### EASTERN COOPERATIVE ONCOLOGY GROUP

Prospective Randomized Trial of Postoperative Adjuvant Therapy in Patients with Completely Resected Stage II and Stage IIIa Non-Small Cell Lung Cancer: Intergroup

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1.0 INTRODUCTION

Non-small cell lung cancer (NSCLC) represents the most common solid organ tumor in the United States (1). Despite nationwide reduction in smoking and increased smoking cessation programs, it appears that the development of new cases of lung cancer will remain constant well into the next century (2). Consequently, continued efforts aimed at improving treatment of this deadly disease are of paramount importance.

In general, NSCLC patients present with metastatic disease or unresectable local disease and are not curable with surgical resection. However, approximately 30% of patients are able to undergo complete resection, many of whom achieve long-term survival (3). Mountain, et al. have published survival statistics for clinically and pathologically staged patients utilizing the new international staging system (4). Pathologic staging following complete resection and mediastinal lymph node dissection results in improved survival data because of more accurate patient grouping. The data of Mountain and others have demonstrated that patients with pathologic Stage I (T1N0, T2N0) disease have long-term tumor-free survival that ranges from 60-70% (5-7). On the other hand, patients with pathologic Stage II disease (T1N1, T2N1) have a 5 year survival ranging from 30-60% (8, 9). Patients with resected IIIa (T1N2, T2N2, T3N2) have poorer 5 year survival ranging from 15-29% (10, 11). In addition to stage, histology may represent an independent prognostic factor. Squamous cell cancers have been associated with improved survival (12).

Following resections for "cure", treatment failures may occur as local-regional recurrence, distant metastases or both. Extra-thoracic metastases are particularly problematic and account for the majority of recurrences following surgical resections. For example, Feld, writing for the Lung Cancer Study Group, documented distant metastases as the first sites of recurrence for completely resected Stage I non-small cell lung cancer in 65-75% of patients (13). Similarly, Pairolero reported that only a minority of patients with Stage I non-small cell carcinoma developed local recurrence only (14). Recurrence patterns for patients with resected Stage II (T1N1) tumors is similar to that reported for Stage I (8, 13, 14). Stage IIIa and IIIb patients also are known to recur both distally and locally but with an even greater probability of distant metastases (11, 15). Because of the high probability of recurrent disease, both local and distant, investigators have evaluated a variety of "adjuvant" therapies over the last several years. For the most part, these studies have been unrewarding. Recently, however, the Lung Cancer Study Group have reported on the results of 3 randomized trials which suggest more effective adjuvant therapy may be possible.

In the first study conducted by the Lung Cancer Study Group NSCLC patients with completely resected Stages II or III adenocarcinoma or large cell carcinoma were randomized to receive intrapleural BCG + Levamisole or post-operative chemotherapy with Cyclophosphamide, Doxorubicin, and Cisplatin (CAP) (400 mg/M²; 40 mg/M³; 40 mg/M³) (17). One hundred forty-one patients were entered on study of whom 130 were evaluable. The median survival of the group receiving CAP exceeded the BCG + Levamisole group by 7 months (22.5 months versus 15.5 months; P = 0.078 [Mantel-Haenszel], P = 0.047 [Wilcoxon-Gehan]). The investigators concluded CAP was beneficial in completely resected Stages II and III NSCLC (i.e., improved disease-free survival). Interestingly, only 17% of all initial recurrences were exclusively local demonstrating the effect surgery has on local control. Not too surprisingly, the majority of relapses (66%) occurred in distant sites indicating the need for a "systemic" therapy more effective than CAP (17).

In a companion study, the Lung Cancer Study Group evaluated the value of post-operative radiotherapy in patients with completely resected Stages II and III squamous cell carcinoma of the lung (16). Patients were randomized to receive postoperative radiation (5,000 cGy in 5 weeks) or no additional therapy. Although there was no difference in survival between the two groups (MS = 32 months versus 37 months; P = 0.678), patients who received radiation had a marked decrease in local recurrence (3% versus 41% of patients experiencing a relapse; P < 0.001 and 1% versus 19% of all patients; P < 0.05). A subset analysis suggested that patients with N2 disease may derive a survival benefit from post-operative radiotherapy (16). However, a prospective randomized trial is necessary to confirm or refute this hypothesis.
Finally, the Lung Cancer Study Group evaluated adjuvant therapy in patients with incompletely resected Stages II and III NSCLC (all histologies). Incompletely resected disease was defined as the presence of positive surgical margins and/or evidence of tumor in the highest paratracheal node sampled during mediastinal dissection (18). Patients were randomized to receive thoracic radiotherapy (4,000 cGy in a split, unconventional course) versus CAP + RT. CAP (400 mg/M²; 40 mg/M²; 40 mg/M²) was administered as in the previous study, i.e., every 4 weeks for 6 courses (17, 18). Again, median survival was prolonged in the group receiving CAP (20 months versus 15 months) as was the percentage surviving at 1-year (68% versus 51%). Although these differences were not statistically significant (P = 0.133), deaths due to cancer in the first postoperative year were less common in the CAP + RT group (0.309/person versus 0.556/person; P = 0.02) (18).

These three Lung Cancer Study Group studies all suggest adjuvant therapy can potentially improve survival of NSCLC patients with pathologically documented Stage II and III disease provided an "adequate" systemic therapy is used. Since these trials were undertaken, there is growing evidence that high-dose Cisplatin is required to achieve optimal results in the treatment of NSCLC (19, 20, 20a). Furthermore, data exist which suggest a combination of Cisplatin plus a vinca alkaloid or an epipodophyllotoxin yields the highest response rates in metastatic NSCLC (20-25). Importantly, even higher response rates have been reported with high-dose Cisplatin combinations used in NSCLC patients with locally advanced, non-metastatic disease (21, 26-29). For example, the CALGB reported an overall response rate of 57% (95% CI = 46% - 68%) using monthly Cisplatin (100 mg/M²) combined with the weekly Vinblastine (5 mg/M²) (26). Similar results were achieved with the same combination in a pilot study at Vanderbilt University (27). Data of a comparable nature have been reported with Cisplatin and Etoposide combinations and also Cisplatin, Vindesine (or Vinblastine) and Mitomycin-C combinations (21, 28, 29).

Although none of the aforementioned drug combinations has yielded clinically meaningful survival benefit in NSCLC patients with metastatic disease, there is a rationale for why a modestly active regimen that is non-curative in metastatic disease may still be capable of improving survival when used as a postoperative surgical adjuvant. First, chemotherapy agents achieve a 1 to 2 log reduction with each successful course of therapy. In the presence of metastatic disease, a 3 log reduction can lower the tumor from 100 million tumor cells to 100,000 cells, but eventually drug resistance develops with resultant progressive disease and death. In an adjuvant postoperative setting, however, the same 3 log reduction might lower the number of cancer cells from 10,000 to 10, a small enough number of residual cells that the host can eradicate by normal immunological clearing.

Second, many drugs are cell-cycle specific and therefore, more effective during the S phase (DNA and protein synthesis) of the cell cycle. In an adjuvant setting, a higher percentage of cells may be in the S phase, in contrast to bulky metastatic deposits where most cells are in the resting phase of the cell cycle.

Third, in preclinical systems, such as Lewis lung carcinoma, following intraperitoneal transplant of tumor cells, visible nodules appear on the ventral surface of the animal within 2 weeks. If Cyclophosphamide is given at that time there is prolongation of survival but no cures. However, if the same dose of Cyclophosphamide is given 2 days after tumor implantation, before visible tumor nodules appear (adjuvant therapy in a murine model), there is a 100% cure rate. Unfortunately, human cancer is spontaneous, not transplanted, and has undergone many doublings by the time of diagnosis.

Fourth, there is increased tumor heterogeneity with chemoresistant clones of tumor cells with increasing tumor size and age (metastatic disease) compared with micrometastatic disease (adjuvant therapy).

Finally, in curable metastatic solid tumors, a macromodel for adjuvant therapy, the extent of disease has a direct correlation with overall survival and cure. Testicular cancer with small pulmonary metastases is routinely curable whereas the same patient with multiple 5-cm pulmonary nodules will have less than 50% probability of cure. Limited small cell lung cancer has a 15% five-year survival,
compared with a 1% five-year survival in extensive cases. Thus, there appears to be a firm hypo-
thesis and actual rationale for why an adjuvant regimen used for micrometastatic disease may be far
more effective than the same regimen employed for gross metastatic cancer (30).

Based on the above considerations, the ECOG and the RTOG plan to undertake a prospective,
randomized trial of adjuvant therapy in NSCLC patients with completely resected Stage II (T1N1M0,
T2N1M0) and Illa (T1N2M0, T2N2M0, T3N1M0, T3N2M0) disease. All patients will be pathologi-
ically staged and will have undergone a "curative" resection of their tumor. Patients with Stage II and Illa
disease will be randomized to thoracic radiotherapy - the current "standard" therapy - versus
chemotherapy plus thoracic radiotherapy. The Cisplatin and Etoposide regimen was chosen because
in the ECOG experience it showed the best one year survival in Stage IV patients. The reasons for
selecting concurrent radiotherapy and chemotherapy over sequential radiotherapy and chemotherapy
are: neither modality is delayed, thereby reducing the potential for proliferation of resistant cells; the
overall duration of therapy is shortened providing fewer opportunities for delays or dose reduction; and
data for the efficacy of post-operative radiotherapy in improving local control support prompt rather
than delayed radiotherapy. In addition, there may be advantages in terms of radiosensitization
although this remains speculative.

2.0 OBJECTIVES

2.1 To determine if combination chemotherapy plus thoracic radiotherapy is superior to thoracic
radiotherapy alone in prolonging survival in patients with completely resected Stage II and
Stage Illa non-small cell lung cancer.

2.2 To determine if combination chemotherapy plus thoracic radiotherapy is superior to
thoracic radiotherapy alone in preventing local recurrence in patients with resected
Stage II and Stage Illa non-small cell lung cancer.

3.0 SELECTION OF PATIENTS

3.1 Patients must have:

3.11 Histologic documentation of non-small cell lung cancer.

3.12 Stage II (T1-2 N1 M0 ) or Stage Illa (T1-2 N2 M0 ; T3 N1-2 M0 ) disease according
to the International Staging System Criteria (Appendix III). A pathologic diagnosis of
Stage II/Illa must have been made at the time of surgical resection (i.e., by
postoperative pathologic diagnosis) to be included in the study.

3.121 Cervical mediastinoscopy is required for any patient whose CT scan shows
a mediastinal lymph node ≥ 1.5 cm in cross-sectional diameter. If the tumor
is in the left upper lobe or left hilar region, level 5/6 lymph nodes with a cross-
sectional diameter ≥ 1.5 cm must be biopsied by extended mediastinoscopy
or thoracoscopy. A complete cervical mediastinal staging includes nodal
stations R2, R4, R10, 7, L10, or L4, L2 if possible. At minimum, three
stations must be sampled: one ipsilateral, 7 and one contralateral. If
microscopic disease is present in one mediastinal nodal level, the patient is
eligible for the study. If more than one level has tumor, or if extranodal
disease is present in even one level, the patient is not eligible. Patients who
are NOT required to undergo cervical mediastinoscopy and who are found
to have extranodal disease at the time of surgical biopsy are eligible.
3.13 Surgery consisting of lobectomy, sleeve resection, bilobectomy or pneumonectomy, as determined by the attending surgeon based on the intraoperative findings.

3.131 Surgery within 56 days prior to randomization. See Section 5.1.

3.1311 For pneumonectomy and sleeve resection patients ≥ 28 days must have elapsed between surgery and study entry.

3.1312 Following a lobectomy or bilobectomy ≥ 14 days must have elapsed between surgery and study entry.

3.14 Undergone a complete resection of the tumor along with a complete intraoperative mediastinal node dissection or nodal sampling. A complete nodal dissection is recommended but not required (see Section 5.13). The nodal tissue must be labeled according to the recommendations of the American Thoracic Society (Appendix IV). All gross disease must have been removed at the time of surgery. All surgical margins of resection must be negative for tumor.

3.141 Though surgeons are encouraged to dissect or sample all accessible nodal levels, the minimal levels acceptable for study entry are as follows: right thoracotomy-levels 4, 7, 10; left thoracotomy-levels 5 and/or 6 & 7.

3.15 ECOG performance status of 0 or 1.

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

3.17 Post operative FEV₁ sufficient for patient to tolerate protocol radiation therapy.

3.18 WBC ≥ 3000 and platelet count ≥ 100,000; serum creatinine ≤ 1.5 mg/dl or creatinine clearance > 60 ml/min. Laboratory values must be obtained ≤ 2 weeks prior to registration.

3.19 ≥ 18 years of age.

3.110 Given written informed consent.

3.111 ECOG patients must be registered on the ancillary laboratory study E4592 at the time of registration to E3590. Submission of one paraffin block of primary tumor or a portion of primary tumor tissue removed directly from the block is mandatory. Please refer to E4592 for details.

3.2 Patients must not have:

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

3.22 Previous or concurrent malignancy other than curatively treated non-melanoma skin cancer or in situ cervical cancer unless a 5-year, no-treatment disease-free interval intervenes.

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

3.24 The presence of T3N0 disease, Stage IIIb (i.e., contralateral N2 or N3) disease or Stage IV (M1) disease.
3.25 Incompletely resected gross disease.
3.26 Microscopic positive bronchial or vascular margins.
3.27 Small cell lung carcinoma (including "mixed" histology).
3.28 Bronchioalveolar carcinoma of lobar or multi-lobar involvement.
3.29 ECOG performance status ≥ 2.
3.210 Superior vena cava syndrome.

4.0 RANDOMIZATION PROCEDURES

Note: The radiotherapy treatment planning should be completed PRIOR to randomization.

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ECOG INSTITUTIONS NOTE: Patients must be registered on the ancillary study E4592 at the time of registration to E3590. Submission of one (1) paraffin block of primary tumor or a portion of primary tumor tissue removed directly from the block is mandatory. Please refer to E4592 for details.

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RTOG/NCCTG/SWOG/CALGB Institutions Eligible for E4592/SWOG 9323/RTOG 94-09/NCCTG 93-24-52: Investigators are strongly encouraged to consider their patients for Laboratory/Clinical Correlative Studies in Non-Small Cell Lung Cancer, Ancillary entry on E4592: Study to EST 3590. This study seeks to determine whether K-ras and p53 mutations, Group A blood antigen and EGF receptor levels, and p105 and Factor 8 levels are predictive of patient survival and local recurrence in patients undergoing defined therapy postoperatively for completely resected Stage II/IIIA NSCLC. Please refer to E4592 for details.

4.1 ECOG Randomization

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A signed HHS 310 Form, a copy of the institution's IRB-approved informed consent document, and written justification for any changes made to the informed consent for this protocol must be on file at the ECOG Statistical Center Data Management Office (ATTN: DATA) before an ECOG institution may enter patients. The signed HHS 310, Institution's informed consent, and investigator's justification for changes will be submitted to the following address:

ECOG Coordinating Center
c/o Quality Control Office
1600 Pierce Street
Denver, CO 80214
FAX 303/233-1614

Patients must not start protocol treatment prior to registration.

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To register eligible patients on study, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office at (617) 632-2022. The following information will be requested:

4.11 Protocol Number
4.12 Investigator Identification

4.121 Institution name and/or affiliate
4.122 Investigator’s name

4.13 Patient Identification

4.131 Patient's name or initials and chart number
4.132 Patient's Social Security number
4.133 Patient Demographics

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4.1331 Sex
4.1332 Birthdate (MM/YY)
4.1333 Race
4.1334 Nine-digit zip code
4.1335 Method of payment
4.14 **Eligibility Verification**

Patients must meet all of the eligibility requirements listed in Section 3.0. The randomization specialist will ask questions from the eligibility checklist to verify eligibility.

4.15 **Stratification Factors**

4.151 **Nodal Status**

N1
N2

4.152 **Histology**

Squamous
Other

4.153 **Weight Loss in Previous 6 Months**

< 5%
≥ 5%

4.154 **Nodal Dissection**

Complete
Sampling

4.16 Treatment and sequence number will be confirmed by mail.

4.2 **RTOG Randomization**

**Note:** A signed HHS 310 Form for this protocol must be on file at the RTOG Office before an RTOG institution may enter a patient.

Investigators will FAX a completed Eligibility Checklist to the Radiation Therapy Oncology Group's Office (215) 928-0153 between the hours of 8:30 a.m. and 4:00 p.m. ET excluding holidays. The RTOG Office will confirm all eligibility criteria and information as per Sections 4.1, ECOG Randomization. The RTOG Registration Desk will then contact the ECOG Central Randomization Desk to enter the patient after which the RTOG Office will contact the institution to relay the treatment assignment for that patient. The ECOG Statistical Center Data Management Office will forward a confirmation of treatment assignment and an ECOG sequence number to the RTOG Office for routing to the RTOG participating institution.

4.3 **NCCTG Randomization**

**Note:** A signed HHS 310 Form for this protocol must be on file at the NCCTG Office before an NCCTG institution may enter a patient.
Consultation with a radiation oncologist regarding protocol treatment is required prior to randomization. The name of the consulting radiation oncologist, the date of consultation, and radiotherapy facility must be given to the NCCTG Operations Office.

The NCCTG Randomization Center will obtain and confirm all eligibility criteria and information as per Section 4.1, ECOG Randomization. The NCCTG Randomization Center will then contact the ECOG Central Randomization Desk to enter the patient after which the NCCTG Randomization Center will contact the institution to relay the treatment assignment for that patient. The ECOG Statistical Center and Data Management Office will forward a confirmation of treatment and an ECOG sequence number to the NCCTG Operations Office for routing to the NCCTG participating institution.

Rev. 12/93 4.4 SWOG Registration/Randomization

Investigators will telephone the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 am and 2:30 pm (PT) Monday through Friday, excluding holidays. The Statistical Center will obtain and confirm all eligibility criteria and information as per Section 4.1, ECOG Randomization. In addition, the Statistical Center will request the date informed consent was signed and the date of IRB approval for each entry. The SWOG Statistical Center will then contact the ECOG Randomization Desk to enter the patient. Next, the SWOG Statistical Center will contact the institution to relay the treatment assignment for that patient. The ECOG Statistical Center and Data Management Office will forward a confirmation of treatment assignment and an ECOG sequence number to the SWOG Statistical Center for routing to the participating SWOG institution.

Rev. 12/93 4.5 CALGB Registration/Randomization

CALGB randomization will be accepted through the Main Institution only. Prior to initiation of therapy, confirm all selection criteria listed in Section 3.0. Call the CALGB Data Management Center (919/286-4704, Monday through Friday, 9 am to 5 pm Eastern Time). The CALGB Registration Desk will then contact the ECOG Central Randomization Desk to enter the patient after, which the CALGB Office will contact the institution to relay the treatment assignment for that patient. The ECOG Statistical Center Data Management Office will forward a confirmation of treatment assignment and an ECOG sequence number to the CALGB Office for routing to the CALGB participating institution.

Rev. 12/93 4.6 Cancellation Guidelines

If a patient does not receive protocol therapy, the patient may be cancelled. Reasons for cancellation should be submitted in writing to the cooperative group Operations Office as soon as possible. The participating cooperative groups (RTOG, NCCTG, SWOG, CALGB) will forward such notification to the ECOG Statistical Center Data Management Office (ATTN: DATA). Data will be collected on all cancelled patients (see Section 10.0). Note: A patient may only be cancelled if no protocol therapy is administered. Once a patient has been given protocol treatment all forms should be submitted.

5.0 TREATMENT PLAN

5.1 Surgery

5.11 Accurate intraoperative surgical staging will be insured by strict attention to the anatomic boundaries between nodal groups described by the American Thoracic
Society regional nodal stations definitions (Appendix IV).

5.12 A pathologically complete surgical resection of the tumor mass by wedge/segmentectomy, lobectomy or pneumonectomy will be performed.

5.13 A complete mediastinal lymph node dissection or nodal sampling must be performed. Complete lymph node dissection is recommended. Complete lymph node dissection involves removing all lymph nodes of the anatomically defined level. Lymph node sampling necessitates opening the pleura and removing representative tissue from each lymph node level. A video illustrating appropriate technique will be available to all participating surgeons (contact the ECOG Study Chair, Dr. Steven Keller). All nodal tissue obtained must be carefully labelled by lymph node level. This must be performed by the operating surgeon in the operating room. Complete mediastinal dissection or sampling includes the following nodal levels:

- Levels 2 and 4*
- Levels 8
- Levels 5 and 6 in all patients when the primary lesion is located in the left lung
- Level 7
- Level 9
- Level 10

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

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

5.2 Chemotherapy Treatment Schedules:

Chemotherapy doses will be calculated on the basis of body surface area determined using the patient’s actual weight.

Chemotherapy will begin simultaneously (or within 24 hours) of initiation of radiotherapy (see Section 5.3). Chemotherapy cycles will be repeated every 4 weeks (28 days) for a total of 4 cycles.

Etoposide (VP-16) 120 mg/M² IV Days 1-3 of each cycle

Cisplatin (DDP) 60 mg/M² IV Day 1 of each cycle

5.21 Recommended Guidelines for Cisplatin Administration

These are guidelines only, the schedule of Cisplatin administration may be different at some participating institutions. Due to the potential risk of anaphylaxis, emergency medications should be available during all first treatments with Cisplatin, including epinephrine, a corticosteroid, and antihistamines.
Time 0 - Have patient void and start IV with 2 liters D5 1/2 NS + 10 mEq KCl/liter to run for 2 hours.

Time 0 - 40 mg Furosemide IV push.

Time 30 minutes - 12.5 gm Mannitol IV push and if patient has voided 200 cc urine.

Time 30-1/2 minutes - Cisplatin IV push (freshly mixed in sterile water); allow for brisk diuresis.

A 2-hour hydration schedule has been chosen for moderate-dose Cisplatin since it is the shortest schedule for which there is good data on prevention of nephrotoxicity. Furosemide is given at time 0 to guarantee that the fluid administered is, in fact, excreted via the urine (rather than entering an ascitic pool, or causing pulmonary edema), and the Mannitol is given to doubly ensure that a brisk diuresis is in progress when the peak plasma level of Cisplatin reaches the renal tubule.

Patients with cardiac, renal, or hepatic disease may need more intensive diuretic therapy to produce the desired 1 liter/hour diuresis. This should be provided using higher doses of Mannitol and Furosemide. If such a diuresis cannot be produced, no Cisplatin should be given to the patient.

5.3 Radiation Therapy

Radiation therapy is to be initiated no earlier than 4 weeks and no later than 6 weeks following pneumonectomy. Following a lobectomy, radiation therapy can begin 2 weeks post surgery and must begin no later than 8 weeks after thoracotomy. The Radiation Oncology Quality Assurance Center will perform a rapid and final review for each patient. A listing of materials required for this review and schedule for their submission can be found in Section 11.0, Records to Be Kept.

5.31 Equipment

All patients will be treated with isocentric equipment with a minimum SSD of 80 cm. Treatment should be given with photon energies of 4-12 MeV; planned exceptions to this should be discussed with Dr. Wagner at 813/972-8424. The use of electron beams is not permitted.

5.32 Treatment Planning

All patients must be simulated prior to the start of radiation therapy. Both the initial portion of treatment, which is to be given with APPA portals and the off-cord boost to be given with lateral and/or oblique portals should be simulated at this time with the patient in the same position for both phases of treatment to facilitate the construction of composite isodose plans. All simulation films should be copied and submitted to the Quality Assurance Center (See Section 10.0). Portal verification films should be taken of each field copied and submitted for review. The use of custom immobilization and support devices such as styrofoam molds is encouraged but not required.
5.33 Target Volume

The desired target volume for treatment on this study will encompass the mediastinal and ipsilateral hilar nodes. The tumor bed is to be included only if invasion of the parietal pleura is documented in the operative pathology report. The target volume is thus to be defined in terms of anatomic landmarks rather than the preoperative appearance of the tumor. A postoperative CT scan is required to document post surgical anatomic changes and to serve as a baseline study for comparison with follow-up studies.

The target volume will include the hilum ipsilateral to the primary tumor as well as bilateral peritracheal nodes. Neither the contralateral hilum nor the supraclavicular fossae are to be included on a routine basis. If, however, it is necessary to treat the tumor bed for a T3 lesion of the upper lobe, the supraclavicular fossa may be included. The exact placement of the field borders will vary somewhat from case to case depending on the postoperative shift of the mediastinal structures. See Appendix V for suggested radiation fields for initial APPA portals. The following are guidelines:

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

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

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

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

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

5.34 Treatment Technique

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

5.342 The remainder of the treatment will be given to the same target volume but with a field arrangement which excludes the spinal cord from the high dose volume and thus keeps the total cord dose to not more than 45 Gy. Oblique fields using angles between 20 and 40 degrees, with medial borders defined by the ipsilateral pedicle of the spine and including the subcarinal space and contralateral mainstem bronchus, are the preferred method. Lateral fields may be used, but for no more than 10 Gy.
Direct posterior spinal cord shields are not acceptable.

5.35 Dose

The entire mediastinal target volume will receive 50.4 Gy/28 fractions/6 weeks with a daily fraction size of 1.8 Gy and treatment once a day for 5 days per week. Patients whose hilar and/or mediastinal metastases were intranodal will receive no boost beyond this dose. **Patients in whom there is pathologic documentation of extracapsular extension of nodal metastases will have these nodal stations boosted with an additional 10.8 Gy/6 fractions. This boost is not optional. It is required for patients with transgression of the nodal capsule and prohibited for those whose disease was purely intranodal.** Pathology reports shall clearly distinguish extranodal extension. Clarification may be required with the pathologist.

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

5.352 Dose inhomogeneity corrections (lung corrections) will NOT be used.

5.353 The dose inhomogeneity across the target volume will be no more than +/- 5%. Isodose distributions will be performed, copied and submitted of the following three planes: 1) at the central axis; 2) 2.0 cm below the superior margin of the field; 3) 2.0 cm above the inferior margin of the field; and 4) for those patients who have a block placed at the superior-medial margin of the field for purposes of shielding the larynx, cervical cord, and upper esophagus, a plane will be calculated 2.0 cm inferior to the block. Isodose curves must account for the contributions of all the treatment fields and for any blocking used. The target volume, heart, lungs, and spinal cord must be clearly displayed on the treatment plan.

5.354 Tissue compensators are required if separations measured from top-to-bottom of the field result in variations in dose from top-to-bottom $\geq$ 10%.

5.36 Normal Tissue Dose

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>Not more than 35 Gy to $&gt;50%$ cardiac volume</td>
</tr>
<tr>
<td>Lung</td>
<td>20 Gy to entire lung</td>
</tr>
<tr>
<td>Esophagus</td>
<td>will tolerate doses required by protocol</td>
</tr>
</tbody>
</table>

5.37 Treatment Interruption

The majority of treatment induced esophageal complaints occur between week 2 and 3 of treatment. Dietary and medicinal regimens of local choice are encouraged. The majority of these complaints are self-limited and do not require breaks, which are specifically discouraged. Indications for interruption include $>10\%$ weight loss and the inability to swallow solids and liquids (all 3 parameters required). In this event, chemotherapy should NOT be delayed. Please discuss any deviations with the Radiation Therapy Coordinators (Dr. Wagner (813-972-8424 or Dr. Herskovic or Shaw).
5.38 Treatment is to be given 5 days per week, once each day. If there are holidays, equipment failure, or treatment interruption, the treatment should recommence as early as possible, and the cause of the delays documented.

5.4 Dose Modifications

Rev. 11/91
All toxicities should be graded according to the Common Toxicity Criteria (Appendix II), the Acute Radiation Morbidity Scoring Scheme (Appendix VI), or the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix VII), as appropriate.

5.41 Adverse Reaction Reporting Requirements

5.411 Deaths

Rev. 9/94, 1/95
Any death from any cause while a patient is receiving treatment on protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related must be reported as follows:

Rev. 9/94
5.4111 ECOG Members - An Adverse Reaction Form for Investigational Drugs (#391RF) must be sent to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 10 working days of the event. Notify local IRB within 10 days.

Rev. 1/95

Rev. 9/94
5.4112 RTOC Members - An Adverse Reaction Form for Investigational Drugs (#391RF) must be submitted within 10 working days of the event to the RTOG. Upon receiving the report from the RTOG will forward the form to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 3 working days.

Rev. 9/94

Rev. 11/91, 9/94
5.4113 NCCTG Members - an Adverse Reaction Form for Investigational Drugs (#391RF) must be submitted within 10 working days of the event to the NCCTG. Upon receiving the report form the NCCTG will forward the form to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 3 working days.

Rev. 12/93, 9/94
5.4114 SWOG Members - Within 10 working days of the event, an Adverse Reaction Form for Investigational Drugs (#391RF) must be sent to the SWOG Operations Office, where it will be forwarded to the ECOG Statistical Center Data Management Office.

Rev. 12/93, 9/94
5.4115 CALGB Members - An Adverse Reaction Form for Investigational Drugs (#391RF) must be sent to the CALGB Central Office within 10 working days of the event. Upon receiving the report form, the CALGB Office will, that same day, forward the form to the ECOG Statistical Center Data Management Office.

5.412 Unexpected Toxicities

5.4121 ECOG Members - for any unexpected toxicity (not reported in the literature or the package insert) an Adverse Reaction Form for Investigational Drugs (#391RF) must be submitted to the NCI and to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 10 working days of the event. Notify local IRB within 10 days.

Rev. 1/95
NOTE: Mailing address for the NCI is:
IDB
P.O. Box 30012
Bethesda, MD 20824
Telephone Number: (301) 230-2330
FAX Number: (301) 230-1059

Mailing address for ECOG ADR reporting is:
ECOG Statistical Center Data Management Office
303 Boylston Street
Brookline, MA 02146-7648
ATTN: ADR

5.4122 RTOG Members - for any unexpected toxicity (not reported in the
literature or the package insert) an Adverse Reaction
Form for Investigational Drugs (#391RF) must be submitted to the
NCI Drugs (#391RF) must be submitted to the NCI and to
the
RTOG within 10 working days of the event. Upon receiving the
report from the RTOG will forward the form to the ECOG Statistical
Center Data Management Office (ATTN: ADR).

5.4123 NCCTG Members - Report in writing to NCCTG Operations Office
within 5 working days: 1) any death on study if clearly related to the
commercial agent; 2) unexplained life-threatening reactions; and 3)
any increased incidence of a known adverse drug reaction that has
been reported in the package insert or the literature. The ADR
report must be documented on an Adverse Reaction Form for
Investigational Drugs (Form FDA 391RF) and mailed to:
NCCTG Operations Office
200 First Street, SW
Rochester, MN 55905
Within 5 working days of receipt of the ADR, NCCTG will forward a
copy to the Statistical Center and to the NCI.

5.4124 SWOG Members - All SWOG investigators are responsible for
reporting of adverse drug reactions according to the NCI and SWOG
guidelines. SWOG investigators must:

Call the SWOG Operations Office, 210/677-8808, within 24 hours of
any suspected adverse event deemed either drug-related, or
possibility drug-related.

Instructions will be given as to the necessary steps to take
depending on whether the reaction was previously reported, the
grade (severity) of the reaction, study phase, and whether the
reaction was caused by investigational and/or commercial agent(s).
The SWOG Operations Office will immediately notify the ECOG
Statistical Center Data
Within 10 days, the investigator must send the completed (original) FDA 1639 form to the NCI:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824

In addition, within 10 days the investigator must send:

- a copy of the above report,
- all data records for the period covering prestudy through the adverse event, and
- documentation of IRB notification, to the following address:

ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, Texas 78245-3217

At the Operations Office, a multilayered review will be performed and any pertinent findings will be forwarded to the ECOG Statistical Center Data Management Office, NCI, Study Coordinator, and Statistical Center along with any supporting documentation.

ECOG form #391RF will be completed by the investigator at any time the FDA 1639 form is used, and will be sent to the SWOG Operations Office where it will be forwarded to the ECOG Statistical Center Data Management Office.

CALGB Members - for any unexpected toxicity (not reported in the literature or the package insert) an Adverse Reaction Form for Investigational Drugs (#391RF) must be submitted to the NCI and to the CALGB within 10 working days of the event. Upon receiving the report form the CALGB will, that same day, forward the form to the ECOG Statistical Center Data Management Office (ATTN: ADR).

Grade 4 Toxicities - Expected

Commercial Agents - expected Grade 4 toxicities need not be reported.

Non-Treatment Related Toxicities

If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the ECOG Flow Sheets which are submitted according to the Records To Be Kept Section (10.0). This does not in any way obviate the need for reporting the toxicities described above.
5.42 Dose Modifications - Etoposide (VP-16) and Cisplatin (DDP)

5.421 Hematologic Toxicity

The following doses (mg/m^2) should be given, based on the counts from the first day of therapy of each cycle:

<table>
<thead>
<tr>
<th>Granulocytes and/or Platelets</th>
<th>VP-16</th>
<th>DDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,800</td>
<td>120</td>
<td>600</td>
</tr>
<tr>
<td>1,000-1,799</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

If granulocytes < 1,000 and/or platelets < 75,000 on a day when both DDP and VP-16 are scheduled to be given, delay therapy 7 days and administer doses based on the counts at that time.

Do not modify DDP doses based on depth of mid-cycle nadir; however, if patient suffers Grade 3 or 4 granulocytopenia complicated by infection, reduce VP-16 to 80 mg/m^2/day x 3 days for all subsequent treatments.

When a dose reduction is made for a decreased PMN or platelet count and the reduced dosage results in no toxicity, the next course should be given at the next highest dose level.

If, following the completion of radiotherapy, chemotherapy treatment must be withheld because of hematologic toxicity, a CBC and platelet must be obtained weekly until the counts reach the limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

5.43 Renal Dysfunction at the Time of Drug Administration

<table>
<thead>
<tr>
<th>Creatinine (mg%)</th>
<th>Percent Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 1.5-2.5</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>* 0%</td>
</tr>
</tbody>
</table>

* Delay Cisplatin until serum creatinine is < 1.5 mg/dl. Restart Cisplatin at 75%. If the creatinine again rises to > 2.0 mg/dl, discontinue therapy. If subsequent cycles at 75% result in a creatinine of 1.5-2.0 mg/dl, reduce Cisplatin to 50%.

5.44 Hepatic Dysfunction at the Time of Drug Administration

<table>
<thead>
<tr>
<th>Bilirubin and/or SGOT</th>
<th>Percent Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5 x nl</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 - 2 x nl</td>
<td>100%</td>
</tr>
<tr>
<td>2.1 - 5 x nl</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 5 x nl</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.45 Neurologic Toxicity

Cisplatin can cause neurotoxicity. Continue full doses of the drug for Grade 2 neuropathy. Patients with weakness or dysesthesia (Grade 3) should have
therapy withheld until these symptoms clear. Therapy would then be resumed at 50% dose and increased by 10% of the original dosage weekly as tolerated by the patient. Patients with Grade 3 neuropathy (limb weakness, apraxia, ataxia, or complete palsy of peripheral nerves, such as the peroneal) should have therapy discontinued.

5.46 Gastrointestinal Toxicity

5.461 Nausea and Vomiting
Severe debilitating (Grade 3) nausea and vomiting will necessitate reduction of Cisplatin. The dose should be reduced 50%, and if then tolerated, increase by 25% increments. Maximal use of antiemetics is encouraged, including pretreatment.

5.462 Esophagitis
See Section 5.37.

5.47 Auditory Toxicity (Cisplatin)
Cisplatin is well known to cause high frequency hearing loss. Continued use of the drug does not always result in further hearing loss, although it may do so. If early hearing loss is noted, the patient should be presented with a discussion of the relative risks of hearing loss versus the potential benefit of continuing Cisplatin therapy, and a decision made on continuation of Cisplatin. Severe hearing loss should be an indication for discontinuation of the drug.

5.48 Anaphylaxis
Patients suffering anaphylaxis or bronchospasm after Cisplatin or VP-16 should be treated immediately with fluids and antihistamines. Grade 3 or 4 allergic reactions will necessitate discontinuation of therapy.

5.49 Alopecia
Alopecia is common with all the drugs and will not alter drug administration.

5.410 Other Toxicity
For any other Grade 3 or 4 toxicity, treatment should be held until patients recover completely or to Grade 1 status. The next dose should be at 50% and if well-tolerated, subsequent doses should be increased by 25% in an effort to regain 100% dosing.

5.5 Supportive Therapy

5.51 All supportive measures consistent with optimal patient care will be given throughout the study.

5.52 The use of radiotherapy and corticosteroids should be clearly indicated on the flow sheets, as should dose and reason for continuation.

5.53 Hyperalimentation may be used, but details must be clearly outlined on flow sheets.
5.6 Duration of Therapy

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

5.62 Development of local, regional or distant recurrence (including CNS metastases) is grounds for removal of a patient from study. This must be documented on flow sheets. Biopsy of recurrence is encouraged (see Section 6.1).

5.63 Unacceptable toxicity from therapy after attempts to modify treatment so it is acceptable will constitute grounds for a patient's discontinuation of treatment but will not be grounds for removal from study. This must be documented on flow sheets.

5.64 Withdrawal of consent will automatically remove a patient from study; the reason must be documented on the flow sheets.

6.0 MEASUREMENT OF EFFECT

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

6.1 Recurrence

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

6.11 Definitions of Site of Recurrence

Local within RT port
Chest - outside RT port
Distant - brain, other

6.2 Disease-Free Survival

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

6.3 Survival

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

Study Parameter Guidelines

Adjuvant Protocols

a) CXR, scans should be done no longer than 3 weeks prior to definitive surgery.
b) CBC, differential, Plt should be done \leq 2 weeks before randomization.
c) All chemistries should be done \leq 2 weeks before randomization.

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

For follow up Hgb, Hct, WBC, Plt, Creatinine: these tests should be done within 48 hours of the day of chemotherapy.

<table>
<thead>
<tr>
<th>Pre-Registration</th>
<th>Weekly During CTX</th>
<th>Every 4 Weeks During CTX</th>
<th>Follow-up*</th>
<th>At Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Studies

- CBC, Differential, Platelet Count
- Creatinine
- Creatinine Clearance
- LFT's
- Lytes
- Ca++, Phosphorous
- TP, Albumin
- Radiologic Studies
  - Chest X-ray, PA & Lateral
  - Chest CT
  - Abdominal CT
  - Head CT
  - Bone Scan
  - PFT's

LFT = bilirubin, SGOT, alkaline phosphatase, LDH.
Lytes = Na, K, Cl, BUN, HCO₃⁻.

Rev. 11/91
1 LFT = bilirubin, SGOT, alkaline phosphatase, LDH.
2 Must be obtained post operatively - required for RT planning.
3 Abdominal CT not necessary if a chest CT includes the entire liver and the adrenal glands. Any adrenal gland showing loss of normal contour, regardless of size, must be biopsied.
4 Head CT is required only in neurologically symptomatic patients. At relapse, patients should undergo a head CT scan to document status of CNS only if they are neurologically symptomatic.
5 A pre-registration bone scan is desirable but not required in an asymptomatic patient with a normal alkaline phosphatase, a preoperative bone scan is required if the patient has bone tenderness or bone pain or an alkaline phosphatase twice the upper limits of normal or higher.
6 CBC, differential, and Platelet Count should be obtained weekly during XRT and every 2 weeks during chemotherapy following completion of XRT.
7 PFT's should be obtained prior to the initiation of XRT. In addition, repeat PFT's should be obtained at the first follow-up visit upon completion of XRT, and 1 year after completion of XRT.
8 Follow-up is every 3 months for 2 years, then every 6 months for years 2-5, then every 12 months thereafter. Obtain chest CT if symptoms. If no symptoms, obtain chest CT; every 6 months years 1 and 2, every 12 months thereafter up to 5 years.
9 Obtain if serum Creatinine > 1.5 mg/dl.
8.0 DRUG FORMULATION AND PROCUREMENT

Rev. 1/95

8.1 Cisplatin (Platinol®, Platinol-AQ®, cis-Diamminedichloroplatinum (II), CDDP, DDP, Platinum, PDD, DACP, cis-Platinum)

8.11 Classification

Heavy metal complex. Alkylating agent.

8.12 Mode of Action

One mode of cytotoxic action appears to be the inhibition of DNA precursors, although RNA and protein synthesis are also inhibited but to a lesser degree (Door and Fritz, 1980). Cisplatin has properties similar to that of a bifunctional alkylating agent producing interstrand and intrastrand crosslinks in DNA. It is apparently cell phase-nonspecific (Bristol, 1980).

8.13 Storage and Stability

Vials of Cisplatin are stored at room temperature. When reconstituted as directed, the solution is stable at room temperature for 20 hours. When further diluted to 0.5 mg/ml with normal saline, it is stable for 72 hours at room or refrigerator temperatures.

Rev. 1/95

8.14 Dose Specifics

60 mg/m² IV Day 1 of each cycle.

8.15 Preparation

The 10 and 50 mg vials should be reconstituted with 10 cc or 50 cc of Sterile Water for Injection, respectively. Each cc of the resulting solution will contain 1 mg of Cisplatin. The desired dose of Cisplatin is often further diluted with 250 ml or more of 0.45%-0.9% NaCl and 5% dextrose, normal saline or 3% sodium chloride.

8.16 Incompatibilities

1. Cisplatin may react with aluminum which is often found in syringe needles or IV sets. The reaction is rapid and may result in formation of a black precipitate and a loss of potency of Cisplatin.

2. Patients concomitantly receiving Aminoglycosides seem to be at greater risk of developing nephrotoxicity.

3. Cisplatin is incompatible in solutions that do not contain chloride ions such as D₂Water.

Rev. 1/95

8.17 Compatibilities

Cisplatin is compatible with mannitol, magnesium sulfate, potassium chloride and etoposide. Consult your pharmacist regarding specific concentrations.

8.18 Route of Administration

Rev. 1/95

IV push at 1 mg/ml. This admixture is stable for 20 hours at room temperature.

8.19 Availability

Commercially available in 10 mg and 50 mg vials of lyophilized powder and as a solution at 1 mg/1 ml.

Rev. 1/95

8.110 Side Effects

1. Hematologic: Myelosuppression (nadir of circulating platelets and leukocytes occur between Days 18-23 with most patients recovering by
Day 39. Leukopenia and thrombocytopenia occur, and are more pronounced at high doses (50 mg/m²); anemia (decrease 2 gm of hemoglobin 100 cc) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia.

2. Dermatologic: Alopecia (uncommon).

3. Gastrointestinal: Nausea and vomiting are common and may persist for up to 24-96 hours; anorexia.

4. Renal: Nephrotoxicity (may be cumulative) is dose-related and relatively uncommon with adequate hydration and diuresis; elevated serum creatinine and BUN.

5. Hepatic: Elevated AST and ALT.

6. Neurologic: Peripheral neuropathy (paresthesias), common and dose-limiting when the cumulative cisplatin dose exceeds 400 mg/m²; rarely seizures; ototoxicity manifested initially by high frequency hearing loss; vestibular toxicity (dizziness) uncommon; tetany (caused by hypomagnesemia); rarely Lhermitte’s sign.

7. Other: Hypomagnesemia, hypocalcemia, hyponatremia, vein irritation, papilledema, rarely retrobulbar neuritis, fatigue, rarely anaphylactic reactions can occur in previously treated patients. These may present with symptoms of tachycardia, confusion, agitation, wheezing, hypotension, and/or facial edema within a few minutes of IV administration. Secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare).

8.111 Nursing Implications

1. Check CBC and platelet count and renal function studies.

2. Maintain adequate hydration, administer hydration, administer diuretics as ordered. Document good urine output. Output should be 100-150 ml/hr.


4. Observe patient for signs of renal failure, hearing loss, neurotoxicity.

5. Note: Cisplatin is incompatible with aluminum. (Do not use aluminum IV equipment.)

6. At the start of therapy, have diphenhydramine, Epinephrine, and Hydrocortisone at the bedside. Observe carefully for signs of allergic reaction (tachycardia, chest pain, confusion, wheezing, agitation, hypotension, and/or facial edema, and erythema) which may occur within minutes of IV administration. If the reactions occur, stop infusion of Cisplatin and call the physician immediately.

8.2 Etoposide (VP-16, VP-16-213, VePesid®, EPEG, Epipodophyllotoxin, NSC #141540)

8.21 Classification

Podophyllotoxin derivative.

8.22 Mode of Action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport, and incorporation, and causes DNA breakage.
8.23 **Storage and Stability**

Rev. 1/95

The injection should be stored at room temperature. Following dilution in 0.9% sodium chloride or 5% dextrose to concentrations of 0.2-0.4 mg/ml the drug is chemically stable for 96 and 48 hours at room temperature, respectively. Bristol-Myers in-house data indicate that etoposide may be stable in 5% dextrose or normal saline for 24 hours (0.6 mg/ml), 4 hours (1 mg/ml), and 2 hours (2 mg/ml).

8.24 **Dose Specifics**

Rev. 1/95

120 mg/m² IV Days 1-3 of each cycle.

8.25 **Preparation**

Rev. 1/95

Generally the desired dosage is diluted in 250-1000 ml of 0.9% sodium chloride injection. Administer as a 30-60 minute infusion. Rapid administration may cause hypotension.

8.26 **Route of Administration**

Rev. 1/95

IV over 30-60 minutes.

8.27 **Incompatibilities**

Physically unstable in D₂W.

8.28 **Compatibilities**

Rev. 1/95

Compatible with Cisplatin 200 µg/ml in D₅NS or NS for 24 hours when protected from light. Addition of mannitol and/or potassium chloride reduces stability to 8 hours in NS, but remains stable for 24 hours in D₅NS in 5%; also compatible with cytarabine and daunorubicin.

8.29 **Availability**

Rev. 1/95

Commercially available as an injection in 100 mg (20 mg/ml) multiple dose vials.

8.210 **Side Effects**

Rev. 1/95

1. Hematologic: Moderate, reversible leukopenia in patients receiving daily IV injections with less than 100 mg/m²; primarily granulocytopenia; nadirs within 7-14 days and recovery within 20 days of administration; anemia. The drug is relatively platelet-sparing.

2. Dermatologic: Alopecia is generally mild, reversible and is reported to occur in 20-66% of the patients, although some patients develop total baldness; rash (rarely), severe pruritus (rarely), radiation recall reaction (rarely), phlebitis, local pain at injection site, pigmentation (rarely).

3. Gastrointestinal: Nausea and vomiting (33% of patients experience immediately after treatment or within 2-6 hours); stomatitis (rarely with conventional doses, more common and more severe in patients who have received radiation to the head and neck and with high doses, e.g., bone marrow transplantation); abdominal pain; anorexia (10-13% of patients) and diarrhea; aftertaste, parotitis, dysphagia, and constipation occur rarely.

4. Hypersensitivity: Anaphylaxis (rarely, 0.7-2% of patients).

5. Hepatic: Hyperbilirubinemia and increased transaminase levels, usually mild, transient and more common in high dose protocols; hepatotoxicity.

6. Cardiovascular: Transient hypotension, associated with rapid administration; hypertension (rarely); other cardiovascular events (e.g., congestive heart failure) thought to be related to large amounts of sodium chloride administered with the drug.
7. Neurologic: Peripheral neuropathy, somnolence, fatigue, headache, vertigo, transient cortical blindness (all rarely); transient confusion with high doses, perhaps due to the alcohol-containing vehicle.

8. Other: (All rarely) fever, muscle cramps, metabolic acidosis, hyperuricemia, substernal discomfort (20%), secondary AML/MDS.

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8.211 Nursing Implications

1. Advise patient of possible hair loss. Instruct how to obtain wig, hairpiece, etc. Reassure them that their hair will regrow following discontinuation of therapy.

2. Burning sensation and thrombophlebitis at the infusion site has been reported, although rarely. (Avoid extravasation.)

3. Monitor blood pressure every 15 minutes during and after IV course for rare possibility of hypotension.

4. Nausea and vomiting, mild, occurs 2-6 hours after treatment. Administer antiemetics.

5. Teach patient importance of maintaining adequate hydration to avoid hyperuricemia.

6. Monitor for anaphylaxis and be prepared.

7. Premedication with antiemetics may be helpful. Prolonging infusion over 1 hour does not lessen gastrointestinal toxicity.

8. Adequate CBC and platelet count necessary.

9. Infuse drug over at least 30 minutes. A more rapid infusion may cause hypotension.

10. Manufacturer recommends protective gloves be used during handling of concentrate and solutions, since skin reactions associated with accidental exposure may occur.

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9.0 STATISTICAL CONSIDERATIONS

9.1 Introduction

The primary objective of this Phase III surgical protocol is to determine if the addition of combination chemotherapy (DDP plus VP-16) to the standard post-operative thoracic radiotherapy will prolong survival in patients with completely resected Stage II and Stage IIIa non-small cell lung cancer.

9.2 Randomization and Patient Accrual

Patients will be assigned to treatments using a stratified permuted block randomization, balanced within main institutions. The stratification factors in this protocol are nodal status (N₁ vs N₂), histology (squamous versus non-squamous), weight loss within 6 months (< 5% versus ≥ 5%), and type of node dissection (sampling vs complete). Randomization is to a control (post-operative thoracic radiotherapy) and a treatment (combination chemotherapy concurrently with post-operative thoracic radiotherapy).

We assume that 20 ECOG institutions with thoracic surgery programs and the RTOG will contribute at least 10 eligible patients with completely resected Stage II and IIIa disease per month.

9.3 Study Duration and Group Sequential Design

A baseline median survival for those receiving thoracic radiotherapy only is estimated 30 months for patients with N₁ nodal status disease and 20 months for patients with N₂ nodal.
status disease. Eighty percent of patients undergoing complete resection are expected to have N2 nodal status disease and the remaining 20% N1 nodal status disease. Though not significant at 5% level, results from the LCSG study of incompletely resected Stage II and III NSCLC indicates that the post-operative combination chemotherapy of CAP plus radiotherapy is at least as beneficial as the radiotherapy alone (18). Hence it seems reasonable to consider a one-sided test of the hypothesis.

Under the assumption that the accumulating data will be analyzed for a total of four interim analyses including the final analysis using an O'Brien-Fleming type group sequential design for detecting early treatment difference, Table 1 gives the power of the one-sided stratified sequential logrank test for detecting 40% increase in median survival at a 5% significance level for several accrual durations and follow-up durations (31, 32). The nodal status, $N_2$ versus $N_1$, has been used in the calculation of the power for it is the most differential prognosis of survival among the four stratification factors.

Therefore, with 3.5 years of accrual and 1.5 years of follow-up for a total of 420 eligible patients, we can expect a reasonable sensitivity (0.852) to detect 40% increase in median survival for the combination chemotherapy concurrent with post-operative radiotherapy from the standard post-operative radiotherapy alone. Assuming 10% ineligibility due to cancellation, pathology exclusion, etc., the accrual goal will be 462 patients.

If the proportion of $N_2$ nodal status disease is 70%, the power of the same design will decrease slightly to 0.845. If the real treatment difference is 50% increase in median survival, the same design can achieve power as high as 0.941. Assumptions regarding patient accrual rate, proportion of patients with $N_1$ nodal status disease, ineligibility rate will need verification as the study progresses, and the correction will be made if necessary. There is sometimes crossing over of patients from one arm to the other, i.e., patients randomized to combination chemotherapy concurrent with radiotherapy who refuse it. If it is likely that this would happen with more than a few patients, the power would be diluted, and the sample size would need to be increased to compensate for it.

### Table 1

<table>
<thead>
<tr>
<th>Accrual Durations</th>
<th>Follow-Up Durations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>36</td>
<td>0.743</td>
</tr>
<tr>
<td>42</td>
<td>0.817</td>
</tr>
<tr>
<td>48</td>
<td>0.874</td>
</tr>
</tbody>
</table>

### 9.4 Interim Analysis and Data Monitoring

In order to effectively monitor the study, a data monitoring committee will be created according to the standard ECOG policy and procedure. Outcome data will be monitored annually mainly for treatment difference, except that the first interim analysis will take place two years after the study activation. The monitoring for treatment difference will be performed using the O'Brien-Fleming type group sequential boundaries (33, 34).

The interim analyses will be carried out approximately every year, except for the first year after study activation. Table 2 gives the group sequential boundaries, nominal
significance (to which p-value from the stratified logrank test should be compared), and the rejection probabilities under the alternative hypothesis for the scheduled repeated analyses at 24, 36, 48, and 60 months after study activation, that is, at the end of the follow-up period.

Table 2
Operating Characteristics of the Group Sequential Design

<table>
<thead>
<tr>
<th>Repeated Analyses</th>
<th>Chronological Times of Analysis (years)</th>
<th>Group Sequential Bounderies</th>
<th>Nominal Significances</th>
<th>Rejection Probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3.74</td>
<td>0.0000924</td>
<td>0.00888</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2.53</td>
<td>0.00576</td>
<td>0.271</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1.95</td>
<td>0.0257</td>
<td>0.410</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1.74</td>
<td>0.0413</td>
<td>0.161</td>
</tr>
</tbody>
</table>

With the scheduled interim analyses, the attainable power of the group sequential design will be approximately 0.851. If the number of repeated analyses is increased to five so that the interim analyses take place every year after study activation until the study closure, the operating characteristics of the group sequential design changes hardly at all.

9.5 Final Analysis

A final analysis will be performed soon after the follow-up period. The statistical analysis will be based mainly on the stratified logrank test for comparison of two treatments. The secondary endpoint of local recurrence rate will be also analyzed and so will the time to such recurrence.
10.0 RECORDS TO BE KEPT

10.1 ECOG Participants

The following forms must be submitted to the ECOG Statistical Center Data Management Office ATTN: DATA (303 Boylston Street, Brookline, MA 02146).

<table>
<thead>
<tr>
<th>Form</th>
<th>To Be Submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>*ECOG Lung On-Study Form (#341)</td>
<td>Within 1 week of registration</td>
</tr>
<tr>
<td>*ECOG CTC Flow Sheet (#466)</td>
<td></td>
</tr>
<tr>
<td>*ECOG Lung Thoracic Surgery Report Form (#526)</td>
<td></td>
</tr>
<tr>
<td>*ECOG Pulmonary Assessment Form (#524)</td>
<td></td>
</tr>
<tr>
<td>*ECOG Lung Pathological Staging Report Form (#525)</td>
<td></td>
</tr>
<tr>
<td>*Operative Reports for the mediastinoscopy and thoracotomy</td>
<td></td>
</tr>
<tr>
<td>*Pathology Reports for the mediastinoscopy and thoracotomy</td>
<td></td>
</tr>
<tr>
<td>Pre-Study Chest CT Report</td>
<td></td>
</tr>
<tr>
<td>ECOG CTC Flow Sheet (#466)</td>
<td>Every month while on study</td>
</tr>
<tr>
<td>ECOG Follow-Up Form (#464)</td>
<td>Every month while on treatment and at completion of treatment</td>
</tr>
<tr>
<td>Parts A, B</td>
<td></td>
</tr>
<tr>
<td>*Parts A, B</td>
<td>Post Treatment Follow-Up:</td>
</tr>
<tr>
<td></td>
<td>- every 3 months if patient is &lt;2 years from study entry</td>
</tr>
<tr>
<td></td>
<td>- every 6 months if patient is 2 to 5 years from study entry</td>
</tr>
<tr>
<td></td>
<td>- every 12 months if patient is &gt;5 years from study entry</td>
</tr>
<tr>
<td>ECOG Pulmonary Assessment Form (#524)</td>
<td>After first follow-up visit upon completion of radiotherapy, and 1 year after completion of radiotherapy</td>
</tr>
<tr>
<td>Rev. 8/92</td>
<td></td>
</tr>
<tr>
<td>ECOG RT Master Form #233</td>
<td>Within 3 months of completion of radiotherapy</td>
</tr>
<tr>
<td>Rev. 11/91</td>
<td></td>
</tr>
<tr>
<td>*ECOG RT Long-Term Follow-Up Form #239</td>
<td>At 6 and 12 months after completion of treatment (optional at 12 months unless a toxicity is being monitored)</td>
</tr>
<tr>
<td></td>
<td>At time of relapse</td>
</tr>
<tr>
<td>ECOG Lung Cancer Relapse Evaluation Form (#476, rev. 12/90)</td>
<td></td>
</tr>
<tr>
<td>Rev. 9/94</td>
<td>Adverse Reaction Form (ADR) for Investigational Drugs (#391RF)</td>
</tr>
<tr>
<td></td>
<td>Within 10 days of reportable toxic event as defined in Section 5.41</td>
</tr>
</tbody>
</table>

* These forms are to be submitted for all cancelled patients according to the above schedule.

10.2 RTOG Participants

Rev. 12/93 ECOG data forms as listed above should be submitted at the required intervals to the RTOG Headquarters, 1101 Market Street, 14th Floor, Philadelphia, PA 19107. Data forms must include the ECOG protocol number and patient sequence number as well as the RTOG study number and project case number.
10.3 NCCTG Participants

ECOG data forms as listed above should be submitted at the required intervals to the NCCTG Operations Office, 200 First Street, SW, Rochester, MN 55905.

10.4 SWOG Participants

The original data forms as listed above should be submitted at the required intervals to the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, MP-557, Seattle, WA 98104-2092. Include the ECOG protocol number and patient sequence number as well as the Southwest Oncology Group study number and patient number. It is not necessary to submit extra copies.

10.5 CALGB Participants

ECOG data forms as listed above should be submitted at the required intervals to the CALGB Data Management Center, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

10.6 ECOG, RTOG, NCCTG, SWOG and CALGB Participants

Rapid Review Materials

The ECOG Radiation Oncology Quality Assurance Center will perform a rapid and final review of all protocol patients. Questions regarding radiation, data collection, and review can be referred to Linda Martin (813) 632-1397.

Send all copied radiation materials listed below to:

Linda Martin, Deputy-Director
ECOG RT Quality Assurance Center
c/o H. Lee Moffitt Cancer Center, Room 1056
12902 Magnolia Drive
Tampa, FL 33612

RAPID REVIEW MATERIALS

These materials must be submitted by express mail within 5 treatment days after the patient begins radiation:

Copy of Lung On-Study Form (#341)
Copy of Thoracic Surgery Report Form (#526)
Copies of Operative and Pathology Reports
Prescription Sheet for Entire Treatment (Primary, nodes)
Calculation Sheets for Initial Fields
Composite Isodose Plan (Treatment Planning)
Simulation Films of ALL Fields (AP/PA & Oblique)
Beam Verification (portal) Films of Initial Fields
Partial Daily Treatment Record
Copy of CT Scan
Name, Address, Telephone # of treating Radiation Oncologist
FINAL REVIEW MATERIALS

These materials must be submitted within 1 week of completion of radiation:

- Completed Daily Treatment Record
- Calculation Sheets of all Field Modifications (boosts)
- Beam Verification (port) Films of all Field Modifications (i.e., boosts or cone-down fields)
- Composite Isodose Distributions in Three Planes

11.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, NCI, state, and Federal regulations concerning informed consent and peer judgment will be fulfilled.

12.0 REFERENCES


Prospective Randomized Trial of Postoperative Adjuvant Therapy in Patients with Completely Resected Stage II and Stage IIIa Non-Small Cell Lung Cancer

INTERGROUP

APPENDIX I

Suggested Patient Consent Form

Research Study

I, __________________________, willingly agree to participate in this study which has been explained to me by Dr. _______________________. This research study is being conducted by the Eastern Cooperative Oncology Group and by ___________________________________________.

(Institution)

Purpose of Study

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

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

Description of Procedures

This study involves the administration of radiation therapy or radiation therapy combined with chemotherapy following surgical resection of lung cancer.

It is not clear at the present time which of these treatments is better. For this reason, the option which is to be offered to me will be based upon chance using a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign one of the options to me, and that the chances of my receiving any one of the treatments offered are approximately equal.

If I am assigned to receive radiation therapy, I will receive 28 daily treatments given 5 days per week over a 6 week period. This treatment will begin no later than 6 weeks and no sooner than 2 weeks after my surgery (depending on the type of surgery required to remove the tumor). Radiation treatment is administered on an outpatient basis.

If I am assigned to radiation therapy plus chemotherapy, the radiation therapy will be given as described above. Chemotherapy will consist of 4 cycles of 2 anticancer drugs, Cisplatin and Etoposide. Both drugs are administered by a vein. The Cisplatin is given on day 1 while Etoposide is give over 2 to 3 hours on days 1, 2 and 3 every 4 weeks. Each cycle of treatment may require a brief 3 to 5 day hospitalization. Radiation therapy will be administered on an outpatient basis.

Following completion of which ever treatment I received, I will be followed on a regular basis for at least 5 years to determine the frequency of tumor recurrence and my survival.

Risks and Discomforts

Drugs and radiotherapy treatments often have side effects. The treatments used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.
Cisplatin can cause bone marrow suppression resulting in a lowering of the red blood cells (which can lead to anemia), lowering of the white blood cells (which can increase the risk of infection), and lowering of blood platelets (which can cause easy bruising and bleeding). Nausea and vomiting are common and may last for up to 3 days after you receive Cisplatin. Other side effects include anorexia (loss of appetite), liver abnormalities (indicated by an elevation in liver function test results), numbness, tingling, or decreased sensation in the hands or feet, decreased hearing (usually high frequency hearing loss), muscle spasms, lowering of minerals in the blood, vein irritation and fatigue. Some less common side effects you could experience are loss of hair, seizures, kidney damage indicated by abnormal kidney function test results (usually avoided by drinking a lot of water), dizziness, decreased vision, and Lhermitte’s sign (shock-like tingling down the spine and throughout the body when the neck is bent). Occasionally, previously treated patients may have an allergic reaction with symptoms of confusion, agitation, wheezing, low blood pressure, rapid heartbeat, or swelling of the face, within a few minutes after receiving the medication. In rare cases, acute leukemia or other cancers may develop after treatment with Cisplatin, especially when it is given along with other anticancer drugs.

Etoposide can cause a lowering of white blood cells (which can increase the risk of infection), lowering of the red blood cells (which can cause anemia), and rarely lowering of the blood platelets (which can cause easy bruising and bleeding). Other side effects include loss of hair which is generally reversible; inflammation, pain, and swelling along vein where drug is given; nausea and vomiting shortly after treatment; abdominal pain; liver abnormalities (indicated by an elevation in blood tests that show liver function); high levels of uric acid; and low blood pressure (if drug is given quickly). Some less common side effects include damage to nerves causing numbness, tingling, pain, or muscle weakness; drowsiness, fatigue, headache, dizziness, changes in vision; fever, muscle cramps metabolic acidosis (excessive acid in body fluids); discomfort deep within the chest; skin rash, skin itching, other skin reactions at areas of prior radiotherapy, darkening of skin, mouth sores (more severe in patients who have received radiation to the head and neck or bone marrow transplantation), loss of appetite, diarrhea, aftertaste in the mouth, inflammation of glands on the neck, difficulty swallowing, constipation, allergic reaction (such as breathing difficulties), cardiovascular events (resulting in congestive heart failure), and elevated blood pressure. In rare cases, acute leukemia may develop after treatment with etoposide.

Chest Radiation Therapy may cause: 1) difficulty, pain or a burning sensation on swallowing. This effect usually begins after the second week of radiotherapy and goes away within 1 month of completion of radiotherapy; 2) fatigue. A tiredness without having done anything to make you tired. Also, a temporary effect which resolves within a month of completion of treatment; 3) skin damages within the port of radiation, the skin may develop a sunburn-like appearance which may itch, feel dry or burn slightly. Although skin color and the sunburn-like reaction resolves within 2-6 weeks after treatment, the skin will permanently be more dry than other skin, and chest hair (if any) may not regrow; 4) decrease in white blood cells and platelets. Decrease in white cell production may predispose me to infection. Decreases in platelets may make me bleed or bruise easily; 5) scarring of the lung (i.e., radiation fibrosis) which may result in chronic shortness of breath and a cough.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests and x-rays will be done to monitor the effects of treatment. Many side effects disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that treatment to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study drugs.

Contact Persons

In the event that physical injury occurs as a result of this research, facilities for treatment of injury will be available; however, I will not automatically be provided with reimbursement for medical care or 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.
Alternatives

Alternatives which could be considered in my case include no additional treatment. 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 the prognosis with my 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. I will be advised of the procedures related solely to research which would not otherwise be necessary. These will be explained to me by my physician. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. My doctor will discuss these with me.

Benefits

Possible benefits which may result from my participation include decreased recurrence and prolonged survival. It is unknown whether I will derive any personal benefit from participation in this study. 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.

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. Refusing 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 that I withdraw from the study, I will continue to be followed and clinical data will continue to be collected from my medical records.

Confidentiality

I understand that a record of my progress while on the study will be kept in a confidential form at __________________________ and also in a computer file at the statistical headquarters of the (Institution) Eastern Cooperative Oncology Group. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA) and the National Cancer Institute (NCI) may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review.

* * * * * * * * * * * * * * * * * * * * *

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

__________________________ __________________________
(Patient Signature) (Date)

__________________________ __________________________
(Witness Signature) (Date)

__________________________ __________________________
(Physician's Signature) (Date)
Prospective Randomized Trial of Postoperative Adjuvant Therapy in Patients with Completely Resected Stage II and Stage IIIa Non-Small Cell Lung Cancer

Intergroup

APPENDIX III

Anatomical Staging for Lung Cancer
(IUCC-AJCC)

TNM CATEGORIES (Note Definitions)

T-Primary Tumor

TX  Tumor proven by the presence of malignant cells in broncho-pulmonary 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 demonstrate tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina.  Any associated atelectasis of obstructive pneumonitis must involve less than an entire lung.

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

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

Definitions

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

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

N0  No demonstrable metastasis to regional lymph nodes.

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

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

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

M-DISTANT METASTASIS

M0  No (known) distant metastasis

M1  Distant metastasis present - Specify Site(s)

STAGE GROUPING OF CARCINOMA OF THE LUNG

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>T0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>TIS</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Prospective Randomized Trial of Postoperative Adjuvant Therapy in Patients with Completely Resected Stage II and Stage IIIa Non-Small Cell Lung Cancer Intergroup

APPENDIX IV

American Thoracic Society Definitions of Regional Nodal Stations

ATS map of regional pulmonary nodes

X Supraclavicular nodes.

2R Right upper paratracheal nodes: nodes to the right of the midline of the trachea, between the intersection of the caudal margin of the innominate artery with the trachea and the apex of the lung.

2L Left upper paratracheal nodes: nodes to the left of the midline of the trachea, between the top of the aortic arch and the apex of the lung.

4R Right lower paratracheal nodes: nodes to the right of the midline of the trachea, between the cephalic border of the azygos vein and the intersection of the caudal margin of the brachiocephalic artery with the right side of the trachea.

4L Left lower paratracheal nodes: nodes to the left of the midline of the trachea, between the top of the aortic arch and the level of the carina, medical to the ligamentum arteriosum.

5 Aortopulmonary nodes: subaortic and para-aortic nodes, lateral to the ligamentum arteriosum or the aorta or left pulmonary artery proximal to the first branch of the left pulmonary artery.

6 Anterior mediastinal nodes: nodes anterior to the ascending aorta or the innominate artery.

7 Subcarinal nodes: nodes arising caudal to the carina of the trachea but not associated with the lower lobe bronchi or arteries within the lung.

8 Paraesophageal nodes: nodes dorsal to the posterior wall of the trachea and to the right or left of the midline of the esophagus.

9 Right or left pulmonary ligament nodes: nodes within the right or left pulmonary ligament.

10R Right tracheobronchial nodes: nodes to the right of the midline of the trachea from the level of the cephalic border of the azygos vein to the origin of the right upper lobe bronchus.

10L Left peribronchial nodes: nodes to the left of the midline of the trachea between the carina and the left upper lobe bronchus, medial to the ligamentum arteriosum.

11 Intrapulmonary nodes: nodes removed in the right or left lung specimen plus those distal to the main stem bronchi or secondary carina.
AJC Lymph Node Map

AJC classification of regional lymph nodes

<table>
<thead>
<tr>
<th>N2 Nodes</th>
<th>N1 Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Mediastinal Nodes</td>
<td>10 Hilar</td>
</tr>
<tr>
<td>1 Highest Mediastinal</td>
<td>11 Interlobar</td>
</tr>
<tr>
<td>2 Upper Paratracheal</td>
<td>12 Lobar</td>
</tr>
<tr>
<td>3 Pre and Retrotracheal</td>
<td>13 Segmental</td>
</tr>
<tr>
<td>4 Lower Paratracheal</td>
<td></td>
</tr>
<tr>
<td>(including Azygos Nodes)</td>
<td></td>
</tr>
<tr>
<td>Aortic Nodes</td>
<td></td>
</tr>
<tr>
<td>5 Subaortic (aortic window)</td>
<td></td>
</tr>
<tr>
<td>6 Para-aortic (ascending aorta or phrenic)</td>
<td></td>
</tr>
<tr>
<td>Inferior Mediastinal Nodes</td>
<td></td>
</tr>
<tr>
<td>7 Subcarinal</td>
<td></td>
</tr>
<tr>
<td>8 Paraesophageal (below carina)</td>
<td></td>
</tr>
<tr>
<td>9 Pulmonary Ligament</td>
<td></td>
</tr>
</tbody>
</table>

Compatibility of AJC and ATS Nodal Classifications

<table>
<thead>
<tr>
<th>Nodal Station</th>
<th>AJC</th>
<th>ATS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Highest mediastinal</td>
<td>Included in station 2</td>
</tr>
<tr>
<td>2.</td>
<td>Upper paratracheal</td>
<td>Essentially unchanged</td>
</tr>
<tr>
<td>3.</td>
<td>Pre- and retrotracheal</td>
<td>If pretracheal, included in Regions 2, 4, or 6 depending on anatomic location; if retrotracheal, included in Region 8</td>
</tr>
<tr>
<td>4.</td>
<td>Lower paratracheal</td>
<td>Boundaries for this critical station are defined</td>
</tr>
<tr>
<td>5.</td>
<td>Subaortic</td>
<td>Renamed aortopulmonary to include nodes along the lateral surfaces of the aorta and left or main pulmonary artery as well as those along the aortopulmonary window</td>
</tr>
<tr>
<td>6.</td>
<td>Paraaortic</td>
<td>Renamed anterior mediastinal nodes; includes some pretracheal and preaortic nodes</td>
</tr>
<tr>
<td>7.</td>
<td>Subcarinal</td>
<td>Unchanged</td>
</tr>
<tr>
<td>8.</td>
<td>Paraesophageal</td>
<td>Unchanged</td>
</tr>
<tr>
<td>9.</td>
<td>Pulmonary ligament</td>
<td>Unchanged</td>
</tr>
<tr>
<td>10.*</td>
<td>Hilar</td>
<td>Designation of “hilar” dropped because of ambiguity of the radiologic use of this term; renamed peribronchial on the left and tracheobronchial on the right; this station is now outside the pleural reflection</td>
</tr>
<tr>
<td>11.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Interlobar</td>
<td>Reclassified as intrapulmonary</td>
</tr>
<tr>
<td>13.</td>
<td>Lobar</td>
<td>Included in Station 11</td>
</tr>
<tr>
<td></td>
<td>Segmental</td>
<td>Included in Station 11</td>
</tr>
</tbody>
</table>

* The critical modifications that are being suggested.
Suggested radiation therapy fields for initial APPA Portals. Treat same volume with obliques of lateral to reach 50.4Gy.

N1 disease with no extranodal extension

N1 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.

N2 disease with no extranodal extension

N2 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.
Appendix VI
Appendix VI Continued
Appendix VII
RTOG/EORTC Late Radiation Morbidity Scheme