a second method utilizing a nonstationary Markov process to model survival, the sample size is calculated by the Lakatos method.47 The power estimate was obtained employing the transition probabilities (death rates) associated with each six month interval as projected from SWOG 8805 and Freiss, et al.27,28 Assuming a logrank statistic will be employed to test for treatment differences, and all patients will be followed for a minimum of two and a half years, then 278 evaluable patients per arm will ensure a 93% probability of detecting a clinically significant difference in survival distributions. Both methods are for a one-sided alternative hypothesis and will reject the null hypothesis at the 95% level (a=0.05, one-sided type I error). Based upon SWOG 8805 it is estimated that 10% of the randomized patients will ineligible; therefore, 612 patients will be needed to be randomized. However, if the ineligibility rate for randomization is significantly different than 10%, then the sample size will be adjusted accordingly.

13.2.3 The sample size was reassessed in September 1996. After two years of accrual there was a stabilization of accrual rates that were incorporated in the non stationary Markov sample size model presented above. The accrual is now assumed to be six patients per month and 2.5 years of follow-up. RTOG 88-08 induction chemotherapy followed by radiotherapy treatment regimen provides a better estimate of survival for the BRT+CT arm than was previously used. Based upon RTOG 88-08, patients with stage IIIA disease should have a one- and two-year survival of 57% and 26%, respectively. Further follow-up of SWOG 88-05, stage IIIA patients, indicates one- and two-year rates of 65% and 42%. Based upon these accrual and survival rates and keeping the type I and II errors the same, the required number of evaluable patients is 484.
The rate of ineligibility as of September 1996 is 5%; therefore, the total required number of patients is 510.

### 13.3 Patient Accrual
The patient accrual is projected at 10.4 cases per month in order to accrue the targeted total accrual in 4.9 years. If the average monthly rate is less than six cases, the study will be re-evaluated with respect to feasibility.

### 13.4 Randomization Scheme (2/1/96)
The treatment allocation will be one using a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables, based upon previous lung studies, are performance status (KPS 70-80 vs. KPS 90-100), T-stage (T1 vs. T2 vs. T3), and contralateral mediastinum sampling or biopsy (yes or no).

### 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) compliance rate of treatment delivery with respect to the protocol prescription; d) the frequency and severity of the toxicities; e) accrual by gender in order to monitor the ratio of males to females.

#### 13.5.2 Interim analyses of study endpoints
There will be two interim analyses of the primary endpoint (survival). The interim analyses will proceed according to the following table when the specified percent of randomized patients have been followed for 2.5 years.

<table>
<thead>
<tr>
<th>Total Accrual</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>33%</td>
<td>0.00250</td>
</tr>
<tr>
<td>67%</td>
<td>0.00296</td>
</tr>
</tbody>
</table>

If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be terminated. The results of these interim analyses will only be reported, in a blinded fashion, the RTOG Data Monitoring Committee as privileged communications. Through examining the above items, the study chair and the statistician can identify problems with the execution of the study. Any problems, 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 for a minimum of 2.5 years. The usual components of this analysis are:
1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.

### 14.0 DISCIPLINE REVIEW

#### 14.1 Radiation Therapy Review
All patients registered to this study will undergo radiotherapy review:
Dr. Turrisi, Radiation Primary Study Chair, will review materials from the first day of treatment, as well as later boost simulations for Arm 2. All materials must be sent to RTOG within one week of initiation of treatment and when appropriate, boost.

All data forms and films will be sent to:

- RTOG Operations Office
- American College of Radiology
Materials to be submitted within one week of initiation of treatment:
1. Simulator films (with drawn target volume) (T3)
2. Port films (double or triple exposure) to verify simulation (T3)
3. CT scan (with nodes identified) (C1)
4. RT calculation sheet (T4)
5. Protocol Treatment Form (T2)

14.1.2 The Radiotherapy Study Coordinator, Dr. Andrew Turrisi will review the completed records from radiotherapy given. Material needed for final review are:
1. Central axis, isodose distribution (T6) off axis calculation 1 cm from cephalad and caudal margin on the sagittal plan of spinal cord
2. Sim and port film verification copies for applicable boost fields. (T8)
3. Treatment record (T5)
4. Radiation Therapy Form (T1)

14.1.3 Boost radiation therapy for all patients in Arm 2.
1. RTOG will review the materials from the boost radiotherapy.
2. The Radiotherapy Study Coordinator, Dr. Turrisi, will review the completed records from the boost radiotherapy. Materials needed for review are listed in Section 14.1.2.

14.2 Surgical Review
14.2.1 There will be surgical review of all thoracic surgical procedures performed on patients enrolled on this protocol. The goal of the review is to ensure that patients have undergone careful prestudy and intraoperative staging.
14.2.2 Dr. Rusch, Thoracic Surgery Coordinator, will review all forms and reports required for this study as specified in Section 12.0, except the Radiation Therapy Forms.

14.3 Medical Oncology Review
14.3.1 Dr. Albain, Medical Oncology Coordinator, will review all forms and reports required for this study, as listed in Section 12.0.

14.4 Internal Audit of Adverse Events (see 7.3.7 and 7.3.8) (2/1/96)
Once received by the RTOG Headquarters, all case information will be sent as color-flagged materials to the Principal Study Coordinators, who will review and respond back to the RTOG office.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS
15.1 The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:
15.1.1 Informed Consent (2/14/95)
The principles of informed consent are described by the code of Federal Regulation Guidelines (§ 46.116, June 18, 1991). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.
15.1.2 Institutional Review (2/14/95)
This study must be approved by an appropriate institutional review committee as defined by the code of Federal Regulation Guidelines (§ 46.107, June 18, 1991).
15.1.3 Drug Accountability
For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained.
Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, and the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.
15.1.4  

**Adverse Experiences (7/1/94, 2/14/95, 7/14/95, 2/1/96, 10/15/96)**

All adverse events (see Appendix V) and those described below must be reported to the coordinating group office as specified. All participating group members may follow their group's Adverse Event Reporting Procedure provided prompt notification is done by phone to RTOG Operations Office (215/574-3214) by either the member institution or by the participating Group's Adverse Event representative.

Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. In phase II and III studies, all deaths considered drug-related must be reported immediately to the ADR representative.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgement as to relationship of the adverse experience to study medication(s) (i.e., "probably", "possible" or "unrelated").

- **RTOG** members must report any adverse experience, if deemed drug related, to the RTOG Operations Office Adverse Drug Reaction (ADR) representative (215/574-3214), who will obtain information on the ADR.
- **ECOG** institutions will notify the ECOG Statistical Center Data Management Office at (617) 632-3610. The ECOG Data Management Office will then call the RTOG Operations Office to report the ADR.
- **CALGB** participants should telephone the CALGB Central Office within 24 hours of the Adverse Event (312/345-0117). The original report should be sent to the CALGB Central Office:
  
  208 S. LaSalle St.,
  
  Suite 2000
  
  Chicago, IL  60604-1104

  A copy of the report will then be forwarded to RTOG Headquarters.

- **SWOG** institutions will notify the ADR representative at the SWOG Operations Office at (210) 677-8808. A copy of the ADR forms must be submitted to the SWOG Operations Office for forwarding to RTOG. SWOG ADR forms should be mailed within 10 days to:
  
  ATTN:  ADR Program
  
  Southwest Oncology Group
  
  14980 Omicron Drive
  
  San Antonio, TX  78245-3217

- **NCCTG** institutions will fax, then report in writing to NCCTG Operations Office (no telephone calls necessary) within five working days:
  
  1. Any ADR that is both serious and unexpected: life threatening (grade 4) or fatal (grade 5).
  2. Any increased incidence of a known ADR that has been reported in the package insert or the literature.
  3. Any death on study, if clearly related to the commercial agent(s) (see Section 7.3.8).

The ADR report must be documented on the ADR form (Form FDA 3500) and the original mailed to:
North Central Cancer Treatment Group  
Operations Office  
200 First Street, SW  
Rochester, MN 55905

• **NCIC CTG**

**Adverse Drug Reactions (ADR) reporting should be based on the RTOG Common Toxicity Criteria (Appendix IV).**

NCIC CTG centres will notify the Central Office (613) 545-6430 within 24 hours of the event. A copy of the RTOG ADR Form 3500 and the NCIC CTG Adverse Event Form must be submitted to the NCIC CTG Central Office within 10 days for forwarding to RTOG.

**GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRs) OCCURRING WITH COMMERCIAL AGENTS**

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 an attributed to the commercial agents (should be reported to the RTOG Operations Office (215/574-3214), within 24 hours of occurrence, your Institutional Review Board (IRB) and written notification to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

(a) Any ADR which is **BOTH** serious (*life threatening [Grade 4] or fatal [Grade 5]*) and unexpected.* Occurrences of second malignancies should also be reported, including: 1) protocol reference number, 2) time from diagnosis to development of second malignancy, 3) any characterization of the second malignancy (*i.e., for AML-FAB sub-type, cytogenetics, etc.*).

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

(c) Any death on study if **CLEARLY** related to the commercial agent(s).

The ADR report should be documented on Form FDA 3500 and mailed to the address below. A copy of the report, all pertinent data forms and a copy of documentation of notification of your IRB, must be sent to the RTOG Operations Office in Philadelphia, PA via respective Cooperative Group Office within 10 days. ECOG

institutions will submit written reports for the Adverse Reaction *(ADR)* Form for Investigational Drugs *(Form 391RF)* in lieu of the Form FDA 3500. ECOG institutions should mail completed forms to the ECOG Statistical Center Data Management Office *(ATTN: ADR)*. The forms will then be forwarded to RTOG.

**Investigational Drug Branch (IDB)**  
P.O. Box 30012  
Bethesda, MD 20824

* **Attn: ADR Program/Data Management**

**Radiation Therapy Oncology Group**

1101 Market Street, 14th Floor  
Philadelphia, PA 19107

* - See NCI Common Toxicity Criteria.
- A list of all known toxicities can be found in either the Background section, Drug Information or Informed Consent Form of the protocol.

- Reactions judged definitely not to be treatment related should not be reported. However, a report shall be submitted if there is only a reasonable suspicion of drug effect.
REFERENCES


RESEARCH STUDY

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

PURPOSE OF THE STUDY

My doctors have determined that I have lung cancer which has spread to where curative surgery is not possible. However, there is no evidence that the cancer has spread beyond the chest, to involve other organs in my body. When the type of lung cancer is called "non-small cell", like mine, the standard form of treatment has been radiation therapy. This type of treatment often prolongs life. A few patients may be cured by it. Recently, chemotherapy and radiation therapy have been combined for the initial treatment for this disease. It appears that tumor shrinkage occurs more often and lasts longer than when radiation is used alone. In fact, the amount of tumor shrinkage from combined chemotherapy and radiation may make it possible to have an operation which removes all of the cancer remaining in the area of the original tumor. The doctors do not know if results from treatment with surgery after chemotherapy and moderate dose radiation therapy will be any better than the results with chemotherapy and higher dose radiation therapy, used alone. Because it involves the permanent loss of some normal lung tissue, surgical removal of the tumor may mean that less radiation therapy can be used, since radiation therapy may cause damage to normal lung tissue. If I receive chemotherapy and radiation therapy without surgery afterward, the amount of radiation I receive will be greater. All patients will receive the same amount of chemotherapy.

The safety and the potential side effects of this regimen of radiation and chemotherapy are well known and there is national experience with the addition of surgery. However, my doctors cannot guarantee that the combination of radiation, chemotherapy and surgery will be more effective or more safe treatment than radiation plus chemotherapy 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 two regimens 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 regimens by computer. The chance of my receiving one of the two therapies is approximately equal.

Whether I am randomized to Arm 1 or Arm 2, I will come into the hospital or clinic and receive two drugs through a needle placed in a vein in my arm (intravenous).
In order to minimize the chance of permanently decreasing the kidney's ability to handle the body's waste, prior to receiving chemotherapy treatment, I will receive extra fluid through a vein. After each dose of cisplatin, I will again be given approximately two pints of fluid. I will receive cisplatin over a period of 60 minutes on days one and eight and VP-16 over a period of 60 minutes daily for five days. This treatment will be repeated in four (4) weeks.

The day the drug treatment begins, I will start radiation therapy to my chest for five days per week for five weeks.

This initial treatment will be completed in approximately 6 weeks. My doctor will then re-evaluate my disease. If my disease spreads or gets worse, I will be taken off treatment and my doctor will discuss alternative treatments with me. If my disease stays the same or gets better, and I am randomized to Arm 1, I will have surgery (thoracotomy) to attempt to remove the primary tumor and the lymph nodes under the breast bone followed by two additional cycles of chemotherapy. If I am randomized to Arm 2, I will not have surgery but will continue with two additional cycles of chemotherapy and radiotherapy without a break.

I will be offered a form to complete, which takes less than 10 minutes, regarding my use of tobacco and alcohol and my dietary habits. I understand that the completion of any or all of these questions is voluntary and that my refusal will not jeopardize my treatment on this study.

I will then be followed by my doctor at regular intervals. Routine laboratory tests including blood, urine tests and x-rays and scans will be done during my therapy so my doctor can check the tumor's response to treatment and my body's reaction to the treatment. VP-16 and cisplatin are commercially available.

**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.

**VP-16 (Etoposide):** This drug can affect several parts of my body in addition to the cancer cells. Sometimes, it could cause nausea or vomiting. These usually develop shortly after the drug is administered and usually last less than 24 hours. I will be given medications for this. Diarrhea is infrequent.

VP-16 can decrease the blood cells produced in the bone marrow. This can lead to:

1. Decreased white cells which may make me more vulnerable to infection.
2. Lower number of red cells which may make me short of breath, weak and fatigued.
3. Lower platelets which may result in easy bruising or bleeding for a longer time.

The drug's effect on the bone marrow is only temporary and transfusions are available if needed to replace these cells until my bone marrow recovers. Blood samples will be taken frequently to monitor the effects of the chemotherapy on my bone marrow.

Temporary hair loss, not only from the scalp but possibly underarms, beard, eyelashes and pubic area can occur. The loss is occasionally total but the hair does grow back when drug treatment is stopped. Giving the drug too rapidly into the vein can lower my blood pressure. To avoid this the drug will be administered over at least 30 minutes. Other complications, although rare, are a tingling sensation in my fingers and/or toes, liver damage, mouth ulcers, temporary blindness, skin rash, discoloration and itching. Very rarely, patients have experienced an allergic reaction to the drug, causing difficulty breathing, chills, fever, a drop in blood pressure and rapid heart beat. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 along with certain other chemotherapy drugs.

**Cisplatin:** This drug can affect several organs (or parts) in my body, in addition to the cancer cells. Nearly everyone experiences some type of stomach upset in the form of loss of appetite, nausea and/or vomiting. Nausea and vomiting usually begin 1 to 6 hours after administration, and usually do not last greater than 24 hours but loss of appetite may persist for up to a week. Drugs will be given to me before and after the cisplatin and may completely avoid or significantly diminish this side effect.
There is a chance of permanently decreasing the kidneys' ability to handle the body's wastes. To avoid this, I must increase my intake of fluids by mouth so that I urinate more frequently. In addition, I will receive fluid into a vein prior to my treatment and fluid after my treatment. Sometimes, the drug can cause high-frequency (above normal speech) hearing loss detectable only by hearing tests (audiograms). Ringing in the ears can occur and is usually reversible.

Cisplatin can decrease the blood cells produced in the bone marrow. This can lead to:
1. decreased white cells and may make me more vulnerable to infection.
2. lower number of red cells which can give me symptoms of shortness of breath, weakness and fatigue.
3. lower platelets which can result in easy bruising or bleeding for a longer time.

The drug's effect on the bone marrow is only temporary and transfusions are available if needed to counteract decreases in these cells until my bone marrow recovers. Blood samples will be taken frequently to monitor these effects of the drug on my bone marrow.

Other complications, although rare, that can occur are loss of taste, allergic reactions and loss of muscle or nerve function which may cause weakness or numbness similar to having my hand "fall asleep", and may be associated with some clumsiness of movement.

Chest Radiation Therapy: Side effects which have been observed in some people undergoing chest radiotherapy include nausea and vomiting and loss of appetite. There is a possibility I may develop difficulty swallowing or a sore throat. This might be more severe if it occurs because I am getting chemotherapy together with radiotherapy. I may need to receive fluids through my vein or food through a tube to my stomach in the rare instance that it is too painful to eat or swallow anything. There is also a possibility of inflammation of the lungs and drop in the white blood count, platelet count and the red blood cells. It is also possible that my lungs may develop scarring. Any of these changes may result in shortness of breath and may develop long after the radiation is over. My doctor will be watching me closely for these problems. There is a very remote possibility of injury to the spinal cord.

Surgery: The complications of surgery (thoracotomy) to remove lung cancer are known. They include: bleeding, infection in the chest (empyema) or in the incision, shortness of breath and pneumonia. Less frequently, patients may experience abnormal heart rhythms or poor healing of the end of the windpipe requiring re-operation for treatment. The overall risk of serious or life-threatening complications is less than 10%.

I understand that I may not participate in this research project if I am pregnant or nursing. There are certain risks to the fetus when the mother is receiving cancer treatment. If I am female of childbearing potential, I understand my doctor will perform a pregnancy test to make sure that I am not pregnant.

If I am a female of childbearing potential I will ensure that I am using an effective method of birth control. If I am a male and my partner is capable of having children, I will ensure that we are both using an effective method of birth control.

If I become pregnant during the course of my treatments, I will notify my physician immediately so that he/she can discuss treatment alternatives with me.

CONTACT PERSONS

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

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

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

**ALTERNATIVES**

Alternatives which could be considered in my case include radiation therapy alone, chemotherapy 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 result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance.

**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, at my investigator's Cooperative Group, 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

TNM Definitions (New International Lung Cancer Staging System)

**Primary Tumor (T)**

TX  Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not 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 canna. 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 canna without involving the canna.

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

**Footnote to TNM 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 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.

**Nodal Involvement (N)**

N0  No demonstratable metastasis to regional lymph nodes.

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

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

N3  Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes.

**Distant Metastasis (M)**

M0  No (known) distant metastasis

M1  Distant metastasis present - Specify site(s)
APPENDIX III

LYMPH NODE MAP
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 (2/14/95)**

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

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

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

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

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

**Investigational Agents**

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

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

i. Phase I Studies Utilizing Investigational Agents

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

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

- All life threatening (grade 4) events which may be due to agent. As above
- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

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

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

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

** See attached NCI Adverse Drug Reaction Reporting Form
APPENDIX VI-A
Thoracic Surgeon's Questionnaire

Please complete this questionnaire following a careful review of the eligibility and surgical sections of this Intergroup protocol and return this form to your Research Associate.

1. This study requires careful documentation of stage of disease prior to registration. CT scan findings are not accepted as sole criteria of nodal status. For example, pretreatment mediastinal sampling is required for most patients. Is this a procedure that you perform routinely and would you agree to do for this protocol?

   YES _______ NO_______
   Comments ________________________________

2. This protocol requires nodal sampling or dissection at thoracotomy at all levels of hilar and mediastinal nodes according to the American Thoracic Society Lymph Node Map. Are you familiar with this nodal mapping system?

   YES _______ NO_______
   Comments ________________________________

   Do you routinely perform mediastinal nodal sampling or dissection at the time of pulmonary resection?

   YES _______ NO_______
   Comments ________________________________

   Do you agree to do it as specified in the protocol?

   YES _______ NO_______
   Comments ________________________________

3. The surgery arm of this study requires an operation for all patients after chemoradiotherapy except those who have progressive disease. Do you agree to attempt resection of all patients if no medical contraindication exists including those patients who achieved only stable disease on CT scan re-evaluation?

   YES _______ NO_______
   Comments ________________________________

4. Please check the item that best describes the scope of your practice:

   _____ general Surgery plus Thoracic Surgery
   _____ mostly Thoracic Surgery, some Cardiac Surgery
   _____ mostly Cardiac Surgery, some Thoracic Surgery
   _____ equal mix of Thoracic and Cardiac Surgery
   _____ only Thoracic Surgery
5. If there are other surgeons at your institution who will be participating in this program, have they also filled out these forms?

YES  NO  (?)

If you have any specific questions about this form or other aspects of the trial, please call:

Valerie Rusch, M.D.
Memorial Sloan-Kettering Cancer Center
Thoracic Surgery Service, Room C-877
1275 York Avenue
New York, NY 10021
Phone: 212/639-5873
Fax: 212/717-3682

Signature of Physician completing this form
Institution Name

Printed Name of Physician  RTOG Institution Number

Telephone number of Physician  Physician's Fax Number

Return this form to your Research Associate

RTOG Research Associates: Once all three questionnaires for your institution have been returned to you, forward the entire packet to:

Radiation Therapy Oncology Group
1101 Market Street
Philadelphia, PA 19107
Attention: Elaine Pakuris

ALL GROUPS: SUBMIT TO YOUR RESPECTIVE GROUP OFFICES

FOR OFFICE USE ONLY

______________________________  ______________________________
Signature of Valerie Rusch, M.D.  Date

Review Comments
This questionnaire is for the Medical Oncologist who will supervise institutional participation in this study. It's not necessary for all medical oncologists at your institution to complete. Please complete this questionnaire following a careful review of the eligibility and chemotherapy sections of this Intergroup protocol.

1. The success of this trial in part depends on accurate staging according to protocol guidelines. All attendings of the appropriate disciplines (medical oncology, radiation oncology, thoracic surgery) must see the patient's pre-registration and must agree upon the stage and protocol treatment plan together. The Medical Oncologist must provide the initial staging classification for the Research Associates and assist in proper designations on the checklist and data forms. This will require a bit more attention than, for example, a phase II or adjuvant trial. Are you willing to adhere to these requirements.

YES ________ NO________

Comments ____________________________________________________________

2. This trial has different radiotherapy requirements and schedules in two arms. Two arms differ in the re-evaluation schedule. It is imperative that in the non-surgery arm there is no break after 45 Gy in the continuation with a modified RT port to 61 Gy?

   a) Are you aware of these differences and will you be able to strictly follow the specific timing of requirements on the Study Calendar?

   YES ________ NO________

   Comments ____________________________________________________________

   b) Are you aware that the re-evaluation in the non-surgery arm occurs during the induction treatment as specified on the Study Calendar?

   YES ________ NO________

   Comments ____________________________________________________________

3. Do you agree to insist upon surgical resection for patients with stable disease according to protocol guidelines?

   YES ________ NO________

   Comments ____________________________________________________________

4. Patients on the preoperative chemotherapy or chemoradiotherapy arm may be at an increased risk of postoperative infection and ARDS.

   a) Are you willing to be involved (peripherally) in the postoperative care and advise your surgeon to use more aggressive antibiotic support earlier than is usually done for a standard thoracotomy without preoperative therapy?

   YES ________ NO________

   b) Are you able to advise the surgery team to follow the patients carefully for early signs of pulmonary decompensation after surgery and during or after the boost phase?

   YES ________ NO________

   Comments ____________________________________________________________
5. Have all thoracic surgeons and radiation oncologists who will be treating patients on these studies with you read the protocols and filled out and returned the appropriate questionnaires to their Research Associates for forwarding to the Operations Office?

YES__________    NO__________

6. If there are other medical oncologists at your institution who will be participating in this program, are they also aware of these points and are they in agreement with these questions (they do not need to fill out the questionnaire)?

YES__________    NO__________

If you have any specific questions about this form or other aspects of the trial, please call:
Kathy S. Albain, M.D.
Loyola University
2160 South 1st Ave./Bldg. 112 Room 109
Maywood, IL  60153-5589
Phone: 708/327-3102
FAX: 708/327-2210
She will review the nuances of the differences between the arms with you in greater detail.

________________________________________________________________________
Signature of Physician completing this form Institution Name
________________________________________________________________________
Printed Name of Physician RTOG Institution Number
________________________________________________________________________
Telephone Number of Physician Physician's Fax Number

Return this form to your Research Associate

RTOG Research Associates: Once all three questionnaires for your institution have been returned to you, forward the entire packet to:

Radiation Therapy Oncology Group
1101 Market Street
Philadelphia, PA  19107
Attention: Elaine Pakuris

ALL GROUPS: SUBMIT TO YOUR RESPECTIVE GROUP OFFICES
________________________________________________________________________
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Signature of Kathy Albain, M.D. Date

Review Comments
________________________________________________________________________
This questionnaire is for Radiation Oncologists interested in participating in the Intergroup randomized comparison of chemoradiotherapy alone vs. chemoradiotherapy prior to resection for patients with pathologically proven N2 or N3 disease (*CT criteria alone are insufficient*). Different doses and schedules are used on each arm of this study, and only patients on the non-surgery arm receive additional RT. Please complete this questionnaire and return it to your Research Associate following careful review of the protocol.

1. Will you be treating patients on this trial at a radiation facility approved for your Cooperative Group?
   
   YES  ________  NO  ________
   
   Comments  ____________________________________________________________

2. Simulation AND start of chemoradiotherapy must begin no later than 3 working days after registration and randomization. Are you able to comply with this requirement?
   
   YES  ________  NO  ________

3. Although all patients receive radiotherapy in this trial, there are critical differences in the RT in the two arms. Please carefully review Sections 6.2 (induction treatment) and 6.5 (additional RT).
   
   a) Do you agree to follow the requirements for simulation as specified in these sections?
      
      YES  ________  NO  ________
   
      b) Are you willing to adhere to specific requirements for the additional RT in the non-surgery arm?
      
      YES  ________  NO  ________
   
      c) The protocol specifically forbids interruptions for esophagitis or neutropenia less than Grade 4 (see Section 6.2.4.3). Are you willing to follow this guideline?
      
      YES  ________  NO  ________
      
      Comments  ____________________________________________________________

4. a) Are you aware that induction RT stops at 45 Gy in the surgery arm, but continues uninterrupted to 61 Gy in the non-surgery arm?
    
    YES  ________  NO  ________
    
    b) For those patients randomized to Arm 2 (no surgery) are you willing to follow the guidelines regarding the additional radiotherapy, as well as the volume and fractionation specifications for this boost in Section 6.5?
    
    YES  ________  NO  ________
    
    c) Are you aware that no patient is to receive the additional RT on the surgery arm (Arm 1)?
    
    YES  ________  NO  ________
5. For those patients who are on the non-surgery arm, it is imperative that the Medical Oncologist collaborate with you to perform the reevaluation while the induction RT is being completed. THERE IS TO BE NO "REST". The timing is depicted on the Study Calendar. Are you willing to:

a) adhere to this schedule

YES_________ NO_________

b) revise the port volumes and fractionation as instructed in 6.5?

YES_________ NO_________

c) continue RT without interruption?

YES_________ NO_________

Comments ________________________________________________________________

6. Because of the risk of ARDS and infection in multimodality protocols, multidisciplinary collaboration is critical. Do you agree to the joint care aspects of this program with medical oncology and thoracic surgery as detailed on the Study Calendars?

YES_________ NO_________

7. If there are other radiation oncologists at your institution who will be participating in this program, have they also filled out one of these forms?

YES_________ NO_________

If you have any specific questions about this form, or any other aspects of this trial, please call:

Andrew T. Turrisi, M.D.
Department of Radiation Oncology
Medical University of South Carolina
171 Ashley Avenue
Charleston, SC 29425-0721
Phone: 803/792-3271
Fax: 803/792-5498

He will review the nuances of the differences between the two arms regarding volumes, fractionation, and schedule with you in greater detail.

________________________________________________________________________

Signature of Physician completing this form Institution Name

________________________________________________________________________

Printed Name of Physician RTOG Institution Number

________________________________________________________________________

Telephone Number of Physician Physician's Fax Number

Return this form to your Research Associate
RTOG Research Associate: Once *all three* questionnaires for your institution have been returned to you, forward the entire packet to:

**Radiation Therapy Oncology Group**  
1101 Market Street  
Philadelphia, PA  19107  
Attention: Elaine Pakuris

**ALL GROUPS: SUBMIT TO YOUR RESPECTIVE GROUP OFFICES**

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______________________________  ________________________________
Signature of Andrew T. Turrisi, III, M.D.    Date

Review Comments  ____________________________________________

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