A PHASE II TRIAL OF NEOADJUVANT THERAPY WITH CONCURRENT CHEMOTHERAPY AND HIGH DOSE RADIOTHERAPY FOLLOWED BY SURGICAL RESECTION AND CONSOLIDATIVE THERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA

Limited Participation Study:
See Section 5.1 and Appendix V

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Activation Date: September 30, 2004
Closure Date: November 19, 2008
Update Date: June 14, 2007
Version Date: June 15, 2006; May 18, 2011
Includes Amendments 1-41-5

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**Patient Population** (See Section 3.0 for Eligibility)
Patients with Stage IIIA (T1-3 N2) or Stage IIIB (N3, excluding supraclavicular involvement) non-small cell lung cancer documented by biopsy or cytology (Pancoast tumors are eligible if pathologic evidence of mediastinal nodal disease is present). Patients must have a serum albumin of ≥ 3.0 g/dL.

**Required Sample Size:** 60
1. Does the patient have histologic proof of non-small cell lung cancer documented by biopsy or cytology?

2. What is the AJCC stage?

3. Is disease measurable?

4. Is the patient ≥ 18 years of age?

5. What is the Zubrod performance status?

6. Is the patient’s life expectancy ≥ 6 months?

7. Is there evidence of metastatic disease?

8. Have mediastinal lymph nodes been proven positive on pathologic sampling, by mediastinoscopy, thoracoscopy, Chamberlain procedure, or transbronchial needle aspirate?

9. What is the N stage?

10. If N3 disease, is this based on clinical or radiographic evidence of supraclavicular lymph node involvement?

11. Does the patient have T4 disease?

12. Based on the evaluations by the Medical Oncologist, Radiation Oncologist, and Thoracic Surgeon, is the patient a potential surgical candidate prior to any therapy?

13. Are all pretreatment evaluations within the timelines specified in Section 3.1.11?

14. Are the pretreatment lab values as specified in Section 3.1.7?

15. Is baseline FEV1 at least 2.0 liters?

16. Has the patient received any prior systemic chemotherapy or radiation to the thorax?

17. Does the patient have hypersensitivity to Cremophor EL?

18. Is there any evidence of superior vena cava syndrome?

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

20. If the patient has reproductive capability, has the patient agreed to utilize effective contraception?

21. Does the patient have an active serious infection or other serious medical condition that would impair ability to complete protocol treatment?
22. Has the patient signed the consent form?

23. Has the institution been certified by the Thoracic Surgery Co-Chair?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed?

3. Is the patient eligible for this study?

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

5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

11. Gender

12. Patient’s Country of Residence

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Treatment Start Date

17. Medical Oncologist

18. Patient’s Thoracic Surgeon

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________ Date ___________________________

RTOG 0229
1.0 INTRODUCTION

1.1 Stage III non-small cell lung cancer (NSCLC) is a common entity with approximately 40,000 patients/year in the United States. Surgical resection or radiotherapy alone will result in cure in less than 10% of patients. Recent randomized studies have demonstrated that chemotherapy followed by surgery or chemoradiotherapy without surgery can result in superior survival compared to surgery or radiotherapy alone. Both strategies, however, have a substantial rate of local relapse as the first site of failure. Therefore, the possibility of improving outcome utilizing trimodality therapy (i.e. chemotherapy, radiotherapy, and surgery) is attractive.

1.2 Rationale for Trimodality Therapy

Pulmonary resection following induction therapy with chemotherapy and radiotherapy to 45 Gy has now been well documented to be feasible and safe. Two large prospective cooperative studies, Southwest Oncology Group 8805 and the recent Pancoast Intergroup study (INT 0160), demonstrated the ability to perform either lobectomy or pneumonectomy following neoadjuvant concurrent chemotherapy and radiotherapy in a multi-institutional setting. The induction radiotherapy in these trials was limited to 45 Gy, primarily due to concern of excess morbidity and mortality that have been attributed to surgical resection following high dose radiotherapy.

The recently reported intergroup trial lead by the Radiation Therapy Oncology Group (RTOG), 93-09 (INT 0139) comparing concurrent chemoradiation +/- surgery did not show a statistically significant difference between the two arms because of an increase in post-operative mortality associated with the addition of surgery following chemoradiation. The current proposed study specifically addresses the issue of post-operative complications by employing strict surgical management requirements. It should be noted that the 93-09 survival curves do appear to separate toward a survival advantage for the addition of surgery, even though the results are not statistically significant. This difference would be magnified if the post-operative toxicities were reduced. It also is possible that the survival advantage is not more significant due to the lower dose of radiotherapy used in 93-09 (45 Gy versus 60 Gy in the current proposed study).

The rationale for the use of combined preoperative chemoradiotherapy, rather than chemotherapy induction alone, may be appreciated by the impact that local control may ultimately have on long-term survival. Combined therapy targeted to improve local and systemic control in non-operative studies has demonstrated that improvements in local control may as well lead to improved overall survival. Both in small cell and in non-small cell carcinoma of the lung, the addition of concurrent radiotherapy to systemic therapy has been shown to improve survival versus chemotherapy alone or sequentially delivered chemotherapy and radiotherapy. In the most recent non-operative phase III study by the West Japan Lung Cancer Group, patients with Stage III non-small cell carcinoma were randomized to concurrent versus sequential chemoradiotherapy treatment. In the 323 patients that were studied, the response rate (84% vs. 66%, p=0.0002) and the median survival (16.5 months vs. 13.3 months, p=0.039), were both improved with the delivery of concurrent versus sequential therapy. Of interest, 35% (42/117) of the patients who failed in the sequential arm of the study recurred with local disease only, the highest single site of recurrence, an indication of the possible role of surgical resection following even optimal medical therapy. Taken as a whole, the surprising improvement in outcome in small cell lung cancer, an ostensibly systemic disease with a more aggressive approach to local control as well as the Japanese results, strongly imply that enhanced local control may yield benefits in terms of systemic disease as well and favorably impact survival.

1.3 Importance of Sterilization of Mediastinal Nodes

In SWOG 8805, the strongest predictor of long term survival after resection was the absence of tumor in mediastinal nodes (three-year survival rates, 44% LN- vs. 18% LN+, p < 0.005). Fifty-three percent of patients with lymph nodes sampled pre-operatively and post-operatively had sterilization of the mediastinal nodes. In a recent analysis of prognostic factors for long-term survival as reported by Bueno and associates, the downstaging of nodal disease was determined to be the best predictor of long-term survival after induction therapy in a series of 103 patients. Patients in whom all nodal disease was eradicated had a five-year survival rate of 35.8% versus patients with persistent N1 or N2 disease who had a five-year survival of only 9% (p < 0.023). In that analysis, the majority of patients received chemotherapy alone as induction, and the rate of nodal sterilization was 26% (18/67 pts). A similar rate was seen in CALGB 8935, a prospective study of chemotherapy induction in stage IIIa disease, in which the proven nodal downstaging of N2 disease was 22% (10/46 pts). In the University of Maryland experience with concurrent chemotherapy and high dose radiation, 14 of 16 (87.5%) patients with pathologically proven
mediastinal adenopathy preoperatively had complete sterilization. This improvement in nodal response may be attributed to the use of higher dose radiotherapy concurrent with chemotherapy.

1.4 Importance of Pathological Complete Response in Pancoast Tumors

In the recent Intergroup study, the most important predictor of outcome was pathological complete response, though the absolute numbers did not achieve statistical significance. Though the rate of pathologic or near CR was 65% in operable patients after chemoradiation (n=83), the actual number of patients who achieved this status on an intention-to-treat basis (n=111) was approximately 50%. The actual pathologic CR rate (eliminating patients with any residual tumor) was approximately half of that (i.e., 25%). In contrast, at the University of Maryland, our recent experience with Pancoast tumors (n=23) demonstrated a pathological or near pathologic response rate of 64% and complete pathological CR rate of 46% when utilizing neoadjuvant high dose radiation and concurrent chemotherapy. In this study, the most common sites of relapse were locally (36% of recurrence) and brain (45%). This pattern of relapse indicates that intensified therapy to these areas may improve results.

1.5 Rationale and risks of higher radiotherapy dose

Though the use of higher radiotherapy doses is attractive, early experiences demonstrated unacceptable morbidity and mortality. Fowler and associates in 1993 reported an excessively high morbidity and mortality in a prospective single institution phase II trial that was stopped early due to a high complication and mortality rates. Patients received 60 Gy of radiation with concurrent 5FU/cisplatin/etoposide. Six patients underwent lobectomy with no perioperative mortality, while 3 of 7 (42%) pneumonectomies died of post-operative complications. Deutch et al. reported a similar series in 16 patients undergoing resection following radiation to 60 Gy and concurrent chemotherapy with carboplatin and VP-16. Of the patients undergoing lobectomy, there were no post-operative deaths, while 2 of 6 pneumonectomy patients died. In contrast, at the University of Maryland, we have demonstrated the safety of lobectomy or pneumonectomy after high dose chemoradiotherapy in 40 patients. Despite this aggressive approach, there were no post-operative deaths and the complication rate was acceptable. We attribute these findings to improvements in radiotherapy technique, the use of vascularized muscle flaps to cover bronchial stumps, careful limitation of intraoperative fluid administration, and avoidance of postoperative barotrauma. Notably, this approach yielded excellent short and long-term results. A 47% complete pathologic response and 87% nodal sterilization rate were documented in this study. Two- and three-year survivals were 71% and 62%, respectively. Disease free survival at two years is 68%. Median survival has not yet been reached. These results compare quite favorably with SWOG 8805 in which the two- and three-year survivals were 42% and 29%, respectively. The use of full dose radiotherapy in trimodality neo-adjuvant treatment protocols is feasible and may substantially improve outcome in this disease.

1.6 Consideration of prophylactic cranial irradiation

Previous studies in small cell lung cancer have shown a benefit in brain control and overall survival associated with prophylactic cranial radiation. Recently, investigators have begun to examine the role of this therapy in patients diagnosed with non-small cell lung cancer. In large multimodality trials as well as in our own institutional experience, a major site of relapse with consequent morbidity and mortality is the brain. A recent report indicates the potential of PCI to decrease CNS relapse from 54% to 13% without any evidence of increased neuropsychiatric impairment relative to controls. Therefore, patients who are rendered disease free by surgery, or if judged not to be operable, have a good response in the judgment of the treating physician, will be advised to participate in RTOG 0214. This study examines the potential benefits of PCI in patients with non-small cell lung cancer.

1.7 Current proposal

Though previous results have been promising and have demonstrated the feasibility of this approach, they represent retrospective experience. As such, there was heterogeneity in chemotherapy regimens, inconsistencies in patient evaluation, use of PCI and other factors, which complicate the interpretation of this promising approach. Therefore, we propose to prospectively evaluate this strategy utilizing the endpoint of mediastinal nodal sterilization for patients with locally advanced tumors.

2.0 OBJECTIVES

2.1 To estimate the mediastinal nodal clearance rates with the pre-operative regimen and the rate of complete pathological response after treatment with pre-operative chemotherapy with paclitaxel/carboplatin and high dose radiation for stage III NSCLC.
2.2 To estimate the feasibility of surgical resection following induction chemoradiation
2.3 To evaluate the disease free and overall survival with this trimodality approach
2.4 To estimate the toxicity of this trimodality approach

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility (9/9/05)
3.1.1 Patients with Stage IIIA (T1-3 N2) or Stage IIIB (N3, excluding supraclavicular involvement) non-small cell lung cancer documented by biopsy or cytology (Pancoast tumors are eligible if pathologic evidence of mediastinal nodal disease is present);
3.1.2 Disease must be measurable;
3.1.3 Mediastinal lymph nodes must be proven positive by pathologic review. All patients must undergo mediastinoscopy, thoracoscopy, Chamberlain procedure, or transbronchial needle aspiration to evaluate extent of nodal involvement. Any lymph node assessed by mediastinoscopy and found to be positive will be defined as N2 disease;
3.1.4 Patients ≥ 18 years of age;
3.1.5 Life expectancy ≥ 6 months;
3.1.6 Zubrod performance status 0-1 (See Appendix II);
3.1.7 Pretreatment laboratory values must be as follows: WBC count: ≥ 3,000/mm³; Absolute granulocyte count: ≥ 1,500/mm³; Platelets: ≥ 100,000/mm³; Total bilirubin: ≤ 1.5 x institutional ULN; Serum creatinine: ≤ 1.5 x institutional ULN; AST and ALT: ≤ 2.5 x institutional ULN; serum albumin: ≥ 3.0 g/dL
3.1.8 Baseline FEV1 must be at least 2.0 liters; if less than 2.0 then VQ scan is required and projected post-operative FEV1 must be > 800 cc based on the following formula using the quantitative V/Q scan: FEV1 = FEV1 x % perfusion to uninvolved lung from quantitative lung V/Q scan report.
3.1.9 Patient evaluation and acceptance by thoracic surgery, medical oncology, and radiation oncology; patient must be a potential surgical candidate prior to the initiation of therapy;
3.1.10 Women of childbearing potential and male participants must practice an effective method of contraception during the study;
3.1.11 Pretreatment evaluations required for eligibility include (9/9/05):
   • A complete medical history & physical examination to include Zubrod performance status, neurologic assessment, recent weight loss, usual weight, concurrent non-malignant disease and therapy;
   • Location, type, and size of measurable lesion must be recorded prior to treatment;
   • CBC with differential, platelet count, electrolytes, and Mg++ within 14 days prior to study entry;
   • SMA-12: Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT and SGPT within 14 days prior to study entry;
   • Women of childbearing potential must have a negative pre-study serum or urine pregnancy test within 14 days prior to study entry.
   • Mediastinoscopy, thoracoscopy, Chamberlain procedure, or bronchoscopy with transbronchial needle aspiration to evaluate the extent of lymph node involvement;
   • CT scan of the chest to include liver, and adrenal glands within 6 weeks prior to study entry;
   • PET scan within 8 weeks prior to study entry. Any suspicious areas outside of the local regional disease requires documented evaluation of these findings to exclude metastatic disease;
   • CT scan or MRI of the brain within 6 weeks prior to study entry;
   • EKG and pulmonary function tests including FVC, FEV-1, and DLCO, within 8 weeks prior to study entry; VQ scan, if applicable, within 8 weeks prior to study entry;
3.1.12 Patients must sign a study-specific informed consent (Appendix I) prior to study entry.
3.2 Conditions for Patient Ineligibility
3.2.1 Small cell lung cancer; distant metastatic disease;
3.2.2 Evidence of clinical or radiographic supraclavicular lymph node involvement;
3.2.3 Bronchialalveolar carcinoma with lobar or multilobar involvement;
3.2.4 (11/17/04) (3/17/06) Unintentional weight loss > 5% within 6 months prior to study entry, or Zubrod performance status 2 or greater;
3.2.5 Primary tumor location prevents delivery of 60 Gy and simultaneously limiting spinal cord dose to 48 Gy;
3.2.6 Patients with malignant pleural effusion;
3.2.7 Clinically evident superior vena cava syndrome;
3.2.8 Prior systemic chemotherapy or radiation therapy to the thorax;
3.2.9 Patients with known hypersensitivity to Cremophor EL;
3.2.10 Patients receiving other investigational therapy;
3.2.11 Pregnant or lactating women are ineligible, as treatment involves unforeseeable risks to the participant and to the embryo or fetus;
3.2.12 Patients with an active serious infection or other serious underlying medical condition that would impair their ability to complete protocol treatment;
3.2.13 Dementia or significantly altered mental status that would prohibit the understanding and/or giving of informed consent.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS
(In addition to required evaluations in Section 3.0)
Not applicable to this study.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (6/14/07)
Participating surgeons must complete and sign the credentialing form, Appendix V, prior to the institution entering any patients onto this study. The institution will fax the completed form to Dr. Krasna, Thoracic Surgery Co-Chair, FAX 410-427-2221, for review. Dr. Krasna will fax his approval to RTOG Headquarters and the institution. Institutions should allow adequate processing time (7-10 days) before calling to register the first patient.

5.2 Registration
5.2.1 Online Registration
Online (versus Dial-in) registration is mandatory for this study. Patients can be registered only after eligibility criteria are met. The RA will register the patient by logging onto the RTOG Web site (www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. A username and password is required. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record.
Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.2.2.

6.0 RADIATION THERAPY Note: Intensity Modulated RT (IMRT) is not allowed.

6.1 Induction Chemoradiotherapy
Concurrently with induction chemotherapy, patients will receive 1.8 Gy per day, five days a week (except holidays), for a total of 50.4 Gy in 28 fractions. This may require an initial AP-PA field
arrangement for the first 45 Gy (25 fractions), and an off cord arrangement for 5.4 Gy (3 fractions). RT will continue with a boost to the primary tumor of 1.8 Gy fractions per day, 5 days a week, for a total of 10.8 Gy in 6 fractions. There will be no break between the completion of the large field RT and the initiation of the boost field arrangement to the primary tumor. Field arrangements should be such that maximal spinal cord dose does not exceed 48 Gy at any level. Postoperative thoracic radiation is not permitted.

6.2 Dose-time factors
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. The first 50.4 Gy will be delivered in 28 fractions, or in 5-6 weeks. Respiratory gating techniques are not permitted.

6.3 Equipment
All fields must be simulated by a standard simulator or a CT simulator used for radiotherapy simulation. Only linear accelerators generating photons with peak energy between 4-10 MeV will be used. All equipment must be isocentrically rotational with minimum source axis distance of 80 cm.

6.4 Dose Uniformity
All doses are to be prescribed and calculated assuming a homogenous patient.

6.5 Prescription

6.5.1 At the mid separation of the central ray for two opposed coaxial equally weighted beams

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

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

6.5.4 At the center of the target area for complex treatment arrangements that are not covered above

6.6 Uniformity requirement
Using a sagittal plane through the spinal cord, the dose from top to bottom cannot exceed 10%. Patient separations at 2 cm from the top and bottom of the field boundaries must be obtained to provide off-axis spinal cord dose. Record max-cord dose daily. 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.

6.7 Normal tissue tolerances
Maximum spinal cord dose is 48 Gy. The entire heart may not receive more than 40 Gy. Up to 50% of the cardiac silhouette may receive up to 60 Gy. 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 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.

6.8 Target volume

6.8.1 The target will be defined by CT scan and clinical evaluation prior to therapy. This volume includes ipsilateral hilar and subcarinal lymph 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 (to the bottom of T10). This target volume must receive the 50.4 Gy (28 fractions) tumor dose. This may require an initial AP-PA field arrangements for the first 45 Gy (25 fractions), and an off cord arrangement for 5.4 Gy (3 fractions).

6.8.2 DO NOT TREAT THE 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 judgment 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.

6.8.3 Additional Radiotherapy (Boost)
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 boost. The target volume includes the tumor, any node measuring 1.0 cm or more on CT scan. 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. Off-axis points will be recorded 2
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 in Section 6.10.1. Spinal cord to be excluded as previously described.

6.8.4 Primary collimation may be used, and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.

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

6.9 Prophylactic Cranial Irradiation

Within four to six weeks of surgery, eligible patients will be encouraged to participate in RTOG 0214. For those patients who choose not to participate, the treating physicians may still opt to offer PCI if the patient is found to be disease free at the completion of surgery. For non-operable patients, PCI will be administered within 6 weeks of completion of consolidation chemotherapy if, in the judgment of the treating physician, it is felt to be of potential benefit.

6.10 Radiation Toxicity Delays, Dose Adjustments

6.10.1 Treatment interruptions are strongly discouraged. Radiation therapy will be held for any grade 4 toxicity and for grade 3 esophagitis and pneumonitis (see table below). Therapy will resume when toxicity has resolved to ≤ grade 2. Patients will be re-evaluated on a weekly basis if radiation is held. Chemotherapy will not be administered during radiation breaks. Regardless of cause, if an interruption greater than 3 consecutive days is planned, sites should contact the Study Chair, Dr. Suntharalingam.

<table>
<thead>
<tr>
<th>Radiation Esophagitis</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-1</td>
<td>Full</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Full</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold</td>
</tr>
</tbody>
</table>

6.10.2 Patients with esophagitis will receive treatment with appropriate analgesics, Carafate, antacids, viscous lidocaine, or dyclonine, as well as dietary supplements as deemed appropriate by the treating physician(s). Amifostine is not permitted.

6.11 Treatment Planning

6.11.1 Treatment planning should be performed in accordance with the prescribed doses (Section 6.1) to each target volume, together with restrictions in dose to normal tissues as given Section 6.7. Treatment planning simulation is required. It is recommended that CT-based treatment planning be utilized whenever possible.

6.11.2 One set of isodose distributions at the midplane transverse plane of the boost target volume should be submitted to RTOG Headquarters as specified in Section 12.0. Sagittal dose distributions are encouraged.

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

- **Spinal Cord Dose:** If compensating filters are not used, the point at which the spinal cord dose is to be calculated is 2 cm below the superior margin of the posterior field. If compensating filters or wedges are used then the point of maximum dose to the spinal cord must be determined. Maximal spinal cord dose should not exceed 48 Gy at any level.

- **Subcarinal Nodes:** Which are assumed to be at mid-plane.

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

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

- **Maximum Normal Tissue Dose:** This is to be calculated at level of the central rays of the boost fields as the maximum total dose at least 2 cm outside of the target volume.
6.11.4 Localization Films
All fields treated require filming on simulator units. Portal verification must be done for all treated fields. Copies of both simulator and portal fields must be submitted to RTOG Headquarters as specified in Section 12.0.

6.12 Compliance Criteria
6.12.1 Total Dose Criteria

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>≤ 5%</td>
<td>Per Protocol</td>
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<tr>
<td>&gt; 5% to ≤ 10%</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&gt; 10%</td>
<td>Deviation Unacceptable</td>
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</tbody>
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6.12.2 Fields Borders

<table>
<thead>
<tr>
<th>Border Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 cm to &lt; 2.2 cm</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>1 to &lt; 1.5 cm OR 2.2 to 3.3 cm</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&lt; 1 cm OR &gt; 3.3 cm</td>
<td>Deviation Unacceptable</td>
</tr>
</tbody>
</table>

6.13 R.T. Quality Assurance Reviews
The Principal Investigator/Radiation Oncology Study Chair, Mohan Suntharalingam, M.D., will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Suntharalingam will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first. These reviews will be on going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.14 Radiation Toxicity Reporting (5/18/11)
As of July 1, 2011, all acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.

6.14.1 Fatal Events
All deaths with the attribution of definite, possible, or probable resulting from protocol radiation therapy must be telephoned to the RTOG Headquarters dedicated AE line (215) 717-2762, to the RTOG Group Chair, and to the protocol study chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to the RTOG Headquarters Data Management AE telephone line at (215) 717-2762.

6.14.2 Life-threatening and Grade 4 Events
All life-threatening (an event which in view of the investigator, places the patient at immediate risk of death from the reaction) and Grade 4 events that are related, possibly related, or probably related to protocol treatment must be reported by telephone to the RTOG Headquarters AE telephone line, (215) 717-2762, to the RTOG Group Chair, and to the study chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

6.14.3 Documentation
All applicable data forms and if requested, a written report from the site principal investigator, must be submitted within 10 working days of the telephone report of any fatal adverse event
with the attribution of definite, possible, or probable relation to protocol radiotherapy and for grade 4 or life-threatening events as specified in Section 6.13.2.

7.0 DRUG THERAPY

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

7.1 Chemotherapy

7.1.1 Induction phase

Patients will receive paclitaxel, 50 mg/m² I.V. in a one-hour infusion and carboplatin, AUC 2.0 I.V. in a thirty-minute infusion once per week for 6 weeks.

7.1.2 Consolidation phase

All patients will be evaluated 4 weeks post-induction chemoradiation. All patients will receive consolidation chemotherapy regardless of whether they proceed to surgical resection or are unresectable. Patients will receive paclitaxel 200 mg/m² I.V. over three hours and carboplatin AUC 6.0 over one hour every 21 days (q 3 weeks) x 2.

Resected Patients: Consolidation chemotherapy will begin no later than 10 weeks post-surgery. Unresected Patients: Proceed directly to consolidation chemotherapy.

7.2 Paclitaxel

7.2.1 Formulation

Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.2.2 Preparation

A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 0.9% NSS, D5W, DS/0.9% NaCl, or DS/RL to a final concentration of 0.3-1.2 mg/ml. Diluted solutions are stable for up to 24 hrs. at room temperature. Dilute solution in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP’s) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g., Millex-GV Millipore Products) into the I.V. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.2.3 Administration

Paclitaxel, at the appropriate dose and dilution, will be given as a one-hour infusion during induction therapy and by three-hour infusion during consolidation therapy. The paclitaxel is mixed in 500 or 1000 cc of D5W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVH% with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the I.V. administration sets (polyethylene or polyolefin), which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

7.2.3.1 Hypersensitivity Prophylaxis

All patients must receive premedication before the administration of paclitaxel in order to prevent severe hypersensitivity reactions. A typical premedication regimen consists of the following given 30-60 minutes prior to paclitaxel: 10-20 mg intravenous (I.V.) dexamethasone, 50 mg I.V. diphenhydramine (or its equivalent), and 300 mg cimetidine or 50 mg I.V. ranitidine. The dexamethasone dose may be increased at the investigator’s discretion if a patient experiences a hypersensitivity reaction when given paclitaxel.

7.2.4 Storage

Paclitaxel vials should be stored between 2°-25°C (36°-77°F).
7.2.5 *Adverse Effects*
- Blood/Bone Marrow: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, tylthitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic failure, hepatic necrosis
- Cardiac: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction

7.2.6 *Supply*
Commercially available.

7.3 *Carboplatin (Paraplatin)*

7.3.1 *Formulation*
Carboplatin is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.3.2 *Preparation*
Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

<table>
<thead>
<tr>
<th>Vial Strength</th>
<th>Diluent Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5 ml</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 ml</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 ml</td>
</tr>
</tbody>
</table>

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

7.3.3 *Administration*
Carboplatin, at the appropriate dose and dilution, will be given over thirty minutes during induction therapy and over one hour during consolidation therapy, immediately after paclitaxel. Dose of carboplatin (mg) = target AUC x (GFR + 25) with a creatinine clearance calculated by the Cockroft-Gault Formula substituted for GFR: For example, a 60-year-old man with a serum creatinine of 1.0 and a weight of 72 kg will have a calculated GFR of 80 mg/min. On day 22 (AUC = 6), his dose of carboplatin would be 630 mg. NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

\[
i.e. \quad \text{GFR} = \frac{(140 - \text{age})(\text{kg wt})}{(\text{serum creatinine})(72)} \] with 15% reduction for women

7.3.4 *Storage*
Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.3.5 *Adverse Effects*
- Blood/Bone Marrow: Myelosuppression
- Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia
- Neurological: Peripheral neuropathy, ocular changes
- Other: Ototoxicity, myalgia, fatigue, allergic reaction

7.3.6 *Supply*
Commercially available.
7.4 Chemotherapy Dose Adjustments

7.4.1 Dose adjustments should be made according to the system showing the greatest toxicity graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Treatment may be delayed for up to 2 weeks beyond planned resumption of the next cycle. If a patient does not fulfill re-treatment criteria by that time, they will be removed from protocol treatment.

7.4.2 Dose Modifications for Paclitaxel and Carboplatin: The following tables summarize the paclitaxel and carboplatin doses to be used when modifications are required:

### Induction Chemotherapy

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Paclitaxel (mg/m²)</th>
<th>Carboplatin (target AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (starting dose)</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>-1</td>
<td>40</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Consolidation Chemotherapy

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Paclitaxel (mg/m²)</th>
<th>Carboplatin (target AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (starting dose)</td>
<td>200</td>
<td>6</td>
</tr>
<tr>
<td>-1</td>
<td>175</td>
<td>5</td>
</tr>
</tbody>
</table>

7.4.3 Dose Modifications During Induction and/or Consolidation Chemotherapy:

7.4.3.1 Hematologic Toxicities: The following table summarizes dose modifications based on hematologic toxicities:

<table>
<thead>
<tr>
<th>ANC (cells/μL)</th>
<th>Platelet count (cells/μL)</th>
<th>Paclitaxel</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1,200 And ≥100,000</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>1,000-1,200 Or 75,000-99,999</td>
<td>-1</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>&lt;1000 Or &lt;75,000</td>
<td>hold</td>
<td>hold</td>
<td></td>
</tr>
</tbody>
</table>

*Repeat counts weekly and resume chemotherapy based on this table.

7.4.3.2 Peripheral neuropathy
If grade 2 peripheral neuropathy occurs, the paclitaxel dose should be decreased by one dose level. If ≥ grade 3 peripheral neuropathy occurs, the patient should be removed from paclitaxel.

7.4.3.3 Gastrointestinal toxicity
If grade 2 mucositis occurs, the paclitaxel and carboplatin doses should be decreased by one dose level. If ≥ grade 3 mucositis occurs, the patient should be removed from protocol treatment.

7.4.3.4 Hypersensitivity reactions to Paclitaxel
Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.
7.4.3.5 Elevation of liver function tests

Paclitaxel is not known to cause hepatic toxicity; however, its elimination may be delayed in patients with severe hepatic dysfunction. Therefore, the dose of paclitaxel in patients with hepatic dysfunction should be modified according to the following table:

<table>
<thead>
<tr>
<th>Serum bilirubin, AST, or ALT</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-1</td>
<td>Full</td>
</tr>
<tr>
<td>Grade 2</td>
<td>-1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold</td>
</tr>
</tbody>
</table>

Patients with ≥ grade 3 hepatic dysfunction should not receive paclitaxel until the abnormal laboratory values improve to ≤ grade 1. Treatment should be resumed after recovery with paclitaxel at one dose level lower.

7.5 Modality Review

The Medical Oncology Co-Chair, Martin Edelman, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Edelman will perform a review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Edelman will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.6 Adverse Drug Reaction Reporting (5/18/11)

7.6.1 As of July 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.04 for grading of all treatment related adverse events. Note: All RTOG case report forms will continue to use CTCAE v. 3.0. A copy of the CTCAE v. 4.0 can be downloaded from the CTEP home page web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0. See the RTOG procedure manual for general Adverse Event Reporting Guidelines.

7.6.2 The following guidelines for reporting adverse events (AEs) apply to any NCI/RTOG research protocol that uses commercial anticancer agents. The following AEs experienced by patients accrued to this protocol and attributed to the commercial agent(s) (definitely, probably, or possibly related) should be reported:

- Any AE which is both serious (life-threatening [grade 4] or fatal [grade 5]) and unexpected (not listed as a known toxicity or is of greater severity or specificity than the listed toxicity);
- Any increased incidence of a known (listed in the drug information, background, or informed consent form section of the protocol) AE;
- Any death on study if clearly related to the commercial agent(s) or within 30 days after treatment must be reported. Any death more than 30 days after treatment that is felt to be treatment related must also be reported.

7.6.3 The following steps must be taken to report serious adverse events that occur while the patient is on this trial:

- Within 24 hours of discovery of the adverse event, call the RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762;
- Within 10 working days, send to RTOG Headquarters: a copy of the FDA form 3500 (MedWatch) including the investigator’s attribution (event is definitely not, unlikely, possibly, probably or definitely related to protocol treatment) in item 5 on the form;
copies of the appropriate case report forms/flow sheets recording the event and any other data/items as requested during the telephone report.

7.6.4 The completed FDA Form 3500 must be mailed or faxed to ALL the following addresses:

<table>
<thead>
<tr>
<th>FDA</th>
<th>Investigational Drug Branch</th>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedWatch</td>
<td>Investigational Drug Branch</td>
<td>RTOG Headquarters</td>
</tr>
<tr>
<td>P.O. Box 30012</td>
<td>1818 Market St., Suite 1600</td>
<td></td>
</tr>
<tr>
<td>5600 Fishers Lane</td>
<td>Bethesda, MD 20824</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>Rockville, MD 20852</td>
<td>301-230-2330 (24 hrs.)</td>
<td>215-717-2762 (24 hrs.)</td>
</tr>
<tr>
<td>Fax 800-332-0178</td>
<td>Fax 301-230-0159</td>
<td>Fax 215-717-0990</td>
</tr>
<tr>
<td>FDA only via internet: <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

7.6.5 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters AE phone line within 24 hours of discovery to ensure proper reporting of adverse events.

7.6.6 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [5/18/11]

Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If the site is reporting in CTCAE, v. 4, the event(s) may be reported as 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy, using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.info.nih.gov. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the following addresses:

<table>
<thead>
<tr>
<th>Investigational Drug Branch</th>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.O. Box 30012</td>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Bethesda, MD 20824</td>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>

All forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 SURGERY

8.1 Pretreatment evaluation

All patients must be evaluated by medical oncologist, radiation oncologist, and thoracic surgeon prior to enrollment to study. All must mutually agree and document that the patient is a potential surgical candidate prior to initiation of any therapy (See Section 3.1.9).

8.1.1 Pretreatment nodal evaluation

Pretreatment surgical evaluation of the mediastinum is required. This can be performed with mediastinoscopy, thoracoscopy, Chamberlain procedure, or transbronchial needle aspirate. Patients proven to have contralateral nodal involvement by TBNA are eligible for study. All patients must have documented N2/N3 disease by pathologic review of mediastinoscopy specimens or TBNA cytology review.

8.2 Evaluation for Surgery

After completion of Induction Chemoradiation, patients will be reassessed per the study calendar. If the patient is felt to be resectable, then surgery will be performed within 8 weeks of completion of Induction Chemoradiation. If patients are not considered to be resectable or operable at that time, they will receive Consolidation Chemotherapy, two additional cycles of carboplatin and paclitaxel and will be followed per protocol. Such patients will be considered not to have achieved the primary study endpoint of nodal clearance if residual nodes are found in the mediastinum by repeat mediastinoscopy, thoracoscopy, or TBNA positivity in a patient no longer
medically fit for resection. These patients may still receive PCI if it is felt by the treating physicians that they may benefit (See Section 6.9).

8.3 Surgical Procedure:

The surgical procedure will consist of lobectomy or pneumonectomy and will be decided upon at the time of surgery. A complete mediastinal nodal dissection will be performed. At the time of surgical resection after the completion of a lobectomy or pneumonectomy, it is a requirement of the study that a muscle flap be placed on the bronchial stump to buttress the bronchus and prevent air leak or infection. In the case of an anticipated lobectomy, it is recommended that an intercostal muscle flap made up of the 5th intercostal with neurovascular pedicle be harvested at the time of the thoracotomy before placing the rib spreader. The flap should then be protected with gauze soaked in saline and/or papaverine. In the case of a pneumonectomy, the serratus anterior muscle is typically utilized and should be harvested in its anterior and inferior portions. It can be left attached to the scapula superiorly but is generally detached posteriorly. This is then placed through the 2nd intercostal space anteriorly.

It is suggested that the flaps then be secured with 4 interrupted 4-0 vicryl sutures to the adventitia overlying the bronchus, 2 anteriorly and 2 posteriorly.

8.3.1 The mediastinum must be reassessed appropriately. Appropriate methods may include: mediastinoscopy, thoraoscopony, Chamberlin, or direct visualization at time of surgical resection. The appropriate nodal stations (as listed below) must be sampled in order to be considered an adequate mediastinal evaluation. At the time of mediastinal evaluation surgeons must document that all appropriate regions have been evaluated. Surgeons are strongly encouraged to sample nodal packets corresponding to appropriate regions. If no nodal tissue is visualized and tissue is unable to be sent for pathologic review, surgeons must document in the operative report that regions were evaluated and were found to be clear. All visible and technically accessible bronchopulmonary, hilar, and mediastinal lymph nodal regions should be removed and submitted, appropriately labeled, to the pathologist whenever feasible. Numbering and or nomenclature outlined in the Lymph Node Map will be used (See Appendix IV). Mediastinal lymph nodes removed at thoracotomy must include nodes from the following regions: (6/15/06)

- For right sided lesions: 4R, 7, 8, 9,10R; and if accessible, 2R
- For left sided lesions: 5, 6, 7, 8, 9,10L; and if accessible, 4L

8.4 Postoperative Period

During the postoperative period minimal I.V. fluids will be used. After pneumonectomy a strict fluid restriction of < 1500 cc/day is adhered to for the first 4 days. In addition, diuretic therapy is strongly encouraged (typically Lasix 20 mg bid is used daily), and additional doses of Lasix are used if blood transfusions are necessary.

8.4.1 Surgical Adverse Events (5/18/11)

As of July 1, 2011, all acute and late adverse events from protocol surgery will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events [CTCAE] version 3.04. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

8.4.1.1 Fatal Events

All deaths with the attribution of definite, possible, or probable resulting from protocol surgery must be telephoned to the RTOG Headquarters dedicated AE line (215) 717-2762, to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

All deaths during and within 30 days of completion of protocol surgery, regardless of attribution, must be reported by telephone within 24 hours of discovery to the RTOG Headquarters Data Management AE telephone line at (215) 717-2762.

8.4.1.2 Life-threatening and Grade 4 Events

All life-threatening (an event which in view of the investigator, places the patient at immediate risk of death from the reaction) and Grade 4 events that are related, possibly related, or probably related to protocol treatment must be reported by telephone to the RTOG Headquarters AE telephone line, (215) 717-2762, to the RTOG Group Chair, and to the Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

8.4.1.3 Documentation

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Field Code Changed
All applicable data forms and if requested, a written report from the site principal investigator, must be submitted within 10 working days of the telephone report of any fatal adverse event with the attribution of definite, possible, or probable relation to protocol treatment and for grade 4 or life-threatening events.

8.4.2 Postoperative Complications

Major morbidities are scored as any event occurring within 30 days following surgery. The complications of surgery will be documented on the Surgical Evaluation Form (S1) as part of the secondary objectives of this study. All patients undergoing surgical resection will be included in the analysis of surgical Adverse Events. Data collection also will include Surgical Operative (S2) and Surgical Pathology (S5) Reports documenting duration of surgery; estimated blood loss; blood transfusions required intra- and perioperatively; and number of postoperative days intubated. The Adverse Events attributed to surgery will include any of the following complications listed below:

- **Pneumonitis/pulmonary infiltrates** (includes pneumonia/empyema that was diagnosed during the postoperative period; specify the organism causing the infection.)
- **Infection** (includes any infection of incision site[s]; **NOTE**: This includes wound infection of surgical incisions for thoracotomy. When there is a wound infection, specify the organism causing the infection in the space provided, and record which surgical incision[s] was infected.)
- **Fistula, pulmonary/upper respiratory** (includes any fistula that developed within the postoperative period; **NOTE**: A patient with a bronchopleural fistula associated with an intrathoracic infection should be reported as having both the intrathoracic infection and a fistula, pulmonary/upper respiratory.)
- **Atelectasis** (includes collapse of either an entire lung or a lobe of the lung or atelectasis severe enough to require medical/operative intervention; **NOTE**: Do not include instances of incidental postoperative basilar atelectasis.)
- **Pneumothorax** (includes lung collapse that is due to air leakage from the lung into the pleural space; to be reported here, the pneumothorax must be severe enough that treatment, i.e., insertion of reinsertion of a chest tube is required.)
- **Prolonged chest tube drainage or air leak** (includes bronchial stump leak)
- **Pleural effusion (non-malignant)** [includes any effusion within the postoperative period that requires treatment, i.e., pleural tap.]
- **Chylothorax**
- **Cardiac ischemia/infarction** (includes any myocardial infarction that occurred within the postoperative period.)
- **Thrombosis/thrombus/embolism** (includes any pulmonary embolus that occurred within the postoperative period.)
- **Supraventricular and nodal arrhythmia** (includes any new atrial arrhythmia that developed within the postoperative period that requires treatment.)
- **Ventricular arrhythmia** (includes any new ventricular arrhythmia that developed within the postoperative period that requires treatment.)
- **Hemorrhage/bleeding associated with surgery, intra-operative or postoperative** (Postoperative period is defined as ≤ 72 hours after surgery; includes hemorrhage that required reoperation for control.)
- **Death**
- **Pulmonary/Upper Respiratory — Other** (includes any surgical or medical complication that occurred during the postoperative period, e.g., cerebrovascular accident; specify details.)

8.5 Surgical Quality Assurance

8.5.1 The Thoracic Surgery Co-Chair, Dr. Krasna, will review the Operative and Surgical Pathology reports for the first case of each participating institution. Further enrollment by that institution may be held based on the results of that review.

Dr. Krasna also will perform a Quality Assurance Review for verification of lymph node removal and protocol compliance after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Krasna will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

8.5.2 Goals of Surgical Quality Assurance
To assure correct surgical staging of patients prior to Induction Chemoradiation;
To assure safety of patients undergoing resection after Induction Chemoradiation;
To assure adequate resection of primary and lymph node dissection after Induction Chemoradiation;
To assure safety of the resection by employing a standard technique for buttressing of the bronchial stump.

8.5.3 Surgical Protocol Compliance Criteria (6/15/06)

- Deviations Minor:
  - Surgical resection outside the defined window (unless prior approval from the Surgery Co-Chair was obtained);
  - Postoperative fluid restrictions not adhered to in the immediate postoperative setting.

- Deviations Major: Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:
  - Substitution for a muscle flap (e.g., use of fat);
  - No documentation of post neoadjuvant/preoperative PFTs or evidence of calculated postresection FEV 1 > 800 cc;
  - Inadequate assessment of pathologic evidence of mediastinal nodal involvement prior to initiation of neoadjuvant therapy.

NOTE: Determination of Evaluable Cases: Patients who are deemed to have an inadequate nodal evaluation at time of surgery as defined by lack of documentation of nodal regions evaluated will be considered inevaluable for the primary endpoint of the study. They will continue to be followed for endpoints of survival.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.1.1 Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, antiemetics, etc. when appropriate. Steroids may be used as antiemetics in this study. Steroids also will be used for prevention/amelioration of hypersensitivity reaction.

The reason(s) for treatment, dosage, and the date of treatment should be recorded on the Treatment Form (TF).

9.2 Non-permitted Supportive Therapy

Treatment with other chemotherapeutic agents, hormones (with the exception of Megace, if used for appetite stimulation, estrogens, and birth control pills), will result in the patient's removal from study.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (9/9/05)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>Weekly During Induction ChemoRT</th>
<th>Reassessment (4 weeks after Induction ChemoRT)</th>
<th>q 3 wks During Consolidation Chemotherapy</th>
<th>Follow Up^</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, Zubrod</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor location, type, and size</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC, diff, platelet</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistries^</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test^</td>
<td>X*</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CXR</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal lymph nodes^</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT chest, liver, adrenals</td>
<td>X*</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT/MRI brain</td>
<td>X*</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
PET Scan
EKG
Pulmonary function tests
Toxicity assessment
VQ scan

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

a. Includes neurologic assessment, recent weight loss, usual weight, concurrent non-malignant disease and therapy
b. Must be done within 14 days prior to study entry
c. Includes SMA-12 (Total protein, Albumin, Calcium, Glucose, BUN, Creatinine, Alkaline Phosphatase, LDH, Total Bilirubin, SGOT and SGPT), electrolytes, and Mg++
d. For women of childbearing potential;
e. Must be done within 6 weeks prior to study entry
f. Must be done within 8 weeks prior to study entry
g. Includes FVC, FEV-1, DLCO
h. Six weeks from completion of treatment, every 3 months for one year, every six months for 2 years, then annually for 2 years
i. As indicated
j. Must be assessed by mediastinoscopy, thoracoscopy, Chamberlain procedure, or transbronchial needle aspirate
k. The PET scan may be done 4-6 weeks after induction chemoradiotherapy but must be done prior to surgical resection.
l. Required if baseline FEV1 is < 2.0 liters.

11.2 Response Assessment

11.2.1 Measurement of Response
Response will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. **Note:** Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluables” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

**Measurable Disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in **millimeters** (or decimal fractions of centimeters).

**Target Lesions:** All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

11.2.1.1 Guidelines for Evaluation of Measurable Disease
All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**Conventional CT and MRI:** These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Response to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to

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surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen (see pathology section).

11.2.2 Response Criteria
Response and progression to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen.

11.2.2.1 Evaluation of Target Lesions by MRI, CT, or Physical Examination
- **Complete Response (CR):** Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement;
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination;
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination;
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

11.2.2.2 Pathologic Evaluation of Target Lesions
- **Pathologic Complete Response (PCR):** Complete resection (R0 resection) achieved and no evidence of viable tumor in the entire resection specimen;
- **Mediastinal Pathologic Complete Response (MCR):** Complete resection achieved with no viable tumor in the mediastinal lymph nodes regardless of primary tumor pathologic status;
- **Progressive Disease (PD):** New sites of disease identified (e.g. malignant pleural studding; multiple pulmonary metastases; etc.);
- **Stable Disease (SD):** Not meeting the criteria of any of the above three.

11.2.2.3 Extent of Surgical Resection
- **RO:** Complete resection of all disease with negative margins and the highest lymph node resected negative for residual tumor;
- **R1:** Complete resection of all disease with pathology of positive margins, pathologic evidence of tumor cells in the highest lymph node resected in the mediastinum, or extracapsular nodal spread;
- **R2:** Gross residual disease left behind after surgical resection.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission [The timeframes below should correlate with those in Section 11.1 and should correspond with those in Appendix I, the sample consent.]

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is to estimate the mediastinal nodal sterilization rate with the pre-operative regimen of chemotherapy with carboplatin/paclitaxel and high dose radiation.

13.1.2 Secondary Endpoints

13.1.2.1 To estimate the rate of complete pathological response after treatment with the pre-operative regimen of chemotherapy with carboplatin/paclitaxel and high dose radiation;

13.1.2.2 To estimate the rate of major morbidities within 30 days of surgery associated with surgical resection following chemotherapy with carboplatin/paclitaxel and high dose radiation in order to establish the feasibility of the surgical procedure of this regimen;

13.1.2.3 To estimate the rate of resectability following chemotherapy with carboplatin/paclitaxel and high dose radiation in order to establish the feasibility of the surgical procedure of this regimen;

13.1.2.4 To estimate the rates of R0, R1, and R2 resections following chemotherapy with carboplatin/paclitaxel and high dose radiation;

13.1.2.5 To estimate overall survival and progression-free survival of patients treated with pre-operative chemotherapy with carboplatin/paclitaxel and high dose radiation at two years;

13.1.2.6 To estimate the toxicity of pre-operative chemotherapy with carboplatin/paclitaxel and high dose radiation.

13.2 Sample Size

The goal of this Phase II study is to improve the rate of mediastinal nodal sterilization from 50%, achieved in SWOG 8805, to 70%. Letting \( r \) represent the clearance rate, the research hypotheses are then \( H_0 : r = 0.50 \) versus \( H_1 : r = 0.70 \). Using a Simon two-stage design\(^{17}\) with \( \alpha = 0.10 \) and 90% statistical power, the first stage requires accrual of 21 patients and the second stage accrual of 24 more patients for a total of 45 evaluable patients.

In 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, 80% of the patients accrued to the surgical arm actually had the surgery. The other 20% had local or distant progression, were medically unfit for surgery after induction chemoradiation, or refused surgery after induction chemoradiation. Assuming similar results for this trial, and that another 5% of patients will be otherwise ineligible or inevaluable, a total of 60 patients are required for this study.

13.3 Patient Accrual
Patient accrual is projected to be 3 patients per month. At that rate, it will take 20 months to reach the required 60 patients. If the average monthly accrual rate is less than 1 patient, the study chairs will re-evaluate for feasibility.

13.4 Analysis Plans

13.4.1 Interim Reporting of Accrual and Toxicity Data
Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The usual components of this report are:

a) the patient accrual rate with a projected completion date for the accrual phase;
b) accrual by institution;
c) the distribution of pretreatment characteristics;
d) the frequency and severity of the toxicities;
e) the status of surgical, medical, and radiation quality assurance reviews.

The statistician will report any problems identified to the study chairs, the RTOG Lung Cancer Committee Chair, and if appropriate, to the RTOG Executive Committee.

13.4.2 Early Stopping
Major morbidities associated with the surgery, as defined in Section 8.4.2, are: pneumonia, emphysema, wound infection, bronchopleural fistula, atelectasis, pneumothorax, pleural effusion, myocardial infarction, pulmonary embolus, atrial arrhythmia, ventricular arrhythmia, postoperative hemorrhage, and other surgical or medical complication which occurred during the postoperative period. Of interest in this study is the occurrence of any of the above major morbidities in the first 30 post-operative days. For each patient, the occurrence of the first major morbidity will count as an event for the estimation of the cumulative incidence of major morbidities association with the surgery. Subsequent major morbidities in the same patient will not be counted again. If the rate of major morbidities within the first 30 postoperative days is estimated to be greater than 40% at any time, the study chairs, the RTOG Lung Cancer Committee Chair, and if appropriate, the RTOG Executive Committee will be notified. The study results will be reviewed and a determination made about continuing the study.

13.4.3 Analysis for Reporting Treatment Results
The null and alternative hypotheses of the study’s primary outcome, the mediastinal nodal sterilization rate, are $H_0: r = 0.50$ and $H_a: r = 0.70$. $H_0$ and $H_a$ will be tested using Simon’s two-stage design test procedure $^{17}$ with $\alpha = 0.10$ and 90% power to detect at least a 20% difference in rates. At the end of the first stage, if at least 12 of the first 21 evaluable patients have mediastinal nodal sterilization, then an additional 24 evaluable patients will be accrued in the second stage. Further, the following table shows the probability of a Type I Error (i.e., the probability of concluding $H_a: r = 0.70$ when $H_0: r = 0.50$ is true) for different numbers of patients with mediastinal nodal sterilization at the end of the first stage. Mediastinal nodal sterilization for each patient is determined by complete mediastinal nodal dissection for resectable patients and by mediastinoscopy, thoracoscopy, Chamberlain procedure, or transbronchial needle aspirate 4 weeks after induction chemoradiation for unresectable patients.

<table>
<thead>
<tr>
<th>Number of First Stage Patients with Mediastinal Nodal Sterilization</th>
<th>Probability of a Type I Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 13</td>
<td>0.191655</td>
</tr>
<tr>
<td>At least 14</td>
<td>0.094624</td>
</tr>
<tr>
<td>At least 15</td>
<td>0.038177</td>
</tr>
<tr>
<td>At least 16</td>
<td>0.013302</td>
</tr>
<tr>
<td>At least 17</td>
<td>0.003599</td>
</tr>
<tr>
<td>18-21</td>
<td>≤0.000745</td>
</tr>
</tbody>
</table>

At the end of the second stage, if at least 27 of the first 45 evaluable patients have mediastinal nodal sterilization, then the null hypothesis $H_0: r = 0.50$ will be rejected in favor of the alternative hypothesis $H_a: r = 0.70$. 

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If, after the first stage, the results indicate that no more patients should be accrued, the first stage results will be published for the primary endpoint and the first stage patients will continue in follow up for the secondary endpoints. If, after the first stage, at least 18 of the 21 patients have mediastinal nodal sterilization (85.7%; exact 95% CI [63.6%, 97.0%]), the null hypothesis will be rejected, the first stage results will be published for the primary endpoint, and the design of a follow-on Phase III clinical trial will be initiated. In this instance, this study will continue according to the design to the second stage of patient accrual and subsequent follow up for the primary and secondary endpoints. Otherwise, the primary endpoint analysis will be done after the second stage is completed and all data supporting the primary endpoint is received in the RTOG HQ. It will include:

- tabulation of all cases entered into the trial; exclusions with reasons;
- accrual by institution;
- distribution of important prognostic baseline variables;
- observed results for the endpoints listed in Section 13.1.

Overall and progression-free survival at two years will be estimated by the Kaplan-Meier method. These survival estimates will be reported for the entire cohort as well as by Pancoast and non-Pancoast status. The rate of major morbidities occurring in the first 30 post-operative days associated with the surgery will be estimated along with its 95% confidence interval. The rates of complete pathological response and toxicity as well as the treatment-related fatality rate will be calculated along with their associated 95% confidence intervals.

Descriptive statistics for pertinent demographic and prognostic factors will be used to describe the patient population with 95% confidence intervals where appropriate.

### 13.5 Gender and Minorities

Some investigators have shown gender to be a prognostic factor in NSCLC. However, the RTOG did not show this to be the case in an analysis. Furthermore, an analysis of race did not indicate an association with outcome. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender and race and treatment. The projected gender and minority accruals are shown below.

**Projected Gender and Minority Inclusion**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>26</td>
<td>30</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects*</td>
<td>27</td>
<td>33</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>23</td>
<td>26</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>More than one race</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Racial Category: Total of all subjects*</td>
<td>27</td>
<td>33</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

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REFERENCES


SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE
A PHASE II TRIAL OF NEOADJUVANT THERAPY WITH CONCURRENT CHEMOTHERAPY AND HIGH DOSE RADIOTHERAPY FOLLOWED BY SURGICAL RESECTION AND CONSOLIDATIVE THERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have locally advanced lung cancer.

WHY IS THIS STUDY BEING DONE?

Prior data from several institutions supports the use of chemotherapy and radiation therapy prior to surgery for treatment of locally advanced lung cancer. Based on experience with patients in a University of Maryland study, this study combines higher dose radiation therapy with chemotherapy.

The purpose of this study is to find out what effects (good and bad) a combination of chemotherapy and high dose radiation therapy followed by surgery and chemotherapy have on you and your lung cancer. Surgery after the chemotherapy and radiation is done to remove any remaining cancer and to decrease the risk of the cancer returning in the lung.

This research is being done to test whether high dose radiation therapy (with chemotherapy) increases control of your lung cancer prior to surgery and because we need to find out if the combination of chemotherapy, high dose radiation, and surgery is safe.
**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 60 people will take part in this study.

**WHAT IS INVOLVED IN THE STUDY? (2/21/05)**

If you take part in this study, you will be given two kinds of chemotherapy, paclitaxel and carboplatin, through your vein once a week for 6 weeks. Along with the chemotherapy, you will receive radiation therapy once a day for about 7 weeks.

Within 8 weeks after the chemotherapy and radiation therapy is finished, some patients will have surgery to remove all or most of the lung cancer. Patients whose cancer has progressed after chemotherapy and radiation is finished will not have surgery. Your doctors will discuss with you whether or not surgery is the right treatment for you.

Additional chemotherapy will be given to all patients, those who had surgery and those who did not have surgery. You will be given two kinds of chemotherapy paclitaxel and carboplatin, through the vein every 21 days x 2 (at 3 and 6 weeks). If you don’t have surgery, you will start this chemotherapy about 4 weeks after the chemotherapy and radiation therapy are finished. If you have surgery, you will start this chemotherapy no more than 10 weeks after the surgery.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

<table>
<thead>
<tr>
<th>Chemotherapy and Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel and Carboplatin 1x/week for 6 weeks plus</td>
</tr>
<tr>
<td>Radiation Therapy 1x/day, 5 x/week, for about 7 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 8 weeks of completion of Chemotherapy and Radiation Therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient starts Chemotherapy within 4 weeks of completion of Chemotherapy and Radiation Therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel and Carboplatin every 21 days x 2 (at 3 and 6 weeks)</td>
</tr>
<tr>
<td>Patients who have had surgery start this chemotherapy no later than 10 weeks post-surgery.</td>
</tr>
</tbody>
</table>
As a cancer patient, if you take part in this study, you also will have the following tests and procedures:

- A physical exam before beginning treatment, weekly during the chemotherapy and radiation therapy, and 4 weeks after the end of chemotherapy and radiation therapy. During additional chemotherapy: Every 3 weeks during chemotherapy, at the end of all treatment, and at follow-up visits: 6 weeks after the end of treatment, then every 3 months for one year, every six months for 2 years, then once a year for 2 years.
- Blood tests before beginning treatment, weekly during the chemotherapy and radiation therapy, and 4 weeks after chemotherapy and radiation therapy. During additional chemotherapy: Every 3 weeks during chemotherapy, at the end of all treatment, and at follow-up visits, and then as advised by your doctor.
- For women who are able to have children, a test prior to beginning treatment to see that they are not pregnant.
- A chest X-ray before beginning treatment.
- A surgical procedure before beginning treatment, in which a lighted instrument or needle is inserted through an incision (cut) in the neck or chest to examine the structures in the chest cavity and the lymph nodes and to take a sample (a biopsy) of tumor.
- A CT scan or MRI of your chest, stomach, and head before beginning treatment, 4 weeks after the end of chemotherapy and radiation therapy, and at follow-up visits.
- A PET scan before beginning treatment, 4-6 weeks after the end of chemotherapy and radiation therapy, and then as advised by your doctor.
- An EKG (a test to measure the electrical activity of the heart) before beginning treatment and, if advised by your doctor, at follow-up visits.
- Tests of your lung function before beginning treatment, 4 weeks after the end of chemotherapy and radiation therapy, and, if advised by your doctor, at follow-up visits.

**HOW LONG WILL I BE IN THE STUDY?**

If you have surgery, you will receive treatment for about 28 weeks. If you don’t have surgery, you will receive treatment for about 18 weeks.

All patients will be followed for 5 years. You will be seen in follow-up visits 6 weeks after the end of treatment, then every 3 months for one year, every six months for 2 years, and then once a year for 2 years.

Your doctor may decide to take you off this study if side effects become very severe, if new scientific developments occur that indicate the treatment is not in your best interest, or if your condition worsens.
You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the chemotherapy and radiation therapy are stopped and you recover from the surgery, but in some cases side effects can be serious or long lasting or permanent.

**Risks Associated with Paclitaxel**

*Very Likely*
- Slow pulse
- Hair loss
- Tingling, numbness, burning pain in hands and feet
- Lower blood counts during treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Inflammation of the lining of the mouth
- Skin redness or rash

*Less Likely*
- Nausea and/or vomiting
- Mouth sores
- Diarrhea
- Inflammation of the lining of the throat and/or intestines
- Tiredness
- Blurred vision and/or the feeling of seeing flashing lights
- Flushing
- Lightheadedness
- Tenderness, hardness, or itching of the skin; rarely, blistering of the skin
- Pain in muscles and joints
- Mood swings

*Less Likely, But Serious*
- Areas of decreased vision or visual awareness
- Reaction to paclitaxel, resulting in injury to the skin, lung, and/or lining of the digestive tract in the chest area that has received radiation
- Cardiovascular changes, such as low or high blood pressure, speeding up or slowing of heartbeat, a blockage of blood flow to the heart, and/or heart attack
- Seizures
- Allergic reactions, which could involve sweating, difficulty breathing, lightheadedness, and/or rapid heartbeat
- Severe inflammation of the small and large intestines and colon
- Severe rash called Stevens-Johnson Syndrome, which can cause fever and red sores in your mouth and eyes
- Changes in liver enzymes in the blood, which may mean damage to the liver that could lead to being hospitalized, or rarely, to death

**Risks Associated with Carboplatin**

**Very Likely**
- Tingling, numbness, burning pain in hands and feet
- Lower blood counts during treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Nausea and/or vomiting
- Tiredness

**Less Likely**
- Muscle pain

**Less Likely, But Serious**
- Allergic reactions, which could involve sweating, difficulty breathing, lightheadedness, and/or rapid heartbeat
- Changes in liver enzymes in the blood, which may mean damage to the liver that could lead to being hospitalized, or rarely, to death
- Blurred vision
- Hearing loss

**Risks from Radiation Therapy**

Radiation therapy to the chest

**Very Likely**
- Difficulty, pain, or burning sensation when swallowing, which is temporary; the use of chemotherapy with radiation may increase this risk. You should avoid acidic or spicy foods and alcoholic beverages.
- Fatigue (tiredness) for no apparent reason, which is temporary
- The skin in the treatment area may become reddened and/or dry, and chest hair may not grow back.
- Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Cough
- Some difficulty breathing, due to lung damage, as described below

**Less Likely, But Serious**
- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular or rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Narrowing of the esophagus (tube to the stomach)

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. The combined use of chemotherapy and radiotherapy, as in this study, may increase the risk of developing symptoms due to lung damage.

**Risks from Lung Surgery**
You will need to review and sign a separate permission form from your doctor/hospital for this surgery. The serious risks of surgery are infection, bleeding, poor healing of the skin and/or muscles in the chest, clots in the legs and/or lung, air leaking from the part of the airway that was operated on, pneumonia, being on a ventilator (breathing machine) for days or weeks after surgery, heart attack, stroke, and/or death.

These risks may be more likely or severe for people in this study than for someone having lung surgery without having had chemotherapy and radiation therapy before surgery.

**Reproductive Risks**
This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone
to become pregnant while you are on this study, you must tell your doctor immediately.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with lung cancer in the future.

The benefit of a combination of chemotherapy and high dose radiation therapy followed by surgery and chemotherapy to patients with lung cancer is unknown. This treatment may keep your lung cancer from growing, and this may provide relief from symptoms and improve your quality of life. This treatment may improve control of your lung cancer. However, none of these benefits is guaranteed, and the effects of a combination of chemotherapy, high dose radiation therapy followed by surgery and chemotherapy may be no different or worse than chemotherapy or radiation therapy alone.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition, whether or not you can get this treatment off study, and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology
Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in lung cancer from the RTOG Lung Committee, the RTOG study chairs, and the study statistician will be reviewing the data periodically throughout the study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

For information about your disease and research-related injury, you may contact:

__________ Name ___________________ Telephone Number _________

For information about this study, you may contact:

__________ Name ___________________ Telephone Number _________

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research

__________ Name ___________________ Telephone Number _________

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at

Visit the NCI’s Web sites for comprehensive clinical trials information at www.cancer.gov/clinicaltrials or for accurate cancer information including PDQ (Physician Data Query) visit www.cancer.gov/cancerinfo/pdq
SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

Patient’s Name __________________________ Signature __________________________ Date __________

Name of Person Obtaining Consent __________________________ Signature __________________________ Date __________
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

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

### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>
APPENDIX III
AJCC Staging

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0 No evidence of primary tumor.
Tis Carcinoma in situ
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)
T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

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

**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph nodes metastasis
N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
### Distant Metastasis (M)

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

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

### STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size (T)</th>
<th>Node Size (N)</th>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
<td>TX</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX IV

American Thoracic Society Nodal Stations

Lymph Node Map Definitions

N2 Nodes – All N2 nodes lie within the mediastinal pleural envelope

1. Highest mediastinal nodes
   Nodes lying above a horizontal line at the upper rim of the brachiocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline

2. Upper paratracheal nodes
   Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes

3. Prevascular and retrotracheal nodes
   Prevascular and retrotracheal nodes may be designated 3A & 3P; midline nodes are considered to be ipsilateral

4. Lower paratracheal nodes
   The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope.

Researchers may wish to designate the lower paratracheal nodes as No. 4s (superior) and No. 4i (inferior) subsets for study purposes; the No. 4s nodes may be defined by a horizontal line extending across the trachea and drawn tangential to the cephalic border of the azygos vein; the No. 4i nodes may be defined by the lower boundary of No. 4s, as described above.

5. Subaortic (aorto-pulmonary window)
   Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope.

6. Para-aortic nodes (ascending aorta or phrenic)
   Nodes lying anterior and lateral to the ascending aorta and aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch

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

8. Paraesophageal nodes (below carina)
   Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes.

9. Pulmonary ligament nodes
   Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein.

N1 nodes – All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura.

10. Hilar nodes
    The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiographically, the hilar shadow may be created by enlargement of both hilar and interlobar nodes.

11. Interlobar nodes
    Nodes lying between the lobar bronchi.

12. Lobar nodes
    Nodes adjacent to the distal lobar bronchi.

13. Segmental nodes
    Nodes adjacent to the segmental bronchi.

14. Subsegmental nodes
    Nodes around the subsegmental bronchi.
Thoracic Surgeon's Questionnaire

Please complete this questionnaire following a careful review of the eligibility and surgical sections of this 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
   _____ Primarily Thoracic Surgery; some Cardiac Surgery
   _____ Primarily Cardiac Surgery; some Thoracic Surgery
   _____ Equal mix of Thoracic and Cardiac Surgery
   _____ Only Thoracic Surgery
APPENDIX V (Continued)

5. Please estimate the number of lobectomies and/or pneumonectomies you perform per year ______

6. Please estimate the number of post-chemoradiotherapy lobectomies and/or pneumonectomies you perform per year ______

NOTE: Surgeons must have performed a minimum of 10 lobectomies/pneumonectomies per year (5 of which have to be resections on patients who are post-chemoradiotherapy administration) in order to participate in RTOG 0229.

7. 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 contact:

Mark Krasna, M.D.
St. Joseph's Medical Center
7505 Osler Dr., Suite 303
Towson, MD 21204
410-427-2220
markkrasna@catholichealth.net
FAX 410-427-2221

Signature of Surgeon completing this form __________________________
Institution Name ________________________________

Printed Name of Surgeon __________________________
RTOG Institution Number __________________________

Telephone number of Surgeon __________________________
Physician's Fax Number __________________________

Return this form to your Research Associate

RTOG Research Associates: Fax the completed form to Dr. Krasna, FAX 410-427-2221.

Dr. Krasna: Please check the appropriate box, sign and date the form, and fax the form to RTOG Headquarters (215-574-0300) and to the institution.

☐ Reviewed and approved  ☐ Reviewed and not approved

Mark Krasna, M.D., Thoracic Surgery Co-Chair Date