RADIATION THERAPY ONCOLOGY GROUP

RTOG 0412/SWOG S0332

PHASE III RANDOMIZED TRIAL OF PREOPERATIVE CHEMOTHERAPY VERSUS PREOPERATIVE CONCURRENT CHEMOTHERAPY AND THORACIC RADIOTHERAPY FOLLOWED BY SURGICAL RESECTION AND CONSOLIDATION CHEMOTHERAPY IN FAVORABLE PROGNOSIS PATIENTS WITH STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER

**SWOG Study Chairs**

Co-Principal Investigator/Medical Oncology
Howard West, MD
Swedish Cancer Institute
1221 Madison St., 2nd Floor
Seattle, WA 98104
206-386-2882/FAX 206-386-2746
howard.west@swedish.org

Medical Oncology Co-Chair
David Gandara, MD
UC Davis Cancer Center
4501 X Street, Suite 3017
Sacramento, CA 95817
916-734-3772/FAX 916-734-7946
david.gandara@ucdmc.ucdavis.edu

Medical Oncology Co-Chair
Kathy Albain, MD
Loyola Univ. Med. Cntr., 2160 South First Ave
Cancer Center, Bldg 112, Rm. 109
Maywood, IL 60153
708-327-3102/FAX 708-327-2210
kalbain@lumc.edu

Radiation Oncology Co-Chair
Laurie Gaspar, MD, MBA
Univ. of Colorado HSC/campus mailbox F706
1665 N. Ursula St., Suite 1032
Aurora, CO 80010
720-848-0154/FAX 720-848-0222
laurie.gaspar@uchsc.edu

Thoracic Surgery Co-Chair
Eric Vallieres, MD
Swedish Cancer Institute
1221 Madison, Suite 400
Seattle, WA 98104
206-215-6800/FAX 206-215-6801
eric.vallieres@swedish.org

**RTOG Study Chairs (Coordinating Group)**

Principal Investigator/Radiation Oncology
Maria Werner-Wasik, MD
Kimmel Cancer Center/Jefferson Medical College
111 South 11th Street
Philadelphia, PA 19107
215-955-7679/FAX 215-955-0412
maria.werner-wasik@mail.tju.edu

Radiation Oncology Co-Chair
Hak Choy, MD
The University of Texas Southwestern
5801 Forest Park Road
Dallas, TX 75390
214-645-7800/FAX 214-645-9183
Hak.Choy@UTSouthwestern.edu

Medical Oncology Co-Chair
Ramaswamy Govindan, MD
Washington University School of Medicine
660 S. Euclid Avenue, Box 8056
St. Louis, MO 63110
314-362-4819/FAX 314-362-7086
rgovinda@im.wustl.edu

Thoracic Surgery Co-Chair
Harvey I. Pass, MD
NYU School of Medicine and Comprehensive Cancer Center
530 1st Avenue, 9V
New York, NY 10016
212-263-7417/FAX 212-263-2042
harvey.pass@med.nyu.edu

Thoracic Surgery Co-Chair
Ara A. Vaporciyan, MD
MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
713-745-4533/FAX 713-794-4901
avaporci@mdanderson.org

**Correlative Studies Co-Chairs on next page**

Activation Date: April 8, 2005
Termination Date: February 19, 2009
Closure Date: December 15, 2006
Update Date: January 26, 2006
Version Date: February 14, 2007
Includes Amendments 1-4
RADIATION THERAPY ONCOLOGY GROUP
RTOG 0412/SWOG S0332

Correlative Studies Co-Chairs

**SWOG Study Chairs**

Molecular Biology Co-Chair  
Paul Gumerlock, PhD  
UC Davis Cancer Center  
4501 X Street, Room 3016  
Sacramento, CA 95817  
916-734-8614/FAX 916-734-2361  
paul.gumerlock@ucdmc.ucdavis.edu

Pathology Co-Chair  
Wilbur Franklin, MD  
Univ. of Colorado HSC/4200 E. 9th Ave  
Dept. of Pathology, Box B216  
Denver, CO 80262  
303-315-1807/FAX 303-315-1835  
wilbur.franklin@uchsc.edu

Quality of Life Co-Chair  
Carol Moinpour, PhD  
SWOG Statistical Center  
1100 Fairview Ave. N., M3-C102  
Seattle, WA 98109  
206-667-4604/FAX 206-667-4408  
cmoinpou@fhcrc.org

**RTOG PET Co-Chairs**  
Jeff Bradley, MD  
Washington Univ./Rad Oncology Center  
4939 Children’s Place, Suite 550  
St. Louis, MO 63110  
314-362-8525/FAX 314-362-8521  
bradley@radonc.wustl.edu

Barry Siegel, MD  
Mallinckrodt Institute of Radiology  
510 South Kingshighway Blvd.  
St. Louis, MO 63110  
314-362-2809/FAX 314-362-2806  
siegelb@mir.wustl.edu

**RTOG Study Chairs (Coordinating Group)**

Translational Research Co-Chair  
David Carbone, MD  
Vanderbilt–Ingram Cancer Center  
2200 Pierce Ave., 685 Preston Research Bldg.  
Nashville, TN 37232  
615-936-3524/FAX 615-936-3322  
d.carbone@Vanderbilt.edu

Pathology Co-Chair  
Elizabeth Hammond, MD  
LDS Hospital/Dept. of Pathology  
8th Ave & C Street  
Salt Lake City, UT 84143  
801-408-5626/FAX 801-408-5020  
Idehammo@ihc.com

Quality of Life Co-Chair  
Benjamin Movsas, M.D.  
Henry Ford Health System  
2799 West Grand Blvd.  
Detroit, MI 48202  
313-916-5188/FAX313-916-3235  
bmovsas@hfhs.org

Comorbidity Co-Chair  
Elizabeth Gore, MD  
Medical College of Wisconsin  
9200 West Wisconsin Avenue  
Milwaukee, WI 53226  
414-805-4465/FAX 414-805-4369  
bethgore@mcw.edu

---

RTOG 0412
This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

This study is supported by the NCI Cancer Trials Support Unit (CTSU) [2/14/07]

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org

- Send completed site registration documents to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- Patient enrollments will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the RTOG. Case report forms (with the exception of patient enrollment forms), clinical reports, and transmittals must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.

- Data query and delinquency reports will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.
INDEX

Schema

Eligibility Checklist

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Additional Pretreatment Evaluations/Management

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Tissue/Specimen Submission

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Nodal Stations
Appendix V - Thoracic Surgeon’s Questionnaire
Appendix VI - Comorbidity Recording Sheet and Charlson Comorbidity Index (CCI)
Appendix VII - Specimen Collection/Shipping Kit Procedure
Appendix VIII - Laboratory Methods for Correlative Studies
Appendix IX - CTSU Logistics
**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0412/SWOG S0332**

**PHASE III RANDOMIZED TRIAL OF PREOPERATIVE CHEMOTHERAPY VERSUS PREOPERATIVE CONCURRENT CHEMOTHERAPY AND THORACIC RADIOTHERAPY FOLLOWED BY SURGICAL RESECTION AND CONSOLIDATION CHEMOTHERAPY IN FAVORABLE PROGNOSIS PATIENTS WITH STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER**

**SCHEMA**

<table>
<thead>
<tr>
<th>R</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stratification</strong></td>
<td><strong>Patients on both arms:</strong></td>
</tr>
<tr>
<td>A</td>
<td>ARM 1 Post-induction Re-Evaluation</td>
</tr>
<tr>
<td>1. <em>Number of involved mediastinal nodal stations</em> (1 vs. ≥ 2 vs. not evaluable)</td>
<td>Induction Therapy: within 2 weeks of anticipated surgery then Surgical Resection</td>
</tr>
<tr>
<td>2. <em>Nodal micrometastases vs. clinically involved nodes</em> (mN2 vs. cN2)</td>
<td>Induction Therapy: then Thoracic RT 50.4 Gy Consolidation Chemotherapy:</td>
</tr>
<tr>
<td>3. T stage (T1 vs. T2-3)</td>
<td>Induction Therapy: plus docetaxel cisplatin/docetaxel (4-6 weeks post-surgery)</td>
</tr>
<tr>
<td>E</td>
<td></td>
</tr>
</tbody>
</table>

*See Section 3.1.3.4 for further details*

See Section 5.0 for details of pre-registration requirements. See Sections 6.0, 7.0, and 8.0 for details of radiation therapy, chemotherapy, and surgery.

**Patient Population:** (See Section 3.0 for Eligibility)
Single, newly diagnosed primary lung parenchymal lesion of Stage IIIA (T1-T3) with ipsilateral involved mediastinal lymph nodes measuring ≤ 3 cm; N2 nodes must be separate from primary tumor.

**Required Sample Size:** 574
1. Is there histologic or cytologic confirmation of adenocarcinoma, large cell carcinoma, squamous cell carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma or non-small cell cancer of the lung, NOS?

2. Is there a Stage IIIA diagnosis including a single primary lesion (T1-T3) with positive ipsilateral mediastinal lymph node(s) [N2] that are separate from the primary tumor on CT scan or surgical exploration and with none of the lymph nodes measuring > 3 cm in largest diameter?

3. Is there measurable disease on chest x-ray and/or contrast enhanced CT scan of the chest?

4. Has positive N2 status been confirmed by one the procedures listed in section 3.0?

5. If applicable, have contralateral mediastinal lymph nodes (1 cm or greater) or lymph nodes of the neck seen on contrast CT scan of the chest or suggested by PET imaging been proven cytologically/histologically negative by one of the procedures listed in section 3.0?

6. If applicable, has pleural effusion been confirmed cytologically negative by thoracentesis or, if deemed too small to tap, thoracoscopy, if feasible?

7. Is Zubrod performance status 0 or 1?

8. Is patient at least 18 years of age?

9. Have all staging procedures and diagnostic evaluations been performed within the timelines and values within the parameters detailed in section 3.0?

10. If applicable, has the patient had a serum pregnancy test?

11. Has the patient had weight loss greater than 5% of body weight in the past 6 months?

12. Has the patient had a prior invasive malignancy within the past 3 years?

13. Does the patient have any severe and active comorbid medical condition(s) as detailed in section 3.2?

14. Has the patient received prior chemotherapy or a biological agent (including Iressa) for the current lung cancer?

15. Has the patient received prior radiotherapy to the region of the current cancer that will result in overlap of radiation treatment fields?

16. Does the patient have known Acquired Immune Deficiency Syndrome?
   (Note: HIV testing is not required for entry into the protocol)
(Continued on the next page)
18. Surgical Oncologist

(Y/N) 19. Tissue/Blood kept for cancer research?

(Y/N) 20. Tissue/Blood kept for medical research?

(Y/N) 21. Allow contact for future research?

22. Specify number of involved mediastinal nodal stations (1 vs. ≥ 2 vs. not evaluable)

23. Specify nodal micrometastases vs. clinically involved nodes (mN2 vs. cN2)

24. Specify T stage (T1 vs. T2-3)

25. Treatment Assignment

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 0412
1.0 INTRODUCTION

1.1 Stage III, or locally advanced non-small cell lung cancer (NSCLC) is the second most frequent stage at the time of presentation, but no consensus treatment standards exist for a significant fraction of these patients. Potentially resectable, N2-lymph node positive NSCLC represents a large proportion of patients presenting with locally advanced disease for whom there are conflicting treatment options, and consequently clinical practice varies widely. Because distant recurrences are more common than localized failures, systemic chemotherapy (CT) is generally felt to be integral in order to minimize risk of relapse. Surgery alone has been associated with poor outcome.

Two small, randomized trials comparing induction therapy followed by surgery with surgery alone were terminated early secondary to highly significant survival differences favoring induction therapy. More recently, a retrospective review of over 700 patients who had N2-lymph node positive NSCLC and underwent surgical resection noted significantly superior survival in the group of patients who received induction chemotherapy based on physician choice compared to those who had resection alone. These studies support the idea of using induction chemotherapy prior to surgery in patients with potentially resectable stage III NSCLC.

An alternative approach that incorporates a combination of chemotherapy and concurrent thoracic irradiation (TRT) was investigated in several trials. The largest of those trials, the phase II SWOG-8805 trial, used cisplatin and etoposide (PE) administered with TRT to patients with stage IIIB as well as IIIA disease, followed by resection for patients who did not demonstrate progression. This study achieved a promising three-year survival of 26% and a markedly superior survival of patients achieving N2 lymph node sterilization after induction compared with those who did not achieve a pathologic complete response in the mediastinum.

While these data suggest that induction therapy followed by surgery seems to produce better survival than surgery alone in locally advanced NSCLC, the question of whether surgery is needed at all in patients with locally advanced therapy following chemoradiotherapy was addressed in the recently completed North American Intergroup trial INT 0139/RTOG 93-09/SWOG-9336. Early results of this study affirm the contribution of surgery, with a superior disease-free survival (DFS) in the arm receiving induction CT/RT followed by surgery. At this point, there are no differences in overall survival (OS) for the two groups, with the improvement in DFS on the surgical arm counterbalanced by increased mortality related to trimodality therapy.

At the present time, it is not clear whether the optimal induction therapy for patients with resectable locally advanced NSCLC should be chemotherapy alone or chemoradiation. Two small, randomized trials have attempted to compare induction chemotherapy alone to induction chemotherapy and radiation prior to surgery. Fleck and colleagues randomized 96 patients to cisplatin-based chemotherapy with or without thoracic irradiation and reported a survival benefit from the bimodality induction approach in terms of radiographic response, resectability, and disease-free survival. A similar trial by Sauvaget and colleagues randomized 92 patients to cisplatin-based chemotherapy alone or a different non-platinum chemotherapy regimen concurrent with radiation, reporting that the induction chemoradiation therapy arm was associated with a numerically higher pCR rate and higher resection rate, but overall survival was not different between the arms. Unfortunately, since neither of these trials has been published, neither is definitive in testing the role of preoperative radiotherapy, and important Stage IIIA N2 subsets were not well delineated. Defining the optimal induction therapy would represent an important advance in the management of locally advanced NSCLC.

Most recently, a randomized Phase III trial of the German Lung Cancer Cooperative Group (GLCCG) was presented. Two hundred fifty eight Stage IIIA and IIIB patients (including those with bulky nodal disease) received two courses of induction cisplatin/etoposide versus chemoradiotherapy (carboplatin and vindesine with concurrent twice daily accelerated hyperfractioned RT to 45 Gy), followed in both groups by surgery. Postoperative RT was given to patients whose induction regimen included chemotherapy only. Only 54-57% of Stage IIIA patients in either arm underwent a complete resection (R0), and MST was not different between the arms (15.5 mo. in chemoradiotherapy and 16.8 mo. in chemotherapy only arm, p=0.97). A full interpretation of the study is difficult due to a high percentage of patients who were not fully resectable. Pathologic response rates were not reported.
The importance of defining subsets of stage IIIA N2 NSCLC is a critical component of management, but most preceding trials have not clarified eligibility criteria well, which limits the applicability of trial results to wider clinical practice. Andre and colleagues\(^7\) clearly illustrated significant clinical heterogeneity based on lymph node size and number of stations involved, with the same study demonstrating a subgroup of less extensive N2 involvement that may be best served by preoperative chemotherapy. While SWOG-8805 and INT 0139 targeted a population of patients with bulkier and multifocal N2 lymph node involvement, for whom incorporation of radiation for additional local control may be valuable, the increased toxicity of TRT with chemotherapy may outweigh the modest benefit of increased local control if resection is to provide definitive local therapy in patients with less bulky and more limited N2 node involvement. Uniform mediastinoscopy and PET scanning in the proposed trial will ensure an optimally characterized patient population that will set a new standard in the study of locally advanced NSCLC.

Taken together, there is evidence from pilot studies that concurrent induction CT/RT is associated with increased pathologic complete response (pCR) rates compared with chemotherapy alone. While the value of surgery in improving DFS has been formally tested and confirmed in a prospective phase III randomized trial of stage IIIA N2 NSCLC, the role of radiation in addition to chemotherapy in the induction phase has not been fully evaluated but is a critical issue, in light of the balance between increased local control and added toxicity that may increase mortality from treatment. This balance is particularly relevant for more limited IIIA N2 disease, in which surgery is more likely to provide adequate local control, in contrast to the more heterogeneous population of IIIA N2 disease studied in INT 0139/RTOG 93-09/SWOG-9336. The relevance of this central question is illustrated by fact that both RTOG and SWOG simultaneously developed independent, parallel trials of this question based on the variability of clinical practice within their memberships, and also that the leaders of all of the cooperative groups achieved a strong consensus that this issue should be addressed in a prospective randomized phase III intergroup trial.

The present trial will allow for the clear establishment of a standard of care for a well-defined, common subset of patients with resectable, limited N2-positive NSCLC. Patients will be randomized to platinum-based chemotherapy alone versus CT/RT with the same chemotherapeutic agents, planning for all patients without progression to undergo resection followed by three cycles of consolidation docetaxel. The present trial builds on the encouraging results seen in INT 0139/RTOG 93-09/SWOG-9336 by maintaining cisplatin and substituting docetaxel for etoposide during induction, and having all patients receive consolidation with docetaxel alone and capitalizing on the very promising results with consolidation docetaxel in prior SWOG experience in SWOG-9504.\(^15\) In addition, this study will define and further stratify the subsets of N2-lymph node positive NSCLC to clarify optimal treatment for this heterogeneous group, assess the prognostic value of postinduction therapy PET scanning, evaluate differences in quality of life between the two induction approaches, and incorporate groundbreaking proteomic and immunohistochemical correlative work while ultimately defining a standard of care for this large group of patients.

### 1.2 Rationale for Chemotherapy Choice

The SWOG-8805 trial established the safety and efficacy of induction chemotherapy and radiation therapy using cisplatin and etoposide in a cooperative group setting,\(^10\) also demonstrating a particularly encouraging three-year survival of 26%. The operative mortality in SWOG-8805 was 6%, and postoperative mortality was comparable to that in surgical series. Patients who had no residual N2 nodal involvement after induction chemo-radiation had a remarkably superior survival compared to those with residual N2 disease despite induction therapy. This survival difference, independent of surgical intervention, raised the question of whether survival of stage III NSCLC may be largely driven by the benefits of chemo-radiation rather than surgical resection. Corroborating this suggestion of curative value of chemoradiation alone, SWOG conducted a subsequent phase II trial (SWOG-9019) demonstrating feasibility and comparable median survival with a non-surgical approach of cisplatin/etoposide and concurrent radiation to 61 Gy.\(^16\) Based on these results, INT 0139/RTOG 93-09/SWOG-9336 randomized 429 patients with Stage IIIA N2 lymph node-positive NSCLC to either cisplatin-etoposide chemotherapy and definitive radiation therapy to 61.0 Gy or the same chemotherapy in combination with radiation therapy to 45.0 Gy prior to surgery, followed by postoperative
chemotherapy. The results of this study demonstrate an improved disease-free survival in the surgical arm (median 13.4 vs. 11.8 months). However, greater treatment-related mortality in the trimodality arm resulted in an identical median survival time (MST) of 22 months for each group. These results raise the question of whether preoperative chemotherapy without radiation therapy could improve the treatment-related mortality compared to induction chemoradiotherapy, possibly still conferring the improvement in disease-free survival.¹¹

While INT 0139 administered cisplatin and etoposide as the chemotherapy regimen, we hypothesize that docetaxel will be more advantageous than etoposide, and therefore will test a preoperative chemotherapeutic regimen employing the identical dose and schedule of cisplatin as in INT 0139, but substituting docetaxel for etoposide. Docetaxel is an active single agent in the first-line therapy of metastatic NSCLC. In addition, it is associated with improved survival in the second-line setting in patients with progressive disease following the use of platinum containing regimens when compared with best supportive care¹⁷–¹⁸ or vinorelbine/ifosfamide.¹⁹ Furthermore, docetaxel possesses radiosensitizing properties. Cisplatin is a widely employed chemotherapeutic agent in NSCLC and can be delivered in full dose with concurrent thoracic radiation, in contrast to carboplatin. A cisplatin-containing regimen was found to be superior to carboplatin-containing regimen in metastatic NSCLC.²⁰

1.3 Rationale for Postoperative Consolidation Chemotherapy

In the SWOG 9504 study, the use of consolidation docetaxel (at a dose of 75 mg/m² administered for three cycles) following induction chemoradiation with cisplatin and etoposide resulted in an impressive three-year survival rate of 37%.¹⁵ Consolidation chemotherapy was feasible in 78% of patients following induction chemoradiation and was generally well tolerated. The major toxicity was grade 4 neutropenia seen in 57% of patients. Also, the Intergroup study (INT 0139) employed consolidation chemotherapy (cisplatin, etoposide), and two thirds of patients were able to receive it postoperatively.¹¹ It is anticipated that docetaxel will be more feasible to administer in the consolidation setting than the two cycles of cisplatin and etoposide utilized in preceding trials.

1.4 Rationale for Radiation Therapy (RT) Dose

Variable radiation therapy (RT) doses have been used in a preoperative setting in combination with chemotherapy (45 Gy - 59.4 Gy standard fractionated or accelerated hyperfractionated RT 42-45 Gy total in twice daily 1.5 Gy fractions). Perioperative mortality varied between 6-12% without much evidence of higher RT doses being associated with increased surgical morbidity or mortality in skillful hands.²¹–²² On the other hand, the pCR rates are not reproducibly higher with escalated RT doses (27% with 59.4 Gy in Tufts study;²¹ 36% with 45.0 Gy in the INT 0139;¹¹ 9.5% with 42.0 Gy hyperfractionated²²). Radiation doses in prior studies, such as INT 0139, were prescribed without any correction for tissue inhomogeneity, i.e., the radiation planning assumed that lung tissue was of equivalent electron density to soft tissue. Orton, et al.²³ analyzed data from a large number of patients treated for lung cancer in an RTOG study and found that the overall correction factors ranged from 0.95 to 1.28, with a mean of 1.05 and distributional standard deviation of 0.05. The largest corrections were for lateral fields, with a mean correction factor of 1.11 and standard deviation of 0.08. Modern radiation therapy planning systems easily and quite accurately correct for tissue inhomogeneity. Therefore, preoperative RT will be given in 1.8 Gy fractions to a total of 50.4 Gy directed to the primary tumor, ipsilateral hilum, and bilateral mediastinum. There will be no routine postoperative mediastinal RT for patients with persistently positive lymph nodes in either arm, as per the Intergroup 0139 design. The RT dose proposed here mimics the dose used in both SWOG 88-05 and INT 0139, since it was well tolerated and associated with acceptable perioperative mortality and impressive pCR rates. Patients with positive resection margins may receive postoperative RT.

1.5 Rationale for Stratification

It is clear that N2 lymph node-positive NSCLC is a heterogeneous clinical entity. Treatment recommendations will be most likely to emerge from trials that provide homogeneous eligibility and uniform staging practices. An important retrospective review of 702 N2 lymph node-positive patients who underwent surgical resection” demonstrated different prognostic groups based on clinical versus microscopic nodal involvement, number of nodal levels involved, and delivery of preoperative chemotherapy. Best five-year overall survival rates were achieved by patients with microscopic single nodal level involved (34%), followed by those with microscopic multi-nodal involvement (11%), and clinical nodal involvement (3-8%). The present trial will stage patients with mediastinoscopy (or other methods specified under Eligibility) and stratify them according to the following recognized prognostic factors: microscopic nodal involvement versus clinical nodal
involvement (nodes >1.0 cm on CT scan), single versus multiple nodal station involvement, gender, and T stage (T1 versus T2-3).  

Patients who had no residual N2 nodal involvement after induction chemoradiation in SWOG-8805 had a remarkably superior survival compared to those with residual N2 disease despite induction therapy. Novel methods of assessing clearance of the primary tumor and mediastinal lymph nodes are needed, in order to select patients for thoracotomy before the day of surgery and avoid unnecessary thoracotomy. PET scan as an imaging predictor of outcome and proteomic analysis as a potential molecular predictor also are being assessed in this trial.

1.6 Supporting Preliminary Data (9/15/05)

Multiple phase II trials of preoperative chemotherapy have been conducted in the 1980s and 1990s, initially in clinical stage IIIA, and subsequently in pathologically staged IIIA patients. For the latter group, MST of 9-33 months (mo.) and three-year survival rates of 26-33% have been reported 3-6, 24-29 (see Table 1 below).

<table>
<thead>
<tr>
<th>Study/Phase</th>
<th>Year</th>
<th>Total Patient Number</th>
<th>pCR</th>
<th>MST (mo.) [surg vs. chemo-surg]</th>
<th>3-yr OS rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth, et al./III</td>
<td>19945</td>
<td>60</td>
<td>NR</td>
<td>11.0 vs. 64.0</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>19984</td>
<td></td>
<td></td>
<td>14.0 vs. 21.0</td>
<td>43%</td>
</tr>
<tr>
<td>Rosell, et al./III</td>
<td>19945</td>
<td>60</td>
<td>3.7%</td>
<td>10.0 vs. 22.0</td>
<td>27.5%</td>
</tr>
<tr>
<td></td>
<td>20006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pass, et al./III</td>
<td>199224</td>
<td>27</td>
<td>35% (nodal clearance)</td>
<td>16.5 vs. 34.0</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>200325</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depierre, et al./III</td>
<td>200226</td>
<td>355 total; 167 N2 patients</td>
<td>11% for all patients; NR for N2 subset</td>
<td>25.0 vs. 18.9 (N2)</td>
<td>39.6% vs. 37.1% (N2)</td>
</tr>
<tr>
<td>Martini, et al./II</td>
<td>199327</td>
<td>136</td>
<td>19/136=14%</td>
<td>19.0 (chemo-surg)</td>
<td>28%</td>
</tr>
<tr>
<td>Betticher, et al./II</td>
<td>200326</td>
<td>90</td>
<td>19%</td>
<td>33.0</td>
<td>33%</td>
</tr>
<tr>
<td>Cappuzo, et al./II</td>
<td>200329</td>
<td>40</td>
<td>2%</td>
<td>19.4</td>
<td>74% 1 year</td>
</tr>
</tbody>
</table>

NR= Not reported

Subsequently, several randomized trials of preoperative chemotherapy were performed in pathologically staged IIIA (N2) patients with very encouraging results of a marked survival improvement in patients receiving induction chemotherapy followed by surgery versus those treated with surgery alone (table above). In the chemotherapy arms, MST of 26-64 mo. was achieved, which represented a statistically significant improvement over surgery-alone arms, with MST of 8-15.6 mos. Two of those studies were terminated early when this significant difference in favor of chemotherapy was observed, and the results widely disseminated by their subsequent publication in prominent medical journals. 3-6 Despite these highly significant differences, these trials have been criticized due to potential imbalances in randomization, the lack of a requirement for pathologic staging, and the poor outcome for surgery alone in one trial. 5-6 In contrast to the encouraging survivals seen on these trials, the rates of complete tumor clearance (= pathologic complete response or pCR) following induction chemotherapy appear to be below 10% in several of these trials, but were not universally reported. None of these early trials addressed the potential role of radiation therapy in the preoperative setting.

The potential value of induction chemotherapy with radiation, either given concurrently or sequentially, was suggested by a series of phase II trials, 6-11, 21-22, 30-31 summarized in Table 2 below.
Table 2

<table>
<thead>
<tr>
<th>Study/Phase</th>
<th>Year</th>
<th>Total Patient Number</th>
<th>pCR</th>
<th>MST (mo.)</th>
<th>3-yr OS rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faber, et al./II</td>
<td>1989</td>
<td>85</td>
<td>20%</td>
<td>36.6</td>
<td>40%</td>
</tr>
<tr>
<td>(Rush Presbyterian)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strauss, et al./II</td>
<td>1992</td>
<td>41</td>
<td>16%</td>
<td>15.5</td>
<td>28%</td>
</tr>
<tr>
<td>(CALGB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albain, et al./II</td>
<td>1995</td>
<td>125</td>
<td>15%</td>
<td>13.0</td>
<td>26%</td>
</tr>
<tr>
<td>(SWOG 8805)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eberhardt, et al./II</td>
<td>1997</td>
<td>94</td>
<td>29%</td>
<td>20.0</td>
<td>36%</td>
</tr>
<tr>
<td>(Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas, et al./II</td>
<td>1999</td>
<td>54</td>
<td>17%</td>
<td>25.0</td>
<td>35%</td>
</tr>
<tr>
<td>(Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vora, et al./II</td>
<td>2000</td>
<td>42</td>
<td>27%</td>
<td>41.0</td>
<td>42.8%</td>
</tr>
<tr>
<td>(Tufts)</td>
<td></td>
<td></td>
<td></td>
<td>(resected pts)</td>
<td></td>
</tr>
<tr>
<td>Choi, et al./II</td>
<td>1997</td>
<td>42</td>
<td>9.5%</td>
<td>25.0</td>
<td>37%</td>
</tr>
<tr>
<td>(Mass General)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albain, et al./III</td>
<td>2003</td>
<td>216</td>
<td>36%</td>
<td>22.1</td>
<td>38%</td>
</tr>
<tr>
<td>(INT 0139)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These studies vary significantly with regard to patient selection (pure Stage IIIA or admixture of IIIB), staging procedures, type of chemotherapy used, RT dose and fractionation, and reporting of results. However, despite this variability, an overall encouraging range of MST emerges (13-41.0 mo.) and a fairly consistent range of pCR (9.5 -27%). Results of the Intergroup 0139 Phase III randomized trial comparing the modified SWOG 8805 program to a non-surgical arm based on SWOG-9019 revealed an unprecedented median overall survival of approximately 22 months in both groups and a disease-free survival benefit with the trimodality approach.

Postoperative mortality ranges from 4-15% in the preoperative studies, and it has not been possible to directly compare treatment-related mortality of an induction chemotherapy approach compared with chemoradiation followed by surgery across such a wide range of treatment plans and settings. The present trial will permit for the first time a direct comparison of the efficacy and toxicity of each approach in a more uniform stage IIIA N2 patient population.

The chemotherapy regimen proposed in the current study, a combination of cisplatin and docetaxel, has been well studied and was used in both ECOG 1594 and TAX 326 studies. In a large Eastern Cooperative Oncology Group Study (ECOG 1594), docetaxel and cisplatin were found to be equivalent to other platinum-containing regimens. In another large randomized phase III study (TAX 326), patients with metastatic NSCLC were assigned to receive docetaxel and cisplatin, vinorelbine and cisplatin, or docetaxel and carboplatin. Patients treated with docetaxel and cisplatin had improved survival rate compared with those who received vinorelbine and cisplatin (median survival rate: 11.3 months vs. 10.1 months, p=0.044; two year survival rates 21% vs. 14%). This improvement in survival was not associated with excessive toxicities. Patients treated with docetaxel-containing regimens had consistently improved quality of life compared with those treated with vinorelbine and cisplatin who in fact experienced decrease in quality of life.

A recently published study employing 3 cycles of cisplatin (40 mg/m² on days 1 and 2) and docetaxel (85 mg/m²) as induction therapy for 90 patients with resectable Stage IIIA N2 lymph node-positive NSCLC demonstrated a pCR rate of 16% and mediastinal sterilization in 60%, while Grade 3/4 non-hematologic toxicity consisted almost exclusively of alopecia and nausea/vomiting. The MST for all patients who received this regimen was 27.6 months, comparing favorably to previous trials that employed induction chemotherapy or chemoradiotherapy in patients with non-bulky, resectable N2 disease. These results suggest that
this combination is feasible, tolerable, and of sufficient efficacy to merit further testing. Several phase I studies of a combination of cisplatin and docetaxel with concurrent thoracic RT demonstrated such a regimen to be well tolerated, with Grade 3 esophagitis as the predominant acute toxicity and with no severe pneumonitis\textsuperscript{34-38} (See Table 3 below).

### Table 3

**Concurrent Cisplatin/Docetaxel and Thoracic Radiation Therapy Studies**

<table>
<thead>
<tr>
<th>Patient Stage</th>
<th>N</th>
<th>Cisplatin Dose</th>
<th>Docetaxel Dose</th>
<th>RT Dose</th>
<th>Surgery (Yes/No)</th>
<th>Acute Toxicity</th>
<th>RR (%)</th>
<th>Periph. mortality</th>
<th>pCR rate (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mudad, et al., 2003\textsuperscript{34}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA/BI</td>
<td>19</td>
<td>25 mg/m\textsuperscript{2} weekly</td>
<td>15-30 mg/m\textsuperscript{2} weekly</td>
<td>64 Gy</td>
<td>N</td>
<td>DLT Grade 3: Esophagitis (N=5) DLT Grade 3: Cough (N=1)</td>
<td>37%</td>
<td>-</td>
<td>-</td>
<td>MST: 10.5 months</td>
</tr>
<tr>
<td>Wu, et al., 2002\textsuperscript{35}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA/BI</td>
<td>18</td>
<td>20 mg/m\textsuperscript{2} weekly</td>
<td>0-30 mg/m\textsuperscript{2} weekly</td>
<td>63 Gy</td>
<td>N</td>
<td>DLT Grade 3: Esophagitis (N=2)</td>
<td>75%</td>
<td>-</td>
<td>-</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kiura, et al., 2003,\textsuperscript{36} Okayama University, Japan DEFINITIVE THERAPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB II</td>
<td>69</td>
<td>30-40 mg/m\textsuperscript{2} on days 1, 8, 29, 36</td>
<td>20-45 mg/m\textsuperscript{2} on days 1, 8, 29, 36</td>
<td>60 Gy</td>
<td>N</td>
<td>Grade ≥ 3: Hematologic 45% Esophagitis 19% Pneumonitis 4.8% (1 death)</td>
<td>78%</td>
<td>-</td>
<td>-</td>
<td>MST: 24 months</td>
</tr>
<tr>
<td>SWOG 0022,\textsuperscript{37} (personal communication, April 2004) DEFINITIVE THERAPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB II</td>
<td>33</td>
<td>50 mg/m\textsuperscript{2} on days 1, 8, 29, 36</td>
<td>20 mg/m\textsuperscript{2} on days 1, 8, 29, 36, plus consolid. x 3 cycles (75 mg/m\textsuperscript{2})</td>
<td>81 Gy</td>
<td>N</td>
<td>Hematologic Grade ≥ 4: 1 in concurrent chemo-RT (12/19 in consolid. phase) Esophagitis &gt; Grade 3: 34%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**Table 3 (Continued)**

Concurrent Cisplatin/Docetaxel and Thoracic Radiation Therapy Studies

Katayama, et al., 2004,38 Okayama University, Japan

**PREOPERATIVE THERAPY**

<table>
<thead>
<tr>
<th>Patient Stage</th>
<th>N</th>
<th>Cisplatin Dose</th>
<th>Docetaxel Dose</th>
<th>RT Dose</th>
<th>Surgery (Yes/No)</th>
<th>Acute Toxicity</th>
<th>RR (%)</th>
<th>Periph. mortality</th>
<th>pCR rate (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA/ BIi</td>
<td>22</td>
<td>40 mg/m² on days 1, 8, 29, 36</td>
<td>40 mg/m² on days 1, 8, 29, 36</td>
<td>40-46 Gy</td>
<td>Y</td>
<td>Hematologic Grade ≥ 3: 65%</td>
<td>73%</td>
<td>0</td>
<td>23%</td>
<td>OS 3 years: 66%</td>
</tr>
</tbody>
</table>

Most recently, Japanese investigators demonstrated efficacy of a regimen consisting of concurrent cisplatin and docetaxel and thoracic RT to 60 Gy in 69 patients with Stage III NSCLC, achieving an MST of 24 months.36 No excessive acute toxicity was encountered and an encouraging low incidence of treatment-related pneumonitis was reported (4.8%). Subsequently, the same chemotherapy combination given with concurrent RT was applied as an induction regimen in 22 patients with Stages IIIA/B NSCLC.38 Six patients also received postoperative chemotherapy consisting of cisplatin and docetaxel. Twenty patients underwent surgery and complete resection was achieved in 19 patients (86%). Pathological downstaging and pathological complete response rate were obtained in 14 (64%) and 5 (23%) patients, respectively. With a median follow-up period of 32 months, the three-year overall survival rate was 66% (and 93% in 14 patients achieving pathological downstaging). It is notable that no perioperative mortality was encountered. Overall, this preoperative regimen appeared to be feasible and highly effective, further justifying its use in the present study.

In a pilot SWOG study, SWOG-0022, cisplatin/docetaxel (cisplatin 50 mg/m² IV on Days 1, 8, 29 and 36 and docetaxel 20 mg/m² IV on Days 1, 8, 15, 22, 29 and 36) was combined with concurrent thoracic radiation therapy to 61.0 Gy as definitive therapy in Stage IIIB NSCLC. Preliminary results demonstrate the feasibility and tolerance of this concurrent chemoradiation regimen.39 Following concurrent chemoradiation, patients received consolidation chemotherapy consisting of three cycles of docetaxel 75 mg/m² q 21 days. Approximately 68% received consolidation therapy following induction chemoradiation. This consolidation therapy was also generally well tolerated, with Grade 3/4 toxicity primarily related to neutropenia. Moreover, it is anticipated that the reduction of radiation dose from 61.0 Gy (uncorrected for tissue inhomogeneity) to 50.4.0 Gy (corrected for tissue inhomogeneity) in the current preoperative trial will be associated with a superior toxicity profile. This study accrued 33 patients before closing on February 1, 2003, and 26 patients were evaluable. There was one Grade 4 anemia reported during the concurrent therapy, and 12/19 Grade 4 toxicities (mainly hematologic) during the consolidation phase. No pneumonitis was reported in the concurrent treatment phase, and two patients had Grade 3 dyspnea during maintenance docetaxel chemotherapy. Acute esophagitis Grade 3 rate was 34%. One patient death is under review for possibly treatment-related causes. The estimate of overall response rate was 64%. Outcome data are pending.37

Thus, the present trial will build on the very promising survival results observed in INT 0139 with cisplatin-based chemotherapy and concurrent radiation therapy, substituting docetaxel, with its potent radiation sensitizing effects and very encouraging results in combination with cisplatin as preoperative chemotherapy in phase II work, for etoposide. At the same time, single-agent docetaxel with pegfilgrastim or filgrastim support is being substituted for the postoperative cisplatin and etoposide incorporated in prior research, since the former agent is likely to be
administered more consistently and has been associated with very encouraging survival benefit as consolidation therapy in preceding SWOG experience.

1.7 Translational Research

1.7.1 Therapy-Related Gene Polymorphisms and Expression, Protein Levels, and Shed Tumor DNA

1.7.1.1 DNA Damage Repair Genes ERCC1 and XRCC1

We hypothesize that expression levels and/or polymorphisms of the DNA damage repair genes ERCC1 and XRCC1 will correlate with patient outcomes in this trial.

Surveillance and repair of DNA damage are essential for maintaining the integrity of the genetic information that is needed for normal development. Several multi-enzyme pathways, including the excision repair of damaged or missing bases, carry out DNA repair in mammals exposed to platinums or radiation. Two of the repair genes, both of which are rapidly up-regulated by ionizing radiation, are the repair cross-complementation group genes ERCC1 and XRCC1.40 Accumulating evidence suggests that increased repair of DNA damage by either increased levels of expression or polymorphic variants is associated with cancer therapy resistance.

ERCC1: Overexpression of ERCC1, which is crucial in the repair of cisplatin (CDDP)-DNA adducts, is reported to negatively influence the effectiveness of CDDP-based therapy for gastric and ovarian cancers. We investigated whether ERCC1 mRNA expression levels were associated with clinical outcomes after treatment with a combination CDDP/gemcitabine regimen for patients with advanced stage non-small cell lung cancer (NSCLC).41 Response and survival were correlated with the level of ERCC1 expression in 56 patients with advanced (Stage IIIb or IV) NSCLC treated as part of a multicenter randomized trial with gemcitabine plus CDDP. mRNA was isolated from paraffin-embedded pretreatment primary tumor specimens and relative expression levels of ERCC1/beta-actin were measured using a quantitative reverse transcription-PCR (TaqMan®) system. Median overall survival was significantly longer in patients with low ERCC1 expression in their tumors (61.6 weeks; 95% confidence interval, 42.4-80.7 weeks) compared to patients with high expression tumors (20.4 weeks, 95% confidence interval, 6.9-33.9 weeks). ERCC1 expression, Eastern Cooperative Oncology Group Performance Status and presence of weight loss were significant prognostic factors for survival in a Cox proportional hazards multivariable analysis. These data suggest that ERCC1 expression is a predictive factor for survival after CDDP/gemcitabine therapy in advanced NSCLC. Although there was a trend toward decreased response with high ERCC1 mRNA levels, this difference failed to reach statistical significance. This result may reflect the impact of gemcitabine and the requirement for ERCC1 expression for CDDP/gemcitabine synergism or may be attributable to the relatively small patient sample size in this study. Thus, prospective studies of ERCC1 as a predictive marker for activity of CDDP-based regimens in NSCLC are warranted. We propose to conduct such a study here.

More recently, Dr. Heinz Lenz and colleagues at USC have shown that a very common polymorphism at codon 118 (exon 4) in the ERCC1 gene, resulting in a single nucleotide C→T change, correlates with significantly different intratumoral levels of mRNA, response to 5-FU/oxaliplatin and survival in patients with colorectal cancer. Patients with the T/T or C/T genotype were significantly more likely to have elevated ERCC1 mRNA levels than patients with the C/C genotype (p = 0.049). The median survival of patients with at least one copy of the T allele was 256 days compared to 531 days without (p = 0.056).

XRCC1: XRCC1 is a DNA repair gene with a central role in single-strand break repair, base excision repair and optimal activity of DNA ligase III. It has been shown to be essential for mammalian (murine) survival and cells lacking XRCC1 are extremely sensitive to ionizing radiation and alkylating agents, and exhibit elevated spontaneous frequencies of chromosome aberrations. Transfection of functional murine XRCC1 into EM9 cells efficiently corrected (94-100%) the high sister chromatid exchange (SCE) defect.

XRCC1 polymorphisms have been associated with different susceptibilities to DNA damaging agents and to the development of certain malignancies.42 Cigarette smokers with the polymorphic XRCC1 399Gln allele have been shown to have significantly more DNA adducts and higher SCE frequencies than smokers with the 399Arg/Arg genotype.
Polymorphisms in codon 399 have been associated with higher AFB1-adducts and somatic mutations, as well as with lung cancer risk, colon cancer risk in Egyptians, and prostate cancer risk. A polymorphism in exon 6 has been shown to have a protective effect against bladder cancer development.

Based on these data, Lenz and colleagues investigated whether the XRCC1 allele 399 polymorphism correlated with response in 45 patients with colorectal cancer treated with the new platinum agent, oxaliplatin combined with 5FU. The XRCC1 399 Arg/Arg Arg/Gln and Gln/Gln polymorphisms were found in 18, 22 and 5 patients, respectively. The Arg/Arg polymorphism was strongly associated with chemotherapy response (observed in 5 of 6 responding patients); the Gln/Gln polymorphism was strongly associated with chemotherapy resistance (4 of 5 patients with the Gln/Gln genotype had disease progression) (p = 0.0063, 99% CI = 0.0043 – 0.0083, two-sided testing). We propose to examine both levels of XRCC1 expression and polymorphic variants in the patients treated on this trial.

1.7.1.2 Microtubule-Related Protein Expression: TUBB-III and MAP4

We hypothesize that expression levels of either TUBB-III, MAP4 or both of these will correlate with patient outcomes in this trial.

Docetaxel is a taxane antimicrotubule agent that has shown efficacy against non-small cell lung cancer (NSCLC). The Gumerlock laboratory at the University of California-Davis has been investigating the molecular mechanisms of antimicrotubule agents in both preclinical drug studies and correlative science studies of tumor tissues from patients on clinical trials. These studies have identified several molecular markers that have the potential to provide information on response to antimicrotubule drugs, including docetaxel. The markers of highest current interest are the beta-tubulin isoform III (TUBB-III) and the microtubule-associated protein Map4.

TUBB-III: Since B-tubulin is the target molecule for taxanes and docetaxel binds directly to it, abnormalities in B-tubulin have attracted considerable attention as possible explanations for poor responses to taxane therapy. Studies of mutations within the B-tubulin genes have shown little evidence for these abnormalities in NSCLC. Recently, there has been examination of unusual expression of alternate isoforms from those normally expressed in lung cells. While initial studies of breast cancer were equivocal regarding expression of TUBB-III, preliminary studies by ourselves and others have shown an association of decreased overall survival of NSCLC patients whose tumors express this normally brain- or nerve-specific isoform of B-tubulin. For example, in a preliminary analysis of SWOG-9509 tumor specimens, median survival time was 14 months in low TUBB-III expressers, compared with 7 months in the high expressing subset. Although these results are provocative, differences do not reach statistical significance due to the relatively low sample size in this retrospective analysis. The current proposal provides a unique opportunity to examine TUBB-III prospectively.

MAP4: Laboratory studies have shown that high expression of MAP4 is associated with a poor response to vinca alkaloid treatment and increased response to taxane treatment. The MAP4 gene is repressed by p53, and following radiation, levels of Map4 are reduced. These reduced levels of Map4, in turn, lead to increased response to vinca alkaloid treatment and decreased response to taxane exposure. We propose to examine expression of TUBB-III and Map4 using IHC in tumor specimens from patients on this trial. If warranted, the status of p53 will also be examined in the tumor specimens.

1.7.1.3 Shed Tumor DNA

Shed tumor DNA can be detected in cancer patient plasma. Dr. Gumerlock’s laboratory has established methodology for its detection and has examined clinical trial patient specimens pre- and post-treatment correlating the results with patient responses and outcome. We will examine patient plasma serially for shed tumor DNA in an exploratory manner to determine any association of the presence of tumor DNA or its disappearance with patient response or outcome. Genes to be examined include mutations in K-RAS and the methylated promoter of p16.

1.7.2 Proteomic Analysis by MALDI-TOF

Outcomes from treatment of NSCLC at all stages vary remarkably, with some tumors progressing in an indolent fashion or being cured after appropriate treatment, while other
NSCLC tumors progress rapidly despite aggressive therapies. The next challenge in improving outcome of this patient population is to develop comprehensive tumor and/or serum protein expression patterns that may allow prediction of response to biomarkers of demonstrated utility for these endpoints. There are currently no biomarkers of demonstrated utility for these endpoints. We hypothesize that application of our diagnostic serum proteomic profile to serial blood samples drawn before and after protocol interventions will be a valuable surrogate marker for response and a potential predictor of recurrence, and that tumor profiles can be refined and tested to be of use for predicting response to therapy and survival.

Carbone and his colleagues from Vanderbilt Ingram Cancer Center recently identified specific proteomic patterns in lung tumors or serum that correlated to clinicopathological variables of lung tumors. They used Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to analyze protein expression profiles in sub-microliter quantities of serum or a few hundred cells from single frozen sections of human surgically resected lung tumors and developed custom software to perform sophisticated statistical and computational analyses on the resulting data. A novel statistical method was used to investigate the pattern of over 1500 proteins from 79 lung tumors using a rigorous training/testing model. Protein profiles patterns could distinguish cancer from non-cancer, primary lung tumors from metastases to the lung, and histological subgroups of tumors as well as identify patients with occult nodal positivity identified only at the time of thoracotomy.

A proteomic pattern from the initial resected primary tumor composed of fifteen distinct MS peaks could divide these NSCLC patients into a poor prognosis group (0% survival at one year) and a good prognosis group (100% survival at one year, \( P < 0.0001 \)), even after correction for known risk factors.

MALDI-MS analyses also were performed with the serum of individuals with and without lung cancer, and it was possible to determine specific mass/charge ratios (proteins) that had discriminatory value. Using 150 cases and 150 matched controls in a training/testing model, we were able to achieve a profile with greater than 92% diagnostic specificity (manuscript submitted). Preliminary data exist that suggests that protein profiles from pre-treatment tumor samples may predict response to therapy. These preliminary results are encouraging, and we propose performing tumor and serum protein analysis in this trial.

1.7.3 Imaging Predictors of Outcome: FDG-PET (2/16/06)

One of the unresolved problems in bi- or trimodality therapy (pre-operative induction, followed by surgery) of non-small cell lung cancer (NSCLC) is the difficulty in predicting the prognosis of patients who completed induction therapy and are scheduled for surgery. A subgroup of those patients whose N2 lymph nodes remain involved with tumor at the time of surgery has poor survival in contrast to those who achieved “tumor clearance” in N2 nodes pre-operatively. SWOG 8805 demonstrated favorable outcome for those who had no evidence of mediastinal lymph node involvement following induction therapy compared to those with persistent disease in the mediastinal lymph nodes (three-year survival 44% versus 18%). In a retrospective study of 103 patients who received induction therapy prior to surgery for stage III NSCLC, five-year survival rates for those with persistently positive disease and for those with mediastinal lymph node clearance were 9% and 36%, respectively. In a multi-center phase II study of docetaxel and cisplatin containing induction chemotherapy, patients who had persistence of metastatic disease in the mediastinal lymph nodes had a significantly worse outcome compared to those with mediastinal lymph node clearance (three-year survival 11% versus 73%).

A majority of the patients treated with induction therapy undergo baseline mediastinoscopy. Repeat mediastinoscopy following induction therapy carries a high risk of bleeding in view of adhesions caused by previous mediastinoscopy and induction therapy. A non-invasive imaging modality for assessing the mediastinum and distant sites to identify those who could potentially benefit from surgery is highly desirable. FDG-PET could potentially play a useful role in this setting.

Positron emission tomography (PET) with the glucose analogue \([^{18}\text{F}]\) fluoro-2 deoxy-D-glucose (FDG) is a useful imaging modality in staging patients with resectable NSCLC. FDG-PET provides a metabolic assessment of tumor. A commonly used measure of tumor FDG uptake,
the standard uptake value (SUV), correlates linearly with the doubling time of the tumor.\textsuperscript{57-58} Since tumor doubling time indicates aggressiveness, a high pre-treatment SUV is predictably associated with a poor outcome in patients with NSCLC.\textsuperscript{59} In a retrospective review of 56 patients who received chemotherapy alone, radiation alone, or combined chemoradiation post-therapy, FDG-PET had a positive predictive value of 98\% for detecting residual viable tumor but over-staged and under-staged the nodal disease in 33\% and 15\% respectively.\textsuperscript{60} It is difficult to draw definite conclusions regarding the utility of FDG-PET imaging for assessing the mediastinal nodal status based on small retrospective series.

There are some preliminary data to indicate that post-therapy FDG-PET may be useful in predicting long-term outcome in patients with unresectable stage III NSCLC treated with either radiation therapy alone or chemoradiation. Patients with post-treatment SUVs of 3.5 or less had a local failure rate of 17\% compared with those with SUVs of greater than 3.5 who had a local failure rate of 77\%. In this study, 45 patients with stage I, II, and IIIA NSCLC were treated primarily with radiation therapy alone and the median time from completion of radiation therapy to PET imaging was 4 months (range 1-18).\textsuperscript{61} In another recent study, PET response, but not CT response, predicted eventual outcome.\textsuperscript{62} The relative death rates for those with PET-based non-response and progressive disease were 5.71 and 13.9 when compared with those with PET-based complete response. RTOG is planning to launch a prospective study in collaboration with American College of Radiology Imaging Network (ACRIN) to define the utility of post-therapy PET imaging in patients with unresectable stage III NSCLC.

Although there are no data available regarding the utility of post-induction FDG-PET in predicting long-term outcome in patients who have undergone surgical resection following induction therapy, Choi et al.\textsuperscript{63} studied that issue in patients following completion of pre-operative chemoradiotherapy. FDG-PET was obtained at baseline and 2 weeks following chemoradiotherapy. A strong correlation was observed between the gradient of residual glucose metabolic rate in the tumor and a complete pathologic response. A complete pathologic response was noted in 6 of 6 patients when the residual glucose uptake was <\textasciitilde 0.050 \(\mu\text{mol/min/g}\). In contrast, no complete pathologic response was observed in any of 6 patients when the residual uptake was \textasciitilde 0.130 \(\mu\text{mol/min/g}\).

FDG-PET scan has become a standard way of re-assessing tumor response post-therapy. Therefore, the present trial will evaluate the role of FDG-PET post-therapy in predicting long-term outcome, as well as pathological response both in the tumor and in the mediastinal lymph nodes. Because of the expectation that many of the baseline FDG-PET studies will have been obtained prior to patient randomization at sites other than the treating institution we believe that it is impractical to obtain digital data from these pre-randomization PET studies necessary for analysis either at the treating institution or at a central core laboratory. Thus, the PET evaluations in this trial will be limited to a subset of patients who have both pre-randomization and post-treatment PET scans at the treating institution (or its affiliated PET facility). We expect this to be at least 40\% of the patients accrued. PET data obtained from sites other than the treating institution (or its affiliated PET facility) will be used for clinical decisions by the treating physician(s), but PET data for such patients will not be used in the analysis for this secondary objective (Section 2.2.5).

SUV measurements on pre-randomization and post-therapy FDG-PET scans will be performed at individual sites. We also plan to use methodology and qualitative response criteria for evaluating the post-therapy FDG-PET images similar to those previously by MacManus, et al.\textsuperscript{64} Visual assessment of response will be used, and the primary tumor and mediastinal nodes will be separately evaluated (see Section 11.3).

PET scans must be performed within 5 weeks of randomization by participating institutions and should be repeated within 3-5 weeks after completion of Induction Therapy (no later than 2 weeks before anticipated surgery; see Section 11.3). Institutions can access the technical requirements for these PET scans at http://www.acrin.org/petcorelab.html. Response by PET will be determined by comparison between pre- and post-Induction PET scans using both the qualitative criteria and SUV measurements described in Section 11.3.
1.8 **Patient-Reported Functional Status**

As significant differences in the toxicity profiles are expected between the two arms, it is important that this study include patient-reported functional status as an endpoint. Functional status data will be critical in fully analyzing the potential advantages and disadvantages between the two arms. The differences in patient-reported functional status between the two arms will be studied utilizing a Trial Outcome Index (TOI) that measures the summed functional well-being, physical well-being, and the lung cancer subscales of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life (QOL) instrument, which is widely used for measuring QOL of patients with lung cancer. The FACT-L is a 36-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). It is composed of 4 primary QOL subscales that measure physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items), plus 9 lung-cancer specific additional concern items (e.g., dyspnea). The full questionnaire can be completed in less than 10 minutes, and the instrument has been demonstrated to correlate well with survival, particularly change in QOL on serial evaluations during treatment. The endpoint in this trial is functional status, not QOL, given the focus of the TOI on physical and symptom status.

Functional status will be assessed via TOI in both arms at four time points: at baseline (pre-treatment), prior to surgery (after the neoadjuvant therapy is completed), at 6 months post-surgery, and 12 months post-surgery. Functional status will be incorporated as a component of study follow up.

1.9 **Comorbidity**

Many factors have been implicated as prognostic for LA-NSCLC, but the only commonly accepted prognostic factors are clinical stage, performance status (PS) and weight loss. Patients with Zubrod PS 0 or 1 and <5% weight loss are said to have a favorable prognosis and are the focus of the majority of research for LA-NSCLC.

Subset analyses of cooperative group studies and single institution reviews have shown that patients selected on the basis of good performance status and weight loss criteria alone represent a diverse patient population. A better understanding of the prognostic factors is necessary for appropriate stratification of patients in protocols, for individualization of patient care, and to compare results across studies.

Comorbid conditions affect prognosis in a variety of clinical situations and are independent of functional status. The impact of comorbid conditions on treatment and prognosis has not been well explored in prospective oncologic studies. In this study, pretherapy comorbidity data will be collected and scored using the Charlson Comorbidity Index (CCI) and Cumulative Illness Rating Scales for Geriatrics (CIRS-G).

The Charlson comorbidity index and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) are validated scales that can be completed from review of detailed past medical history and physical examination. Neither scale correlates with functional status and both provide independent information.

2.0 **OBJECTIVES**

2.1 **Primary Objective**

To prove that the preoperative regimen, consisting of thoracic radiation therapy given concurrently with chemotherapy followed by surgical resection, results in a significant improvement in overall survival compared to preoperative chemotherapy alone followed by surgical resection, with both arms receiving postoperative consolidation therapy.

2.2 **Secondary Objectives**

2.2.1 Comparison of progression-free survival, median survival time, and toxicity and response rates (clinical and pathologic) in both treatment arms;

2.2.2 Evaluate the correlation of the pCR with the disease-free and overall survival;

2.2.3 To investigate the association of DNA damage repair genes (ERCC1 and XRCC1), microtubule-related proteins (TUBB-III and MAP4), and shed tumor DNA with patient responses and outcomes to the platinum/taxane/radiation therapy in this trial;

2.2.4 To employ MALDI-TOF proteomic analysis of tumor and serum to identify protein profiles associated with response to therapy and prognosis;
2.2.5 To evaluate the role of FDG-PET post-therapy in predicting long-term outcome, as well as pathological response both in the tumor and in the mediastinal lymph nodes;

2.2.6 To assess patient-reported functional status as an endpoint with potentially relevant differences between the two arms;

2.2.7 To determine the impact of comorbid conditions on survival.

3.0 PATIENT SELECTION

All queries regarding eligibility should be directed to RTOG Headquarters, 215-574-3189.

3.1 Conditions for Patient Eligibility (9/15/05) (10/31/05) (2/16/06)

3.1.1 Pathologically proven diagnosis of single primary lung parenchymal lesion of Stage IIIA (T1-T3) [according to AJCC Staging, 6th edition; see Appendix III] with ipsilateral positive mediastinal nodes within 3 months of registration, with none of the mediastinal lymph nodes exceeding 3 cm in largest diameter;

3.1.1.1 Histologic (biopsy) or cytologic (needle aspiration or sputum) proof of non-small cell histology must satisfy both of the following:
   ▪ Adenocarcinoma, large cell carcinoma, squamous carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma or non-small cell lung cancer NOS;
   ▪ Documentation of non-small cell carcinoma may originate from the mediastinal node biopsy or needle aspiration only if a distinct lung primary separate from the nodes is clearly evident on the CT scan.

3.1.2 Measurable disease by chest x-ray and/or contrast-enhanced CT scan;

3.1.3 Positive ipsilateral mediastinal node or nodes (N2), with or without positive ipsilateral hilar nodes (N1); N2 nodes must be separate from primary tumor by either CT scan or surgical exploration, and the maximum diameter cannot exceed 3.0 cm.

3.1.3.1 N2 status must be confirmed to be positive by one of the following: mediastinoscopy, mediastinotomy (Chamberlain procedure), transesophageal biopsy using endoscopic ultrasound guidance, thoracotomy, video-assisted thoracoscopy, Wang needles, or fine needle aspiration under bronchoscopic or CT guidance. PET positivity in the ipsilateral mediastinal lymph nodes will not be sufficient to establish N2 nodal status.

3.1.3.2 A nodal biopsy or aspiration can only be omitted in the special circumstance in which ALL of the following are true:
   ▪ Paralyzed left true vocal cord documented by bronchoscopy or indirect laryngoscopy;
   ▪ Nodes visible in the AP (Level 5) region on CT scan;
   ▪ Distinct primary tumor separate from the nodes is visible on CT scan;
   ▪ No evidence of subcarinal nodal involvement by CT scan.

3.1.3.3 Regardless of method of documentation of N2 disease (see Section 3.1.3.1), the following must be documented:
   ▪ From the Operative and Pathology reports, all mediastinal nodes shown to be both positive and negative (including contralateral nodes) must be designated on the I1 form according to the Lymph Node Map in Appendix IV.
   ▪ If the procedures to document N2 eligibility were done at a non-member facility, the patient is still eligible if the study institution PI reviews the outside pathology slides and report with the study institution’s pathologist in conjunction with the outside operative report, and generates a report that verifies the original diagnosis and lymph node mapping, as consistent with the staging requirements of the protocol.
   ▪ Patient stratification with regard to involved lymph nodes will be based on the pathological findings (number of nodal stations involved) or both pathological findings and thoracic CT scans (micro- versus macro-metastases). PET scan findings alone will not constitute the basis for stratification. For left sided lesions, the following nodal levels should be biopsied: 5, 6; for right sided lesions levels 2R, 4R, 2L and 4L. Level 7, whenever possible, should also be sampled to rule out microscopically involved lymph nodes. Investigators are strongly encouraged to biopsy multiple stations of mediastinal lymph nodes at the time of invasive staging in addition to those nodes that are abnormal on PET or CT scan.
3.1.3.4 Review of pre-randomization studies (PET, CT, chest x ray, pathologic results of mediastinal staging) will define mediastinal lymph node status for appropriate randomization stratification, as follows:

**Number of Stations Involved**
- If, on review of the pathology report, only one station has been biopsied and that station is positive for cancer, the patient will be classified as N2LX (nodes not evaluable); patients with a paralyzed vocal cord and enlarged aorto-pulmonary window nodes also will fall into this category;
- If, on review of the pathology report, more than one station has been biopsied and only one station is positive for cancer, the patient will be classified as N2L1 (one station involved);
- If, on review of the pathology report, more than one station has been biopsied and two or more stations are positive for cancer, the patient will be classified as N2L2 (two or more stations involved).

**Nodal Micrometastases And Lymph Node Size**
- Patients with any non-subcarinal nodes with a short axis diameter on CT > 1 cm shall be classified as cN2 (clinically involved lymph nodes);
- Patients with subcarinal nodes with a short axis diameter on CT > 1.2 cm shall be classified as cN2 (clinically involved lymph nodes);
- Patients in whom all non-subcarinal nodes are ≤ 1 cm and subcarinal nodes ≤ 1.2 cm shall be classified as mN2 (microscopically involved lymph nodes).

3.1.3.5 Patients with subcarinal lymphadenopathy either by size criteria or by PET positivity must have a mediastinoscopy or other means of mediastinal lymph node biopsy for direct histologic assessment, regardless of the site of the primary tumor.

3.1.3.6 If lymph nodes in the contralateral (opposite the primary) mediastinum and neck are visible on the contrast CT scan of the chest and are > 1.0 cm or if contralateral involvement is suggested by PET scan, then the nodes must be confirmed to be negative by one of the diagnostic procedures listed in Section 3.1.3.1.

3.1.4 N3 status must be confirmed to be negative histologically/cytologically if contralateral mediastinal lymph nodes ≥ 1.0 cm are seen on CT scan or if PET scan suggests contralateral mediastinal positivity.

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

3.1.5.1 When the pleural fluid is present either prior to or after pre-study mediastinoscopy or exploratory thoracotomy, a thoracentesis must be performed to document that the pleural effusion is cytologically negative;

3.1.5.2 When pleural fluid is present on the CT scan and not on the chest x-ray, but is deemed too small to tap safely under either CT or ultrasound guidance, a thoracoscopy should be done, if feasible, to document the absence of pleural metastases and to document that the pleural effusion is cytologically negative

3.1.6 Appropriate stage for protocol entry, including no distant metastases, based upon the following diagnostic workup:

3.1.6.1 History/physical examination within 8 weeks prior to registration;

3.1.6.2 Pre-Induction Therapy FDG-PET within 5 weeks prior to randomization. **NOTE:** If the baseline PET study is performed at the treating institution (or its affiliated PET facility) and it is expected that the post-treatment PET study will be performed at the same site, then the PET data will be used for the analysis of the secondary endpoint (Section 2.2.5). To be included in this analysis, the patient’s PET studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner is mandatory. PET scanners with sodium iodide (NaI) detectors are not acceptable (also see Section 11.3);

3.1.6.3 An MRI of the brain (or CT scan of brain, if MRI medically contraindicated), chest x-ray and/or CT scan of the lungs and upper abdomen to complete T and N staging and exclude other ipsilateral or contralateral parenchymal lesions and liver or adrenal metastases within 5 weeks prior to registration;

3.1.6.4 Designation of operability and resectability by the surgeon who would potentially perform the thoracotomy within 3-4 weeks prior to registration;

3.1.7 Zubrod Performance Status 0-1;

3.1.8 Age ≥ 18;
3.1.9 Adequate bone marrow function, defined as follows:
3.1.9.1 Absolute neutrophil count (ANC) $> 1,800$ cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;
3.1.9.2 Platelets $> 100,000$ cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;
3.1.9.3 Hemoglobin $> 10.0$ g/dl based upon CBC/differential obtained within 2 weeks prior to registration on study (Note: The use of transfusion or other intervention to achieve Hgb $> 10.0$ g/dl is acceptable);
3.1.10 Adequate renal function, defined as follows: creatinine clearance must be at least 60 ml/min; this may be measured or calculated according to the following formula:
   $\frac{(140\text{-age}) \times \text{body weight in kg}}{72 \times \text{serum creatinine}}$
3.1.11 Adequate hepatic function, defined as follows: Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase $\leq 2.5 \times$ ULN for the institution;
3.1.12 Adequate pulmonary function, defined as follows:
3.1.12.1 FEV1 at least 2.0 liters; if less than 2.0 liters, the predicted post-resection FEV1 must be at least 0.8 liters based on the following formula using the quantitative V/Q scan:
   \[ \text{Predicted post-resection FEV1} = \text{FEV1} \times \% \text{ perfusion to the residual, unresected lung} \]
3.1.12.2 Diffusion capacity should be $\geq 50\%$ predicted;
3.1.13 Serum pregnancy test (if applicable);
3.1.14 Weight loss $\leq 5\%$ of body weight over the preceding 6 months;
3.1.15 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility
3.2.1 Palpable lymph nodes present in the supraclavicular areas or higher in the neck, unless proven to be benign on excisional biopsy;
3.2.2 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. Carcinoma in situ of the breast, oral cavity, or cervix are all permissible;
3.2.3 Prior systemic chemotherapy or biological agent (including Iressa) for the study cancer; note that prior chemotherapy for a different cancer is allowable;
3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.5 Severe, active comorbidity, defined as follows:
   3.2.5.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
   3.2.5.2 Transmural myocardial infarction within the last 6 months;
   3.2.5.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of randomization;
   3.2.5.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of randomization;
   3.2.5.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
   3.2.5.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
3.2.6 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
3.2.7 Prior allergic reaction to the study drug(s) involved in this protocol or patients with a history of severe hypersensitivity to other drugs formulated with polysorbate 80;
3.2.8 Pre-existing $\geq$ grade 2 peripheral neuropathy.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT
4.1 Additional Pre-treatment Evaluations/Interventions
In addition to the required pretreatment evaluations in Section 3.0, investigators must offer the following evaluations to their patients:
4.1.1 Specimens for Translational Research (see Section 10 for details): Tissue from Pre-Treatment Biopsy, tumor tissue from surgery, blood;

4.1.2 Patient-Reported Functional Status: Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy-Lung (FACT-L);

4.1.3 Comorbidity Assessments: Charlson Comorbidity Index (CCI) and Comorbidity Recording Sheet.

4.2 Additional Pre-treatment Evaluations/Interventions

The following evaluation/intervention is highly recommended as part of good clinical care of patients on this trial, but not mandatory.

4.2.1 Bronchoscopy is recommended for any patients with suspected endobronchial disease or for patients suspected of having lesions that are ≤ 2 cm from the main carina.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (5/2/05) (9/13/05) (10/31/05)

All participating surgeons must complete and sign the Thoracic Surgeon’s Questionnaire, Appendix V, prior to the institution entering any patients onto this study. Participating surgeons who will be performing the exploration after induction therapy must have specialty training and be board certified in cardiothoracic surgery. U.S.-trained surgeons must have active certification by the American Board of Thoracic Surgery, and non-U.S.-trained surgeons must have similar certification of cardiothoracic training. Note to Research Associates: Question 9 on the Thoracic Surgeon’s Questionnaire (Appendix V) must be answered “yes.” Fax the completed form to Dr. Harvey Pass, Thoracic Surgery Co-Chair, at (212) 263-2042 for review and approval. Dr. Pass will then fax his approval to RTOG and the institution. Institutions should allow adequate processing time (7-10 days) before calling to register the first patient.

5.1.1 Canadian Pre-Registration Requirements (10/31/05)

Prior to clinical trial commencement, Canadian institutions must complete and submit Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form to RTOG Headquarters. Canadian institutions must also complete the "Request for Clinical Medication by Fax" form included in the "Health Canada study approval broadcast.” The form must be faxed to RTOG Headquarters at 215-574-0300 prior to registering the first patient. Headquarters will fax the completed form to Sanofi-Aventis once all regulatory documents are received. Please allow one week prior to registering your first case to receive your shipment.

5.2 Registration

5.2.1 Online Registration (10/31/05)

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate.
- The institution must complete the Password Authorization Form at http://www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. 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, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed.

Questions regarding Radiation Therapy should be directed to Dr. Werner-Wasik or Dr. Gaspar (preferably by e-mail or alternatively by phone).

6.1 Induction Therapy Dose Specifications (Arm 2)

6.1.1 Patients on Arm 2 will receive treatment 5 days per week, in once daily fractions. **Total dose will be 50.4 Gy in 28 fractions.** There are no field reductions, and all fields treat the same volume and must be treated each day. A minimum of three days concurrent therapy is required, i.e., therapy should begin on Monday, Tuesday, or Wednesday of the first week. Radiation therapy (RT) commences on day 1 of chemotherapy. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT.

6.1.2 The prescription dose will be specified to cover 95% of the PTV, i.e., by looking at the DVH for the PTV, 95% of the PTV will receive 50.4 Gy.

6.1.3 Direct posterior spinal cord blocks are not allowed.

6.2 Technical Factors

6.2.1 **Beam Energy:** Megavoltage accelerators with a minimum source to isocenter distance of 100 cm are required. Electron beams, 60Co beams, 4 MV accelerators and 80 cm SAD units are not acceptable. **Only 6MV-10 MV energy photon beams** are to be used for any field arrangement, including oblique or other fields.

6.2.2 **Beam Shaping:** Custom blocks (5 HVL) individually shaped for each field or MLC (multi-leaf collimation) should be used to protect normal tissues outside the target volume.

6.3 Localization, Simulation, and Immobilization

6.3.1 Localization (check or port) films will be done before the start of treatment for each port treated. This procedure will be repeated weekly for institutional QA review. Simulation and first day portal beam verification films for each treatment field must be submitted to RTOG in hardcopy, paper copy, or on CD for review per Section 12.0.

6.3.2 **Simulation:** Simulation is mandatory and volumetric treatment planning CT study is mandatory. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having 3-5 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes, and 8-10 mm thick slices of the remaining regions are to be obtained. The administration of intravenous contrast during CT simulation is highly desirable, since it allows a better definition of the involved lymph nodes. Careful attention should be paid to the outlining of the tumor and lymph nodes on axial CT images. The lymph nodes should be outlined using a “mediastinal window” setting and any tumor interfacing with lung parenchyma, with the “lung window” setting. A conventional simulation using a fluoroscopic image intensifier capability should be performed for each patient in addition to a CT simulation, to assess the extent of respiratory movement in cranio-caudal direction for the purpose of adjusting treatment margins (see Section 6.4.3).

6.3.3 **Compensating Filters or Wedges:** In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may be used as two-dimensional tissue compensator.

6.4 Treatment Planning/Target Volumes

6.4.1 **Dose Calculation:** The method used for tissue heterogeneity calculations will be reported. Both the corrected and uncorrected dose distributions will be calculated and submitted to RTOG Headquarters (see Section 12.1).
It is required that this trial be based on corrected dose distributions; however, different institutions use different algorithms to calculate heterogeneity corrections. Different dose calculation algorithms may result in significant variations in specific dose parameters, such as ICRU point dose, mean dose, and various dose-volume histogram threshold parameters. For this reason, each institution is required to submit two plans, one with heterogeneity corrected (upon which the dose is prescribed) AND the second with heterogeneity uncorrected (for the same monitor units derived from the heterogeneity corrected plan), for the RTOG database. The heterogeneity corrected (prescription) plan usually will have a higher reference point dose than the uncorrected plan.

Doses are to be calculated with heterogeneity correction, i.e., correction is to be made for density differences between air spaces, lung, water-density or bony tissue. Treatment planning should be performed in accordance with the prescribing doses to each target, together with restrictions in dose to normal tissues as given in Section 6.5.

6.4.2 Isodose Distributions: Isodose plots will be obtained at: a) the central axis level b) 2.0 cm from the top, and c) 2 cm from the bottom of the field. The isodose plans must reflect utilized blocks and compensators. These must be composite plans accounting for the total dose from each component field. Critical structures (spinal cord) and target volume must be clearly delineated on each plot.

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

Spinal Cord: 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 fields. 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 50.0 Gy. No posterior spinal cord blocks are allowed.

6.4.3 Irradiation Portals
Three-dimensional (3D) CT-planned conformal radiotherapy is required for this protocol. This protocol does not mandate any specific field arrangement to be used. The PTV is to be treated with any combination of coplanar or noncoplanar three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. Multiple non-coplanar field arrangements are preferred, but the use of AP-PA fields (followed, if dictated by the maximum spinal cord dose, by the off-cord oblique fields) is allowed.

6.4.4 Although the prescription method is different, the definitions of volumes will be in accordance with the 1993 ICRU report # 50 (Prescribing, Recording and Reporting Photon Beam Therapy).

6.4.4.1 Gross Tumor Volume (GTV) is defined as all known gross disease identified by the planning CT and other clinical information. GTV includes the primary tumor (GTV-P) and involved ipsilateral hilar and ipsilateral mediastinal lymph nodes (GTV-N), defined as either:
- Measuring >1 cm (short axis measurement) on the diagnostic and/or planning thoracic CT scan
- Demonstrating hypermetabolic uptake on PET scan
- Harboring tumor cells as per mediastinoscopy/mediastinotomy

NOTE: Only those hilar and mediastinal lymph nodes that are either suspected or known to have tumor metastases (by virtue of enlargement on CT scan and/or increased uptake on PET scan) and/or known to be involved as per lymph node biopsy will be included in the GTV. If there is doubt which nodes were involved or if nodal sampling was inadequate, treating all ipsilateral hilar and mediastinal nodes is permitted.

6.4.4.2 Clinical Tumor Volume (CTV) includes the area of subclinical involvement around the GTV (GTV-P + GTV-N). The CTV is the GTV plus the margin for micro-extensions of the tumor, which is 1.0 cm (CTV=GTV+1 cm). Ipsilateral supraclavicular irradiation is allowed when necessary for primary tumor coverage. Contralateral hilar or supraclavicular treatment is not allowed. There will be no elective nodal irradiation.

6.4.4.3 Planning Tumor Volume (PTV) is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the GTV. This margin accounts for variations in treatment delivery, including variations in setup between treatments, patient motion during treatment, movement of the tissues that contain the CTV (e.g. respiration), and size variations in the
tissue containing the CTV. A 0.5 cm margin is required to account for setup uncertainties for typical thoracic patient setups. The margin for motion can be explicitly determined using an ITV approach or measured. The PTV is a geometric concept and will be created by adding 0.5 = margin for motion. If motion is not explicitly measured, a maximum margin of 1.5 cm from the CTV to PTV may be used (PTV=CTV + 0.5 to 1.5 cm). It is the treating physician's decision what margin to use, depending on observed motion of the tumor detected by the fluoroscope (in general, the margin will be smaller for upper lung tumors and larger for lower lung tumors). More margin may be necessary in the cranio-caudad direction than in the other directions. Investigators will document how much margin (beyond the normal margin) was added, based on fluoroscopy findings, on the RT Prescription (Protocol Treatment) Form (T2).

There will be one gross target volume (GTV) to be treated throughout the entire treatment course (i.e., there are no field reductions planned).

6.5 Critical Structures
The normal tissues including the right lung, the left lung, and the spinal cord need to be contoured in their entirety (see Section 6.4.2). Any GTV within the lung should not be excluded from the digitized lung volume.

6.5.1 It is expected that the lungs will be the primary dose-limiting structure. Every effort to keep the total lung (defined as the lung volume of both lungs minus the PTV) dose to a minimum should be made.

6.5.2 In the following table, organs and doses by volume are guidelines for the three-dimensional plan. Physicians/dosimetrists should make every effort not to exceed these tolerance levels, if feasible. All normal tissues assume treatment at 1.8 Gy/fx (corrected).

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume*</th>
<th>Tolerance Dose</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>V_{20} **</td>
<td>&lt;30% and preferably &lt; 25%</td>
<td>Clinical pneumonitis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1/3, 2/3, 3/3</td>
<td>65 Gy, 55 Gy, 45 Gy</td>
<td>Clinical stricture and perforation</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Point dose</td>
<td>60 Gy</td>
<td>Clinically Manifested Nerve Damage</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Maximum dose</td>
<td>50 Gy</td>
<td>Myelitis</td>
</tr>
<tr>
<td>Heart</td>
<td>1/3, 2/3, 3/3</td>
<td>60 Gy, 45 Gy, 30 Gy</td>
<td>Clinical Pericarditis</td>
</tr>
<tr>
<td>Liver</td>
<td>1/2, 2/2</td>
<td>35 Gy, 25 Gy</td>
<td>Clinical Hepatitis</td>
</tr>
</tbody>
</table>

*Total lung volume = (volume of right lung + volume of left lung) minus PTV
**V_{20} is defined as the total lung volume receiving a dose of 20.0 Gy or more

6.6 Documentation Requirements (9/15/05)
6.6.1 Copies of the treatment plan and dose volume histograms corrected and uncorrected for heterogeneity will be submitted. DVHs will include PTV, spinal cord, and total lung volume (volume of right lung + left lung − PTV). See Section 12.0 for data submission.

6.7 Compliance Criteria

<table>
<thead>
<tr>
<th>Target Coverage Criteria</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% - 100% PTV covered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>92% - 95% PTV covered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 92% PTV covered</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Critical Structure Dose Criteria

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

### PTV Margins Criteria

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 cm to ≤ 2.5 cm</td>
<td>2.5-3.5 cm †Variation Acceptable</td>
<td></td>
</tr>
<tr>
<td>1 cm</td>
<td>&gt; 3.5 cm †Deviation Unacceptable</td>
<td></td>
</tr>
</tbody>
</table>

†Unless documented that increased margins were necessary due to tumor motion as observed during fluoroscopy.

**6.8 R.T. Quality Assurance Reviews**

Dr. Werner-Wasik will perform an RT Quality Assurance Review for the first case from each institution, after complete data is received for that case. If feedback is necessary regarding the prescribed dose, Dr. Werner-Wasik will contact the treating physician.

After the first case from each institution is reviewed, Drs. Werner-Wasik and Gaspar will perform an RT Quality Assurance Review after complete data for the next 25 cases enrolled has been received at RTOG Headquarters. Drs. Werner-Wasik and Gaspar will perform the next review after complete data for each additional 50 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 ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

**6.9 Radiation Adverse Events**

**6.9.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis** are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 40 Gy, usually within the first six months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

**6.9.2 Esophagitis**

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaïne, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, notify Dr. Werner-Wasik or Dr. Govindan.

**6.9.3 Therapy Interruptions**

Efforts should be made to avoid interruptions in therapy. Routine holidays are understood. Note: Fevers, cytopenias, or < 3 grade esophagitis do not in general constitute reasons for interruptions. Radiotherapy interruptions or delays will be permitted only for febrile neutropenia, Grade 4 esophagitis/mucositis or skin toxicity, Grade > 3 pulmonary toxicity. If neutropenic fever occurs and radiation is withheld, G-CSF may be initiated to expedite neutrophil recovery. However, G-CSF may not be used on days that radiation is being administered and cannot be given on weekends during a regular uninterrupted radiotherapy course.

If interruptions longer than 3 treatment days occur, Dr. Werner-Wasik or Dr. Gaspar should be notified (preferably by e-mail or alternatively by phone). If an interruption of longer than one
A week is required, resumption of therapy is at the discretion of the radiation oncologist. The reason for treatment interruption must be documented in the patient’s chart.

Missed RT doses will not be doubled or delivered twice daily (hyperfractionated) for patients missing one or more days but should be rescheduled at the end of the treatment period. If interruptions of therapy of up to one week become necessary, irradiation should be completed to the prescribed dose. Total number of fractions and elapsed days are to be carefully reported.

6.10 Radiation Adverse Event Reporting
All acute and late adverse events from 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 home page (http://ctep.info.nih.gov). See Section 7.8 for Adverse Event Reporting.

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. Questions regarding chemotherapy should be directed to Dr. Govindan or Dr. West (preferably by e-mail or alternatively by phone).

7.1 Induction Therapy
Induction therapy (chemotherapy or chemoradiotherapy) will begin within 7 days of randomization.

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Cisplatin 75 mg/m² over 1 hour <strong>followed by</strong> Docetaxel 75 mg/m² over 1 hour</th>
<th>Days 1, 22</th>
<th>Dexamethasone 8 mg orally twice daily for six doses beginning 24 hours before docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2*</td>
<td>Cisplatin 50 mg/m² over 1 hour <strong>followed by</strong> Docetaxel 20 mg/m² over 1 hour</td>
<td>Days 1, 8, 22 and 29</td>
<td>Dexamethasone 8 mg orally twice daily for three doses beginning 12 hours before docetaxel</td>
</tr>
</tbody>
</table>

*Arm 2: On days when cisplatin and/or docetaxel are given, chemotherapy ideally should be given prior to RT.

7.1.3 Suggested Hydration and Anti-Emetic Regimen Prior to Cisplatin (Arms 1 and 2)
Prior to cisplatin, begin intravenous hydration with 1,000 ml NS + 20 mEq KCl + 4 gms MgSO₄ at 250 cc/hr over two hours. The recommended anti-emetic is a combination of 5 HT3 antagonist and dexamethasone. Lorazepam may be used as needed. A combination of dexamethasone and 5 HT3 antagonist is STRONGLY RECOMMENDED only for patients enrolled on Arm 1.

After cisplatin infusion, complete the remaining 500 cc of hydration fluid over two hours. The patient should be encouraged to drink as much liquid as possible overnight if an outpatient; otherwise, an additional two liters of fluid should be given IV over the next 12 hours if the patient is an inpatient.

7.1.4 Dexamethasone Premedications
**Note:** DEXAMETHASONE IS REQUIRED. Treatment can be delayed by one day for those who have not taken dexamethasone premedication.

7.2 Re-Evaluation Following Induction Therapy
Patients will be re-evaluated within 2 weeks of anticipated surgery. See Section 8.2 for details.
### Consolidation Chemotherapy (After Induction Therapy and Surgery) (9/15/05)

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Days of Therapy</th>
<th>Dexamethasone premedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 75 mg/m²</td>
<td>Days 1, 22, 43</td>
<td>Dexamethasone 8 mg orally twice daily for six doses beginning 24 hours before docetaxel</td>
</tr>
<tr>
<td>over 1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandatory growth factor: pegfilgrastim 6 mg s.c.</td>
<td>24 hours after each docetaxel administration</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Filgrastim 5 mcg/kg s.c. | Once daily for 10 days, starting 24 hours after each docetaxel administration |}

7.3.1 Consolidation therapy will begin 4-6 weeks after surgery. Occasionally an extra week may be required to recover from surgery. If longer than a week is deemed necessary, Dr. Govindan should be notified. The reason(s) for delay in the initiation of Consolidation Chemotherapy should be documented.

7.3.2 **Dexamethasone Premedication**

DEXAMETHASONE IS REQUIRED. Treatment can be delayed by one day for those who have not taken dexamethasone premedication.

7.3.3 **Growth Factor Support During Consolidation Chemotherapy (9/15/05)**

PEGFILGRASTIM OR FILGRASTIM SUPPORT IS REQUIRED. Pegfilgrastim 6 mg must be given subcutaneously 24 hours after docetaxel, or filgrastim 5 mcg/kg must be given daily for 10 days, starting 24 hours after each administration of docetaxel.

7.4 **Study Agents**

7.4.1 **Cisplatin (CDDP) [Platinol®]**

NOTE: Refer to the commercial package labeling for full prescribing information.

7.4.1.1 **Description**

Cis-diaminedichloroplatinum (Platinol® or cisplatin) is a heavy metal complex and is water soluble. It is a white lyophilized powder with a molecular weight of 300.1.

7.4.1.2 **Mechanism of Action/Kinetics**

Cisplatin acts as a bifunctional alkylating agent. After a single IV dose, increased concentration is found in the liver, kidneys and small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes and a secondary phase ranging from 58 to 73 hours. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates into CNS poorly.

7.4.1.3 **Formulation**

Cisplatin is available as 50 mg and 100 mg vials of dry powder, which are reconstituted with 50 ml and 100 ml of Sterile Water for Injection USP, respectively.

7.4.1.4 **Administration**

Cisplatin should be given immediately after preparation as a slow intravenous infusion over 60 minutes. Needsles or intravenous sets containing aluminum parts that may come in contact with cisplatinum (Platinol®) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes. Protect from light.

7.4.1.5 **Storage/Stability**

The intact vials may be stored at room temperature (15-25° C) for the lot life indicated on the package. Do not refrigerate. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. The reconstituted solution is stable for 20 hours at room temperature, although, due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The desired dose of cisplatin is diluted with 250-1000 ml of saline and/or dextrose solution. Varying concentrations of 0.225-5% sodium chloride and 5% dextrose may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.
7.4.1.6 **Adverse Events**

- **Renal:** A dose-related, cumulative renal tubular injury can occur. Adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.
- **Neurologic:** A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common, particularly at cumulative doses < 400 mg/m.
- **Hematologic:** Mild leukopenia and thrombocytopenia occur in 25-30% of patients but are rarely dose limiting. Anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.
- **Gastrointestinal:** Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea, a delayed (72-96 hour) reaction may occur, requiring additional therapy. Anorexia and taste changes also may occur.
- **Hypersensitivity:** Allergic reactions are reported in up to 20% of patients. Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.
- **Other:** Electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, and retrobulbar neuritis are reported.

7.4.1.7 **Supply**

Cisplatin is commercially available.

7.4.2 **Docetaxel (Taxotere®)**

**NOTE:** Refer to the commercial package labeling for full prescribing information.

7.4.2.1 **Description**

In the late 1960s the National Cancer Institute large-scale plant screening program found that a crude extract of the bark from the Pacific yew, Taxus brevifolia, had activity against the P388 mouse leukemia. In the 1971, Wani, Taylor et al. isolated and characterized paclitaxel, the active principle of the extract. It has become evident that paclitaxel has activity against several human malignancies including refractory ovarian cancer and breast cancer. Several years ago, researchers at Rhone-Poulenc Rorer with the cooperation of the French "Centere National de Recherche Scientifiques (CNRS)" were able to prepare docetaxel, a semisynthetic analog of paclitaxel, using a precursor extracted from the needles of the European yew, Taxus baccata, a renewable source.


7.4.2.2 **Mechanism of Action**

In vitro, docetaxel promotes tubulin assembly in microtubules and inhibits depolymerization thus stabilizing microtubules, which is different from the action of other spindle poisons in clinical use. This can lead to bundles of microtubules in the cell, which by blocking cells in the M phase of the cell cycle, results in the inability of the cells to divide.

Comparing docetaxel and paclitaxel using the “tubulin in vitro assay”, the concentration required to provide 50% inhibition of microtubule disassembly (orIC50) is 0.2 µM for docetaxel and 0.4 µM for paclitaxel.

7.4.2.3 **Formulation**

Docetaxel for injection concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water for injection) vial. The following strengths are available:

- **Docetaxel** (NDC 0075-8001-80) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for docetaxel 80 mg, 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.
- **Docetaxel** (NDC 0075-8001-20) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for docetaxel 20 mg, 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton available as 80 mg/m² mL vials.
(15% overfilled) with a 7 mL vial of solvent (ethanol 95% in water, 15% overfilled). (The vials contain 94.4 mg/2.36 mL docetaxel and 7.33 mL ethyl alcohol 95% to compensate for liquid lost during preparation.)

7.4.2.4 Preparation

NOTE: Docetaxel Vials Must Be Reconstituted With Accompanying Solvent Before Final Dosage Form Preparation.

Preparation of the Initial Diluted Solution

1) Gather the appropriate number of vials of docetaxel for Injection Concentrate and diluent (13% ethanol in water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2) Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/mL will result.
3) Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4) The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Preparation of the Final Dilution for Infusion

1) Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.
2) Thoroughly mix the infusion by manual rotation.

As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

Note: Docetaxel must be prepared in glass or polyolefin containers and administered via non-PVC tubing due to leaching of diethylenehexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the vehicle in which docetaxel is solubilized. Non-PVC tubing and connectors, such as the IV administrations sets (polyethylene or polyolefin), which are used to infuse parenteral nitroglycerin, must be used. No other solutions are to be infused through the line by which docetaxel is being administered. Inject the diluted docetaxel solutions into the non-PVC infusion bad containing 5% Dextrose in Water of 0.9% Sodium Chloride Solution. The volume of the infusion should be adjusted in order to have a final docetaxel concentrations ≤ 1 mg/mL. Mix by manually rotating the infusion bag.

7.4.2.5 Administration

The drug will be administered to the patients as an IV infusion under ambient room temperature and lighting conditions. A peristaltic infusion pump is recommended.

7.4.2.6 Storage/Stability

Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Docetaxel is stored at 4°C and should be protected from light. The solvent vials may be stored at room temperature or at 4°C. Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 4 hours (including the administration time).

7.4.2.7 Adverse Events

- Cardiovascular: Peripheral edema, pleural effusions, and ascites occur in up to 40% of patients. Dexamethasone administration will not eliminate this reaction but will make it milder.
- Dermatologic: Hair loss and changes in the color of nails or the appearance of ridges in nails occur in up to 75% of patients. Hair will grow back and fingernails will have the same color after docetaxel is stopped.
- Gastrointestinal: Severe and dose-limiting mucositis occurs in up to 10% of patients; also, nausea, vomiting, and diarrhea.
- Neutropenia: Severe and dose-limiting myelosuppression occurs in up to 85% of patients. The onset is 4-7 days, with a nadir at 21 days.
- Hepatic: Reversible elevations in transaminases occur in 18% of patients. Patients with elevations in SGOT > 1.5 X normal and an alkaline phosphatase > 2.5 X normal have decreased docetaxel clearance and appear to be more likely to suffer severe toxicity, including death.
- Neurologic: Myalgias and paresthesias are common, occurring in up to 50% of patients and may be dose limiting. Motor neuropathy, including weakness, occurs in up to 10% of patients.
- Hypersensitivity reactions, including rash, angioedema, flushing, and hypotension occur infrequently in patients premedicated with dexamethasone.

**7.4.2.8 Supply (10/31/05)**

**U.S.** - Docetaxel is commercially available in the U.S.

**Canada** - Docetaxel (Taxotere®) is being supplied free of charge to Canadian institutions.

**Distribution**

Canadian institutions must complete the "Request for Clinical Medication by Fax" form included in the Health Canada study approval broadcast. The form must be faxed to RTOG Headquarters at 215-574-0300 prior to registering the first patient. Headquarters will fax the completed form to Sanofi-Aventis once all regulatory documents are received. Please allow one week prior to registering your first case to receive your shipment.

Sanofi-Aventis will ship medication and shipping documents via Purolator courier to the site pharmacist. The site pharmacist will need to confirm receipt of the medication shipment by signing and dating one copy of the shipping documents and returning them to Sanofi-Aventis in the pre-addressed and postage paid envelope provided with the shipment.

**Re-supply**

To receive Taxotere re-supply, complete the "Request for Clinical Medication" form included in each drug shipment and fax it to Sanofi-Aventis as per the instructions on the form.

**Destruction**

All Taxotere vials must be destroyed at the site, at a locally authorized facility for this type of product. Supporting documents such as facility's certification and documentation of the method of destruction will have to be collected.

The investigator is responsible for maintaining documentation describing the amount of investigational product provided by Sanofi Aventis, dispensed and destroyed. Discrepancies in product accountability must be explained and documented.

**7.4.3 Pegfilgrastim (Neulasta™)**

**NOTE:** Refer to the commercial package labeling for full prescribing information.

**7.4.3.1 Pharmacology**

Both filgrastim and pegfilgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function show that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared with filgrastim.

**7.4.3.2 Formulation**

Neulasta™ (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxy-polyethylene glycol. Filgrastim is obtained from the bacterial fermentation of a strain of *E. coli* bearing a genetically engineered plasmid containing the human G-CSF gene. Neulasta™ is supplied in 0.6-ml pre-filled single-dose syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight),
in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

7.4.3.3 Administration
The pegfilgrastim will be injected subcutaneously into rotating sites on the abdomen, arms, and legs. Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration. Pegfilgrastim should not be administered if discoloration or particulates are observed. Pegfilgrastim can be self-administered by the patient. Each patient or a designated caregiver will be instructed by the nursing staff in the proper method for the antiseptic subcutaneous administration of pegfilgrastim. Prior to administration at home, these skills must be competently demonstrated by the patient or caregiver. Patients/caregivers will also receive written instruction concerning medication storage (refrigeration).

7.4.3.4 Storage
Neulasta™ should be stored refrigerated at 2° to 8° C (36° to 46° F); syringes should be kept in their carton and protected from the light until time of use. Shaking should be avoided. Before injection, Neulasta™ may be allowed to reach room temperature for a maximum of 48 hours but should be protected from the light. Neulasta™ left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta™ should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta™ should be discarded.

7.4.3.5 Adverse Events
Neulasta™ is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Drugs such as lithium may potentiate the release of neutrophils; patients who are taking lithium should have more frequent monitoring of their neutrophil counts. The predominant toxicity attributed to Neulasta™ in clinical trials was medullary bone pain of mild to moderate severity. Other adverse experiences included nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. Leukocytosis (WBC > 100 x 10^9/L) was observed in less than 1% of subjects. A rare case of hypoxia was also observed. Reversible elevations in LDH, alkaline phosphatase, and uric acid were also observed.

7.4.3.6 Supply
Neulasta™ is commercially available.

7.4.4 Filgrastim (r-metHuG-CSF) (9/15/05)
7.4.4.1 Description: Filgrastim is a colony-stimulating factor that regulates the production of neutrophils within the bone marrow. Endogenous filgrastim is a glycoprotein produced by monocytes, fibrocytes, fibroblasts, and endothelial cells, which has been shown to have minimal direct in vivo or in vitro effects on the production of other hematopoietic cell types. r-metHuG-CSF is a 175–amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia coli (E. coli) bacteria into which has been inserted the human granulocyte colony stimulation factor gene and has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E. coli. Because r-metHuG-CSF is produced in E. coli, the product is non-glycosylated and thus differs from G-CSF isolated from human cell.

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

7.4.4.3 Administration: Filgrastim may be given subcutaneously or i.v. at 5 µg/kg/d to protect against new episodes of febrile neutropenia in cycles 2-4 of chemotherapy on Sequence A and during cycles 3 and 4 on Sequence B in patients who have experienced such a complication.

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

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

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

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

7.4.4.7 Supply: Filgrastim is commercially available.

7.5 Dose Modifications

7.5.1 Dose Modification Guidelines

- The dose levels and dose modifications are specific for each Arm during Induction Therapy.
- There is only one dose level reduction during Induction Therapy.
- ALL DOSE REDUCTIONS ARE PERMANENT. There will be no dose escalation or re-escalation during Induction Therapy.
- Use of prophylactic colony stimulating factors is PROHIBITED in Arm 2 (chemoradiation) during Induction Therapy. Colony stimulating factors may be used therapeutically only if the patient is admitted for neutropenic fever. In that case, radiation therapy should be held, and daily growth factor administered until recovery of neutrophils. Upon resumption of radiation therapy, the growth factor should be stopped.
- If, in the opinion of the investigator(s), there is any reason to omit weekly chemotherapy the investigator(s) should contact Dr. Govindan or Dr. West (preferably by e-mail or alternatively by phone).

7.5.2 Induction Therapy: Arm 1 (Chemotherapy)

7.5.2.1 Dose Levels for Chemotherapy Modification for Arm 1 (Chemotherapy)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE LEVEL</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Full</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-1 Level</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Full</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-1 Level</td>
<td>60 mg/m²</td>
</tr>
</tbody>
</table>
### 7.5.2.2 Hematological Adverse Events (AEs): Dose Modification for Day 22 *(9/15/05)*

<table>
<thead>
<tr>
<th>AND</th>
<th>ANC ≥ 1,500/µl AND Platelets ≥ 100,000/µl</th>
<th>Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANC &lt; 1,500/µl OR Platelets &lt; 100,000/µl</td>
<td>Check weekly. Initiate therapy when ANC ≥ 1,500/µl AND Platelets ≥ 100,000/µl</td>
</tr>
<tr>
<td></td>
<td>If after 2 weeks delay, ANC &lt; 1,500/µl OR Platelets &lt; 100,000/µl</td>
<td>Call Drs. Govindan or West</td>
</tr>
<tr>
<td></td>
<td>If febrile neutropenia develops during cycle 1</td>
<td>No dose reduction. Pegfilgrastim 6 mg s.c. to be administered 24 hours after chemotherapy OR Filgrastim 5 mcg/kg s.c. once daily for 10 days, to be administered starting 24 hours after chemotherapy</td>
</tr>
</tbody>
</table>

### 7.5.2.3 Renal AEs: Dose Modification for Day 22

<table>
<thead>
<tr>
<th>Calculated Creatinine Clearance &lt; 50 ml/min</th>
<th>Administer hydration and delay one week</th>
</tr>
</thead>
<tbody>
<tr>
<td>If after one week delay:</td>
<td></td>
</tr>
<tr>
<td>Calculated Creatinine Clearance ≥ 50 ml/min</td>
<td>Give full dose, but increase pre- and post-cisplatin hydration</td>
</tr>
<tr>
<td>Calculated Creatinine Clearance ≤ 50 ml/min</td>
<td>Omit cisplatin, and continue therapy with docetaxel alone</td>
</tr>
</tbody>
</table>

### 7.5.2.4 Neuropathy: Dose Modification on Day 22

- For grade 3 or 4 neuropathy, discontinue cisplatin and docetaxel.
- For grade 2 neuropathy, decrease the doses of cisplatin and docetaxel to dose level -1.
- No dose reduction for grade 1 neuropathy.

### 7.5.2.5 Stomatitis

If stomatitis is present on day 1 of any cycle, treatment should be withheld until the stomatitis has resolved. If grade 3 or 4 stomatitis occurs, retreatment after recovery should be with a one level dose reduction of docetaxel. No dose reduction is required for cisplatin.

### 7.5.2.6 Gastrointestinal AEs

If Grade 4 vomiting occurs despite antiemetic prophylaxis, retreatment after recovery should be with one level dose reduction of docetaxel. No dose reduction is required for cisplatin.

If Grade ≥ 3 diarrhea occurs despite anti-diarrheal treatment, subsequent retreatment after recovery should be with a one level dose reduction of docetaxel. No dose reduction is required for cisplatin.
7.5.2.7 Hepatic AEs: Dose Modifications (docetaxel)

<table>
<thead>
<tr>
<th>ALK PHOS:</th>
<th>AST or ALT:</th>
<th>≤ ULIN</th>
<th>&gt;1X but ≤ 1.5X</th>
<th>&gt;1.5X but ≤ 5X</th>
<th>&gt;5X ULIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ ULIN</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Hold*</td>
<td></td>
</tr>
<tr>
<td>&gt;1X but ≤ 2.5X</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>-1 Dose Level</td>
<td>Hold*</td>
<td></td>
</tr>
<tr>
<td>&gt;2.5X but ≤ 5X</td>
<td>Full Dose</td>
<td>-1 Dose Level</td>
<td>Hold*</td>
<td>Hold*</td>
<td></td>
</tr>
<tr>
<td>&gt;5X ULIN</td>
<td>Hold*</td>
<td>Hold*</td>
<td>Hold*</td>
<td>Hold*</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

*Hold until recovered (maximum 21 days), and then re-treat at –1 dose level of docetaxel. "Recovered" is defined as meeting the study baseline eligibility criteria.
ULN = Upper limit of normal for institution

Note: A maximum of one dose reduction per patient is allowed.

7.5.2.8 Fluid Retention

For the purposes of AE evaluation, fluid retention will be defined as the development of edema greater than trace, cytologically negative pleural effusion, ascites or pericardial effusion and will be graded as mild, moderate or severe.

<table>
<thead>
<tr>
<th>Edema</th>
<th>Severity (Grade)</th>
<th>Effusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Mild (1)</td>
<td>Asymptomatic; No intervention required</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Moderate (2)</td>
<td>Symptomatic; Intervention may be required</td>
</tr>
<tr>
<td>Symptomatic, resulting in drug discontinuation</td>
<td>Severe (3)</td>
<td>Symptomatic; Intervention urgently required</td>
</tr>
</tbody>
</table>

*Report the highest grade of edema or effusion

If symptomatic, patients developing fluid retention may be treated with diuretics at the investigators’ discretion. A recommended option: spironolactone 25 mg three times daily and furosemide 20-40 mg PRN.

For Grade 3 AEs, drug should be withheld until the AE resolves to grade 1; then, reinstitute docetaxel with one level dose reduction.
7.5.2.9 Hypersensitivity Reactions
Acute hypersensitivity reactions to docetaxel should be managed as outlined in the following table:

<table>
<thead>
<tr>
<th>Severity of Symptoms</th>
<th>Treatment Guidelines</th>
</tr>
</thead>
</table>
| **Mild (Grade 1) symptoms:** Localized cutaneous reactions such as mild pruritus, flushing, rash | • Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient;  
• Then, complete docetaxel infusion at the initial planned rate. |
| **Moderate (Grade 2) symptoms:** Any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg | • Interrupt docetaxel infusion;  
• Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms.  
• Resume docetaxel infusion after recovery of symptoms; depending on the physician’s assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the 1-hour infusion rate).  
• Depending on the intensity of the reaction observed, additional oral or IV pre-medication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion (e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, and finally, administer at the 1-hour infusion rate). |
| **Severe (Grade 3 symptoms) and Anaphylaxis (Grade 4): Any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema** | • Immediately discontinue docetaxel infusion.  
• Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms.  
• Patient will be taken off the study. |

Any hypersensitivity reaction should be recorded as an adverse event.

In case of late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine). Additional oral or parenteral pre-medication with antihistamine may also be given for the next cycle of treatment, depending on the intensity of the reaction observed.

Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

7.5.2.10 Other Non-Hematological AEs
Manage ≤ grade 2 AEs symptomatically, if possible, and retreat without dose reduction.

If AEs ≥ grade 3, docetaxel and cisplatin should be withheld until resolution to ≤ grade 1, then reinstituted, if medically appropriate, after recovery with a one level dose reduction for both drugs. If there is delay beyond 2 weeks, call Drs. Govindan or West.
7.5.3 **Induction Therapy: Arm 2 (Chemoradiation)**

7.5.3.1 Dose Levels For Chemotherapy Modification for Arm 2 (Chemoradiation)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE LEVEL</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Full</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-1 Level</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Full</td>
<td>20 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-1 Level</td>
<td>10 mg/m²</td>
</tr>
</tbody>
</table>

7.5.3.2 Myelotoxicity Modification for Days 8, 15, 22, or 29

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 1,250/µl AND Platelets &gt; 100,000/µl</td>
<td>Full Dose</td>
</tr>
<tr>
<td>ANC &lt; 1,250/µl OR Platelets &lt; 100,000/µl</td>
<td>Skip chemotherapy; check weekly, and resume chemotherapy at full doses when ANC ≥ 1,250/µl AND Platelets &gt; 100,000/µl</td>
</tr>
<tr>
<td>If febrile neutropenia develops during Induction Therapy,</td>
<td>Administer one dose level reduction of both drugs</td>
</tr>
<tr>
<td>Hold therapy until ANC ≥ 1,250/µl AND Platelets ≥ 100,000/µl</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Granulocyte growth factors such as filgrastim or pegfilgrastim should not be administered while the patient is receiving radiation therapy; however, filgrastim may be administered for severe infection associated with neutropenia, provided radiation therapy is withheld while the patient receives filgrastim.

7.5.3.3 Renal AEs : Modification for Days 8, 15, 22, or 29

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated Creatinine Clearance &lt; 50 ml/min</td>
<td>Administer hydration, and delay one week</td>
</tr>
<tr>
<td>If after one week delay:</td>
<td></td>
</tr>
<tr>
<td>Calculated Creatinine Clearance ≥ 50 ml/min</td>
<td>Give full dose, but increase pre- and post-cisplatin hydration.</td>
</tr>
<tr>
<td>Calculated Creatinine Clearance ≤ 50 ml/min</td>
<td>Omit cisplatin. No modification for docetaxel.</td>
</tr>
</tbody>
</table>

7.5.3.4 Neuropathy
For grade 3 or 4 neuropathy, discontinue cisplatin and docetaxel. For grade 2 neuropathy, decrease the doses of cisplatin and docetaxel to dose level –1. No dose reduction for grade 1 neuropathy.

7.5.3.5 Stomatitis
If stomatitis is present on day 1 of any cycle, treatment should be withheld until the stomatitis has resolved.

If grade 3 or 4 stomatitis occurs, retreatment after recovery should be with a one level dose reduction of docetaxel. No dose reduction is required for cisplatin.
7.5.3.6  
**Gastrointestinal AEs, Including Dysphagia**

If Grade 4 vomiting occurs despite antiemetic prophylaxis, retreatment after recovery should be with one level dose reduction of cisplatin. No dose reduction required for docetaxel.

If Grade ≥ 3 diarrhea occurs despite anti-diarrheal treatment, subsequent retreatment after recovery should be with a one level dose reduction of docetaxel. No dose reduction required for cisplatin.

For Grade ≥ 3 dysphagia, hold both the drugs and re-evaluate one week later; resume therapy when dysphagia has improved to grade ≤ 2, with one level dose reduction for both cisplatin and docetaxel.

7.5.3.7  
**Hepatic AEs: Dose Modifications (docetaxel)**

<table>
<thead>
<tr>
<th>AST or ALT:</th>
<th>ALK PHOS:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ ULIN</td>
</tr>
<tr>
<td>≤ ULIN</td>
<td>Full Dose</td>
</tr>
<tr>
<td>&gt;1X but ≤ 2.5X</td>
<td>Full Dose</td>
</tr>
<tr>
<td>&gt;2.5X but ≤ 5X</td>
<td>Full Dose</td>
</tr>
<tr>
<td>&gt;5X ULIN</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

*Hold until recovered (maximum 21 days), and then re-treat at –1 dose level of docetaxel. “Recovered” is defined as meeting the study baseline eligibility criteria.

ULN= Upper limit of normal for institution

**Note:** A maximum of one dose reduction per patient is allowed.

7.5.3.8  
**Fluid Retention**

For the purposes of AE evaluation, fluid retention will be defined as the development of edema greater than trace, cytologically negative pleural effusion, ascites or pericardial effusion and will be graded as mild, moderate or severe.

<table>
<thead>
<tr>
<th>Edema</th>
<th>Severity (Grade)</th>
<th>Effusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Mild (1)</td>
<td>Asymptomatic; No intervention required</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Moderate (2)</td>
<td>Symptomatic; Intervention may be required</td>
</tr>
<tr>
<td>Symptomatic, resulting in drug discontinuation</td>
<td>Severe (3)</td>
<td>Symptomatic; Intervention urgently required.</td>
</tr>
</tbody>
</table>

*Report the highest grade of edema or effusion

If symptomatic, patients developing fluid retention may be treated with diuretics at the investigators’ discretion. A recommended option: spironolactone 25 mg three times daily and furosemide 20-40 mg PRN

For Grade 3 AEs, docetaxel should be withheld until the AE resolves to grade 1; then, reinstitute docetaxel with one level dose reduction. No dose reductions or delay required for cisplatin.

7.5.3.9  
**Hypersensitivity**

See Section 7.5.2.9. Patients with severe hypersensitive reactions to docetaxel will be taken off protocol and will be treated at the discretion of the attending physician.

7.5.3.10  
**Other Non-Hematological AEs**

If other non-hematological AEs ≥ grade 3 (except for nausea and vomiting) occur, both drugs should be held for 1 week before re-evaluation and then reinstituted at a one level dose reduction if AE is ≤ grade 2. For specific guidelines regarding dose modifications for vomiting, see section 7.5.3.6. If delay beyond 2 weeks is anticipated, the investigator(s) should contact Drs. Govindan or West.
7.5.4 Consolidation Chemotherapy: Modification of Docetaxel

7.5.4.1 General Guidelines For Dose Modification During Consolidation
- The dose levels and dose modifications are specific for Consolidation Therapy.
- There are only two dose level reductions during Consolidation Therapy.
- All eligible patients will begin Consolidation docetaxel at full dose (even if a dose level reduction was required during Induction Therapy).
- There will not be any dose re-escalation following any dose reduction during Consolidation Therapy.
- For any chemotherapy related questions the investigator(s) should contact Dr. Govindan or Dr. West (preferably by email, alternatively by phone).

7.5.4.2 Dose Levels For Chemotherapy Modifications During Consolidation

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE LEVEL</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Full</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-1 Level</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td></td>
<td>-2 Level</td>
<td>45 mg/m²</td>
</tr>
</tbody>
</table>

7.5.4.3 Hematological AEs: (9/15/05)
PEGFILGRASTIM OR FILGRASTIM SUPPORT IS REQUIRED. Pegfilgrastim 6 mg must be given subcutaneously 24 hours after docetaxel, or filgrastim 5 mcg/kg must be given daily for 10 days starting 24 hours after each administration of docetaxel.

Dose modifications based on complete blood counts Day 1 of each cycle.

<table>
<thead>
<tr>
<th>ANC ≥ 1,500/µl AND Platelets &gt; 100,000/µl</th>
<th>Full Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt; 1,500/µl OR Platelets &lt; 100,000/µl</td>
<td>Check weekly. Initiate therapy when ANC ≥ 1,500/µl AND Platelets &gt; 100,000/µl</td>
</tr>
<tr>
<td>If after 2 weeks delay, ANC &lt; 1,500/µl OR Platelets &lt; 100,000/µl</td>
<td>Call Drs. Govindan or West</td>
</tr>
<tr>
<td>If febrile neutropenia develops during cycle 1</td>
<td>One level dose reduction of docetaxel. A maximum of two dose reductions allowed. Pegfilgrastim or filgrastim to be administered as before.</td>
</tr>
</tbody>
</table>

Patients with Grade 4 thrombocytopenia should be retreated after recovery with a one level dose reduction.

7.5.4.4 Neuropathy
For grade 3 or 4 neuropathy, discontinue docetaxel. For grade 2 neuropathy, decrease the dose of docetaxel to dose level –1. No dose reduction for grade 1 neuropathy.

7.5.4.5 Stomatitis
If stomatitis present on day 1 of any cycle, treatment should be withheld until the stomatitis has resolved.

If grade 3 or 4 stomatitis occurs, retreatment after recovery should be with a one level dose reduction of docetaxel.

7.5.4.6 Gastrointestinal AEs
If Grade 4 vomiting occurs despite antiemetic prophylaxis, retreatment after recovery should be with one level dose reduction of docetaxel.
If Grade ≥ 3 diarrhea occurs despite anti-diarrheal treatment, subsequent retreatment after recovery should be with a one level dose reduction of docetaxel.

7.5.4.7 Hepatic AEs: Dose Modifications (docetaxel)

| AST or ALT: | 
| ALS PHOS: ≤ ULIN | >1X but ≤1.5X | >1.5X but ≤5X | >5X ULIN |
| ≤ ULIN | Full Dose | Full Dose | Full Dose | Hold* |
| >1X but ≤2.5X | Full Dose | Full Dose | -1 Dose Level | Hold* |
| >2.5X but ≤5X | Full Dose | -1 Dose Level | Hold* | Hold* |
| >5X ULIN | Hold* | Hold* | Hold* | Hold* |

*Hold until recovered (maximum 21 days), and then re-treat at –1 dose level of docetaxel. “Recovered” is defined as meeting the study baseline eligibility criteria.

ULN= Upper limit of normal for institution

Note: A maximum of one dose reduction per patient is allowed.

7.5.4.8 Fluid retention

For the purposes of AE evaluation, fluid retention will be defined as the development of edema greater than trace, cytologically negative pleural effusion, ascites or pericardial effusion and will be graded as mild, moderate or severe.

| Edema | Severity (Grade) | Effusion* |
| Asymptomatic | Mild (1) | Asymptomatic; No intervention required |
| Symptomatic | Moderate (2) | Symptomatic; Intervention may be required |
| Symptomatic, resulting in drug discontinuation | Severe (3) | Symptomatic; Intervention urgently required. |

*Report the highest grade of edema or effusion

If symptomatic, patients developing fluid retention may be treated with diuretics at the investigators’ discretion. A recommended option: spironolactone 25 mg three times daily and furosemide 20-40 mg PRN.

For Grade 3 AEs, drug should be withheld until the AE resolves to grade 1, then reinstitute docetaxel with one level dose reduction.

7.5.4.9 Hypersensitivity Reactions

See section 7.5.2.9. Patients with severe hypersensitive reactions to docetaxel will not receive any further therapy with docetaxel and will be taken off protocol and treated at the discretion of the investigators.

7.5.4.10 Other non-hematological AEs

Manage AEs ≤ grade 2 symptomatically, if possible, and retreat without dose reduction.

If AEs ≥ grade 3, docetaxel should be withheld until resolution to ≤ grade 1, then reinstituted, if medically appropriate, after recovery with a one level dose reduction. If there is delay beyond 2 weeks, please contact Drs. Govindan or West.

7.6 Criteria for Removal From Protocol Treatment

Example of text for this section includes:

- Progression of disease;
- Unacceptable adverse event to the patient (at the discretion of the treating physician); reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.
7.7 **Modality Review**

7.7.1 Drs. Govindan and West 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.

7.7.2 Drs. Govindan and West will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Drs. Govindan and West will perform the next review after complete data for each additional 50 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.

7.8 **Adverse Event Reporting—RTOG AE TELEPHONE LINE (215) 717-2762**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page [http://ctep.info.nih.gov](http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page [http://www.rtog.org/regulatory/regs.html](http://www.rtog.org/regulatory/regs.html). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

7.8.1 All serious adverse events (SAEs) will be reported using the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. The following AEs experienced by patients accrued to this protocol and attributed to the protocol treatment (definitely, probably, or possibly related) should be reported:

- Death on study (from start of protocol treatment to 30 days post protocol treatment)
- Hospitalization or prolongation of hospitalization on study (from start of protocol treatment to 30 days post protocol treatment)
- Life threatening event
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Intervention required to prevent permanent impairment/damage

7.8.2 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**, file a report using the **Adverse Event Expedited Reporting System** (AdEERS). **Use the patient’s case number as the patient ID when reporting via AdEERS**;
- Reporting requirements and timing of reporting are dependent on the Phase of the trial, grade, attribution, and whether the event is expected or unexpected as determined by the protocol and/or Investigator’s Brochure. **Please read the protocol thoroughly for this important information**.
- AEs reported through AdEERS also **must be reported in routine study data submissions (appropriate case report forms)**.

7.8.3 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 using the **NCI/CTEP Secondary AML/MDS Report Form** available at [http://ctep.info.nih.gov](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 (MedWatch) or a report via the AdEERS system and **must be mailed within 30 days of AML/MDS diagnosis** to the following addresses:
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. NCI will be creating a pathway for this on the AdEERS site in the future.

Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment must be telephoned to RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762 within 24 hours of discovery. Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG Headquarters via the AE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 10 days.

7.8.4 The table below summarizes the requirements for reporting serious adverse events (SAEs).

### Summary of Expedited Reporting Requirements for All Studies

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3* Hospitalization</th>
<th>Grade 4* Hospitalization</th>
<th>Grade 5* Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>Expected</td>
<td>Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>AdEERS</td>
<td>AdEERS</td>
<td>*</td>
<td>AdEERS</td>
<td>AdEERS</td>
</tr>
<tr>
<td>Probable</td>
<td>AdEERS</td>
<td>AdEERS</td>
<td>*</td>
<td>AdEERS</td>
<td>AdEERS</td>
</tr>
<tr>
<td>Definite</td>
<td>AdEERS</td>
<td>AdEERS</td>
<td>*</td>
<td>AdEERS</td>
<td>AdEERS</td>
</tr>
</tbody>
</table>

AdEERS – ADVERSE EVENT EXPEDITED REPORTING SYSTEM

*For Hospitalization Only: Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain Phase II and Phase III protocols. In those situations, the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. For example, an expected Grade 3 event that is definitely related to an investigational agent is only to be reported if the patient is hospitalized using the generic reporting criteria. In a trial of an investigational agent in which Grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

RTOG telephone number available 24 hours daily: (215) 717-2762 or (800) 227-5463, ext. 4189.

Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

A list of agent specific expected adverse events can be found in the protocol document and/or consent form.

**Known/expected** adverse events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, noted in the drug insert, or in the Investigator's Brochure.

**Unknown/unexpected** adverse events are those thought to have resulted from the protocol treatment.

### 8.0 SURGERY

Questions regarding Surgery should be directed to Dr. Pass or Dr. Vallieres (preferably by e-mail or alternatively by phone).

#### 8.1 Evaluation for Surgery (1/26/06)

8.1.1 Three to five weeks after completion of Induction Therapy and within 2 weeks of anticipated surgery, all patients will be re-evaluated as follows:

- History and physical by medical oncologist;
- Evaluation by thoracic surgeon;
- EKG;
- Pulmonary Function Tests: Diffusion capacity; the quantitative V/Q scan or split functions need not be repeated unless the FEV1 is worse than pre-study;
- Laboratory: Repeat lab evaluations in Sections 3.1.9 and 3.1.11 (repetition of the creatinine clearance is not necessary);
- Imaging: PET scan, chest and upper abdominal CT scan to include entire liver, and brain MRI with contrast (substitute CT scan if the MRI is medically contraindicated). A bone scan is not required unless there is new bone pain or new elevation of the alkaline phosphatase or LDH.
- Repeat the bronchoscopy only if the pre-treatment bronchoscopy results impact on resectability, such as proximity to carina or extent of resection.

8.1.2 Radiographic response determinations (CR, PR, SD, PD) will be required for this study (see Section 11.2.2.1). Whenever possible, a biopsy should be obtained to confirm distant progression. All patients who fit the criteria for no progression in the chest or elsewhere, including all patients who have stable disease on re-evaluation, will proceed to surgery.

8.1.3 If there is progressive disease (PD) or distant disease identified, the patient will go off protocol treatment. Sites will submit Post-Induction Evaluation Form (F0). If it is the opinion of the attending thoracic surgeon that the patient has developed a problem that makes surgery medically or technically unsafe, or if the patient refuses surgery, the Primary Study Coordinator for surgery, Dr. Pass, or, in his absence, Dr. Werner-Wasik, should be notified and this information will be documented. Patients with progressive disease will receive further non-operative therapy at the discretion of their treating physician(s).

8.1.4 Surgery will be performed 4-8 weeks after completion of Induction Therapy. Occasionally, an extra week will be required to recover from toxicity of Induction Therapy. If longer than a week is deemed necessary, Dr. Pass or Dr. Werner-Wasik should be notified. Site will document the reason(s) for delay on the Post-Induction Evaluation Form.

8.2 Surgical Guidelines/Extent of Resection
8.2.1 At thoracotomy, a lobectomy or pneumonectomy will be performed at the discretion of the attending thoracic surgeon. A procedure other than a lobectomy or pneumonectomy (e.g., a wedge) will be considered a major deviation. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins; this is not subject to quality assurance review. Documentation of margins by frozen section at surgery is strongly recommended. NOTE: Frozen tissue from surgery is preferred for translational research (see Section 10.2.3).

8.2.2 Lesions with direct extension into parietal pleura or chest wall should be resected with an en bloc chest wall resection. Lesions with direct extension into pericardium or diaphragm should have en bloc resection of those structures with an attempt made to achieve a minimum of 2 cm gross, or 1 cm microscopic, margins. These are recommendations subject to quality assurance review (i.e., if it is not a chest wall lesion but a pleura invasion, this must be reviewed).

8.2.3 A formal systematic mediastinal lymph node dissection will be performed in all cases. Numbering and/or nomenclature outlined in the Lymph Node Map will be used (see Appendix IV). Mediastinal lymph nodes removed at thoracotomy should include nodes from the following regions:

8.2.3.1 For right sided lesions: 4R, 7, 9, 10R; and if accessible, 2R. If the 4R, 7, 9, and 10R levels are not performed, it will be considered a major deviation. 2R is recommended but is not subject to quality assurance review.

8.2.3.2 For left sided lesions: 5, 6, 7, 9, 10L; and if accessible, 4L. If the 5, 6, 7, 9, and 10L levels are not performed, it will be considered a major deviation. 4L is recommended but is not subject to quality assurance review.

8.2.4 The attending thoracic surgeon and medical oncologist must review and sign all post-surgical forms.

8.3 Post-Operative Period
During the post-operative period minimal IV 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.

8.3.1 Surgical Adverse Events
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 3.0. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.info.nih.gov). See Section 7.8 for Adverse Event Reporting.
Post-Operative 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 reinserstion 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.)

Surgical Quality Assurance Reviews

8.4.1 The Thoracic Surgery Co-Chair, Dr. Pass will review surgical staging prior to Induction Therapy and at surgical resection (i.e., the Operative and Surgical Pathology reports for the initial evaluation of lymph nodes and the surgical resection).

8.4.2 Drs. Pass and Vallieres will perform a Quality Assurance Review for verification of lymph node removal and protocol compliance after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Drs. Pass and Vallieres will perform the next review after complete data for each additional 50 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.

8.4.4 Goals of Surgical Quality Assurance

- To assure correct surgical staging of patients prior to Induction Therapy;
- To assure safety of patients undergoing resection after Induction Therapy;
To assure adequate resection of primary and lymph node dissection after Induction Therapy.

8.4.5 Surgical Protocol Compliance Criteria

- Deviations Minor:
  - Surgical resection outside the defined window (unless prior approval from the Surgery Co-Chair was obtained);
- Deviations Unacceptable: Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:
  - Inadequate nodal dissection and/or numbering at thoracotomy;
  - No documentation of post neoadjuvant/preoperative PFTs or evidence of calculated postresection FEV1 < 800 cc;
  - Inadequate assessment of pathologic evidence of mediastinal nodal involvement prior to initiation of Consolidation Chemotherapy.

9.0 OTHER THERAPY

9.1 Post-operative Radiation Therapy

There will be no routine post-operative RT, irrespective of the type of Induction Therapy received. Patients with positive resection margins (microscopic or macroscopic) and those with known residual tumor will go off protocol treatment. These patients can receive post-operative RT at their physician's discretion. It is recommended that patients on Arm 1 (chemotherapy alone) receive 60.0 Gy, and patients on Arm 2 (chemoradiotherapy) receive 15-20.0 Gy. Please contact Dr. Werner-Wasik or Dr. Gaspar with any questions regarding this issue (preferably by e-mail and alternatively by phone).

9.2 Permitted Supportive Therapy

9.2.1 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The use of erythropoietin (i.e., Epogen®, Procrit®) is permitted. Sucralfate slurries may provide symptomatic relief of mucositis and esophagitis.

9.2.2 Post-treatment pneumonitis attributed to radiation should be treated with prednisone after excluding microbial causes.

9.3 Non-permitted Supportive Therapy

9.3.1 Administration of granulocyte growth factor (filgrastim, pegfilgrastim, or sargramostim) is NOT allowed during the Induction Therapy for patients assigned to Arm 2 (chemoradiation).

9.3.2 Amifostine is not allowed at any time during treatment.

10.0 TISSUE/ SERUM/BUFFY COAT SUBMISSION

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I)

10.1 RTOG Tissue Bank

The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Tissue Bank provides tissue specimens to investigators for translational research studies, which are planned portions of this study included in the secondary endpoints. Translational research studies will integrate important research findings about DNA damage, repair genes, and microtubule genes into this treatment protocol.

A portion of the specimens submitted for the translational research in this study (see Section 10.2) will be banked at the RTOG Tissue Bank (if not exhausted by the translational research procedures). Specimen Plug Kits and Specimen collection/shipping Kits are available from the RTOG Tissue Bank to participating institutions. See Appendix VII.

Specimen requirements are described in Section 10.2. The following documents must be provided in order for the case to be evaluable for the Tissue Bank:

10.1.1 A Pathology Report documenting that the submitted block, core, or slides contain tumor. The report must include the protocol number (0412/S0332) and patient’s case number (or attach the RTOG label). The patient’s name and/or other identifying information should be removed from
the report. The surgical pathology numbers and information must NOT be removed from the report.

10.1.2 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; if for translational research, this should be stated on the form. The form can be accessed at http://www.rtog.org/pdf_forms.html?members/forms=specimen.pdf; no password required. The form must include the protocol number (0412/S0332) and the patient’s case number (or attach the RTOG label).

10.1.3 For serum specimens the following materials must be provided to the RTOG Tissue Bank: A Specimen Transmittal Form documenting the date of collection of the serum; the protocol number (0412/S0332) and the patient’s case number (or attach the RTOG label) and method of storage (for example, stored at -20°C) must be included. See Section 10.2.3 for specifics of specimen preparation.

10.1.4 Submit materials (as described in Section 10.2) for Tissue Banking to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
holly.goold@ihc.com

10.2 Specimen Collection for Translational Research

In this study, Dr. Franklin will examine TUBB III and MAP4 by immunohistochemical analysis of paraffinized sections from pre-treatment and surgical resection tissue samples. Dr. Gumerlock will evaluate ERCC1 and XRCC1 in buffy coat samples and shed tumor DNA in patient plasma. MALDI-TOF analysis will be conducted by Dr. Carbone on serum samples (2) and frozen tissue from the pre-treatment biopsy; plasma samples potentially also may be used for this analysis.

10.2.1 Tissue from Pre-Treatment Biopsy (9/15/05)

Tissue blocks of pretreatment biopsy specimens are preferred. If this is not possible, a 2 mm plug of tumor tissue should be removed from the tumor tissue block and submitted. This method is preferable to submission of unstained slides, which lose antigen reactivity over time with storage. A Specimen Plug Kit to facilitate removal of tissue in this way can be obtained from the RTOG Tissue Bank (see Appendix VII, Section A). If the submitting facility is not comfortable obtaining a plug from a block, the entire block may be sent to the tissue bank at LDS Hospital, where the tissue bank staff will remove the plug and return the entire remaining block to the submitting facility. Please notify the tissue bank in writing if this procedure is requested when submitting the block.

If submission of a tissue block or plug of tissue is not possible, then tissue blocks should be sectioned at a thickness of 5 microns and placed onto SuperFrost/Plus slides (Fisher Scientific). Sites will submit fifteen sections per case (fewer will be accepted if tissue availability is limited). Slides with cells from needle aspirates also are acceptable. Label specimens with the patient case number and the protocol numbers (0412/S0332). Blocks/slides should be shipped at ambient temperature to the RTOG Tissue Bank (address above) as described in Section 10.3.1. DO NOT SHIP ON DRY ICE.

NOTE: In addition, snap frozen pre-treatment tumor samples should be sent, if available, for proteomic analysis (see Section 10.2.2).

10.2.2 Pretreatment Tissue for MALDI-TOF

A subset of participating sites will have the capacity to prepare pre-treatment tumor tissue by snap freezing in liquid nitrogen without OCT media. Label specimens with the patient case number and the protocol numbers (0412/S0332) or attach the RTOG label. These specimens should be stored at -80°C for MALDI-TOF analyses and shipped as described in Section 10.3.2.

10.2.3 Tumor Tissue from Surgery (9/15/05)

Fresh frozen tissue (snap frozen tissue) from surgery is preferred. A Specimen Collection/Shipping Kit with instructions and all required supplies can be obtained from the RTOG Tissue Bank (see Appendix VII, Section B).
Additionally, tumor tissue from surgery that is fixed and paraffin-embedded is acceptable and should be handled exactly as described in Section 10.2.1.

10.2.4 Blood (9/15/05)
Sites will collect blood at 2 time points: (1) pre-treatment and (2) at the start of the third cycle of Consolidation Chemotherapy. At pre-treatment collection, 15 ml of blood will be collected from each patient, one 5 ml red top tube for serum, and either two 5 ml tubes or one 10 ml purple top tube (with EDTA) for plasma and cellular analyses. At the second time point (start of the third cycle of Consolidation Chemotherapy), only the 5 ml red top tube will be collected.

The red top tube should be allowed to clot for 30 minutes at room temperature, then be spun down in a standard clinical centrifuge at ~2500 RPM at 4ºC for 10 minutes. The supernatant (serum) should be collected and frozen in the 1 ml aliquot cryovials and then frozen at -80ºC before shipment on dry ice. Use cryovial tubes supplied in the Tissue Bank kit and clearly label as “Serum.” All tubes must be labeled with the patient case number and protocol number (0412/S0332) or attach the RTOG label.

EDTA tubes should be spun in a standard clinical centrifuge at ~2500 RPM at 4ºC for 10 minutes. Centrifuge within one hour of collection. If the interval between specimen collection and processing is anticipated to be greater than one hour, then the tube(s) should be kept on ice until centrifuging is done.

Collect the supernatant (plasma) from the EDTA tubes, aliquot and freeze the plasma in the three (3) 1 ml cryovials supplied in the Tissue Bank kit and clearly label as “Plasma.” All tubes must be labeled with the patient case number and protocol number (0412/S0332), or attach the RTOG label. The plasma samples need to be frozen at -80ºC before shipment on dry ice.

After the plasma has been removed, carefully remove the buffy coat layer (see diagram of buffy coat in Appendix VII Section B for a visual description of the buffy coat layer) and place it into the three (3) cryovials supplied in the Tissue Bank kit and clearly label as “Buffy Coat.” All tubes must be labeled with the patient case number and protocol number (0412/S0332) or attach the RTOG label. The buffy coat layers should be stored at room temperature and placed into the ambient compartment of the shipping box when mailed to the Tissue Bank (please see Appendix VII Section B for detailed information on collection/shipping).

10.3 Specimen Shipping
10.3.1 Fixed Tissue from Pretreatment Biopsy
Specimens of paraffin-embedded fixed tissue blocks or slides of fixed tissues or cells should be shipped to the RTOG Tissue Bank in appropriate mailing containers with adequate wrapping or cushioning to protect the specimens. These specimens should be sent at ambient temperature, not on wet or dry ice, and should be sent by standard delivery method to the address above. Pertinent paperwork as described in Sections 10.1.1-10.1.4 should be included in the mailing container. Fixed tissue specimens for patients on this study may be sent in batches, if it is within 30 days of collection.

10.3.2 Frozen Tissue, Serum, Plasma, and Buffy Coat Cells (9/15/05) (10/31/05)
A Specimen Collection/Shipping Kit with instructions and all required supplies can be obtained from the RTOG Tissue Bank (see Appendix VII, Section B). Cryo tubes containing frozen tissue, serum, plasma, or buffy coat cells must be wrapped in an absorbable material (i.e., paper towels) and placed in an airtight plastic freezer bag (i.e., resealable bag). Pack frozen specimens in the supplied (or other) heavy grade Styrofoam box with dry ice. Seal the box with plastic tape. All pertinent paperwork as described in Sections 10.1.1-10.1.4 should be placed in a plastic bag, sealed tightly and taped to the outside top of the Styrofoam box. Tissue, serum, plasma, or buffy coat cell specimens requiring specific infectious precautions should be indicated clearly, with the specific source of infectious concern listed, if known. Pack the Styrofoam shipping container in a cardboard box and mark the box “Biohazard.” Frozen tissue, serum, or plasma specimens for patients on this study may be sent in batches, if it is within 30 days of collection. Frozen specimens must be sent by overnight express to the RTOG Tissue Bank. NOTE: Do not include fixed tissue blocks, slides, or buffy coat specimens in the frozen compartment. Fixed tissue, slides, and buffy coat specimens should be sent in the ambient compartment of the shipping container. Specimens should be sent only Monday through Wednesday. Saturday deliveries will not be accepted.
10.4 Summary of Collection, Storage, and Shipment of Specimens for Translational Research
(9/15/05)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Collection/Storage</th>
<th>Shipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has pretreatment biopsy</td>
<td>Red top: make serum and freeze aliquots; Purple top: make plasma, spin and freeze aliquots</td>
<td>Freeze and store</td>
</tr>
<tr>
<td></td>
<td>Purple top: after removing plasma from EDTA tube, collect buffy coat layer and aliquot and store refrigerated until shipped</td>
<td>Send to Tissue Bank at ambient temperature</td>
</tr>
<tr>
<td></td>
<td>Frozen tissue (if possible) and freeze in aliquots</td>
<td>Freeze and store</td>
</tr>
<tr>
<td></td>
<td>Paraffin block or plug tissue sample</td>
<td>Send to Tissue Bank</td>
</tr>
<tr>
<td>Patient has surgery</td>
<td>Frozen tissue (if possible) and freeze in aliquots</td>
<td>Freeze and store</td>
</tr>
<tr>
<td></td>
<td>Paraffin block or plug tissue sample</td>
<td>Send to Tissue Bank</td>
</tr>
<tr>
<td>Start of 3rd cycle of Consolidation</td>
<td>Red top: make serum and freeze aliquots</td>
<td>Send all frozen samples to Tissue Bank</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10.5 Reimbursement (9/15/05) (10/31/05)
RTOG will reimburse submitting institutions $300 per case for fresh or flash/snap frozen tissue or for buffy coat samples, $200 per case for a block or core of material, or $100 per case for unstained slides or for serum or plasma specimens. One payment will be made for EACH instance of submissions for a patient (i.e., pre-treatment, surgery, etc.); thus, multiple payments are possible for some sample types for each case. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.6 Confidentiality/Storage
(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.) The RTOG Tissue Bank is approved by LDS Hospital’s IRB and meets all tissue bank regulations.

10.6.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.6.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.
### 11.0 PATIENT ASSESSMENTS

#### 11.1 Study Parameters (10/31/05) (2/16/06)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Post-Consent/Pre-Randomization</th>
<th>During Induction Therapy</th>
<th>Post-Induction Therapy Re-Evaluation&lt;sup&gt;n&lt;/sup&gt;</th>
<th>Post-surgery During Consolidation Therapy</th>
<th>Follow up&lt;sup&gt;°&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, Zubrod</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Histologic/cytologic assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mediastinal Eval</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor Response Eval</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event Eval</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with Diff, ANC, Calc Creatinine Clearance,</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFTs&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG-PET</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI of brain</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan of lungs and upper abdomen</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, DLCO</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung ventilation</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion scan</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trans. Research</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue submission</td>
<td>X</td>
<td></td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood draws</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional status &amp; Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT-L TOI</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Comorbidity: CCI and Recording Sheet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- a. Within 8 weeks prior to registration;
- b. Within 2 weeks prior to registration;
- c. Within 5 weeks prior to registration;
- d. Within 5 weeks prior to registration; Note: If an MRI is medically contraindicated, a CT scan of brain may be substituted;
- e. Highly recommended; required if FEV1 < 2.0 pre-study and if FEV1 is worse post-induction;
- f. LFTs must include alkaline phosphatase, bilirubin, and SGOT;
- g. Recommended pre-treatment for any patient with suspected endobronchial disease or for patients suspected of having lesions ≤ 2 cm from the main carina; recommended post-Induction only if initial bronchoscopy results impact on resectability;
- h. CBC with differential and ANC weekly during Induction Therapy and Consolidation chemotherapy; calculated creatinine clearance and LFTs prior to each dose/cycle of chemotherapy during Induction and Consolidation therapies;
- i. Post-Induction calculated creatinine clearance is not required;
- j. If an MRI is medically contraindicated, a CT scan of the brain may be substituted;
- k. Must include entire liver and adrenals;
l. Patient-reported functional status is done at 6 and 12 months post-surgery;
m. At surgery;
.n. Within 3-5 weeks after completion of Induction Therapy and no later than 1-3 weeks before surgery;
o. Follow up at 1 month after surgery; every 3 months for 1 year; every 6 months for 2 years; then annually.
p. See Section 10.2.4.
q. Highly recommended but not mandatory.

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 “evaluable” 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, 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:** 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 surgical resection. Response will be measured through evaluation of 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 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 CT or Physical Examination
- **Complete Response (CR):** Disappearance of all target lesions as measured by 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 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 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.

### 11.3 FDG-PET Imaging (11/18/05) (2/16/06)

**NOTE:** The first (staging) PET scan is mandatory; the second (post-induction) PET scan is optional although highly recommended. The electronic submission of the PET scan images to the RTOG/ACRIN is optional although highly recommended. Electronic submission of PET scan images is reimbursed (see below). Your institution (nuclear medicine) does not have to be credentialed with ACRIN in order to submit PET scans electronically, although if you are planning to submit the PET scan electronically, the submission should be performed according the specifications outlined below.

**Submission of PET data:** Each institution is required to call or e-mail Anthony Levering at RTOG Headquarters before submitting PET data for the first time:

Anthony Levering  
(215) 574-3244  
alevering@phila.acr.org

#### 11.3.1 PET Equipment

A dedicated BGO, LSO, or GSO PET scan unit must be used for both the pre-treatment and post-treatment PET studies in those patients whose PET data will be used in the analysis for the secondary objective (Section 2.2.5). The PET scanner must be capable of performing both emission and transmission images, in order to allow for attenuation-corrected PET images. The ability to calculate standardized uptake values (SUVs) also is mandatory. For questions regarding whether the PET scanner to be used is in compliance with this protocol, contact the PET Core Lab.

#### 11.3.2 Pre-FDG Injection: Participant Preparation

Participants must fast for a minimum of 4 hours prior to the injection of FDG for the PET scan. Blood glucose will be measured and recorded prior to the injection of FDG and must be ≤ 200 mg/dl. FDG will be synthesized and prepared in accordance with the institution’s standard procedures or obtained from a commercial supplier.

#### 11.3.3 FDG Injection

The administered activity of FDG should be based on the recommendation of the manufacturer of the specific PET scanner being used for the study. The recommended FDG dose is 0.14-0.21 mCi/kg. The actual FDG dose should be 10-20 mCi. A dose at the higher end of the range is recommended, if feasible, with appropriate reduction in the per kilogram dose for heavier patients (in accordance with the manufacturer’s recommendation).

#### 11.3.4 PET Imaging

Emission imaging will be started 45-60 minutes after FDG injection. The participant will empty his/her bladder immediately before the acquisition of images. The participant will be scanned supine and should be scanned with arms up, if possible. If PET data will be used to help with radiotherapy planning, it is recommended that the scan be done in a position as closely
approximating the radiation therapy treatment position as possible (the use of the participant’s customized radiation therapy immobilization device during the PET scan would be optimal).

The scanned volume will be from the upper/mid-neck to the proximal femurs. A series of transmission scans will be performed (to account for tissue attenuation) in addition to emission scans. The duration of acquisition for emission data should be in accordance with the manufacturer’s recommendations and the data must be corrected for scatter, random events, and dead-time losses using manufacturer’s software. Bed positions should be overlapped to avoid large changes in sensitivity at the joints between the bed positions.

11.3.5 Post-PET Imaging: Participant Care
The participant will empty his/her bladder again immediately following PET imaging.

11.3.6 Image Reconstruction and Analysis
Image reconstruction will depend on the scanner manufacturer. An iterative reconstruction method is recommended, with preference for OSEM reconstruction, 8 subsets, 2 iterations, followed by smoothing with a 6-mm 3D Gaussian kernel. Both visual/qualitative and quantitative (SUV) PET data analysis will be performed.

11.3.7 Determination of Standardized Uptake Value (SUV)
For the purposes of this study, the relevant SUV for calculation and reporting will be the “peak SUV” within the primary gross tumor volume and the most FDG-avid regional lymph node. This will be determined by the nuclear medicine physician visually identifying the region or regions on the PET images that qualitatively appear to have the most intense FDG uptake and that correspond to known tumor based on other data (such as CT scan). A circular region of interest 0.75 to 1.5 cm in diameter centered on the maximum-value pixel will be drawn, and the manufacturer’s algorithm will be used to calculate the mean SUV within this region; this value will be reported as the peak SUV. If two or more regions of interest are analyzed, the one with the higher peak SUV will be reported for the purposes of this protocol.

The SUV obtained and used for the primary endpoint of this study will not be corrected for body-surface area or other measure of patient size/shape. We will, however, also collect patient height and weight data and will perform exploratory analysis of SUV corrected for body-surface area to determine whether performing this correction provides more useful data than conventional, uncorrected SUV.

11.4 Post-treatment PET Imaging
11.4.1 The post-treatment PET scan is to be done according to the same specifications described in detail above (Section 11.3). The PET scan needs to be done on the same scanner (or, if this is not feasible, on the same model PET scanner) within the same institution used for the pre-treatment PET.

The post-treatment PET scan will be done approximately 3-5 weeks after the completion of all radiotherapy/chemotherapy that the participant has received and within 2 weeks of anticipated surgery. It will be done no sooner than 3 weeks after the completion of radiotherapy.

11.4.2 Post-treatment PET Scan Protocol Compliance
Per protocol: Post-treatment PET scan done according to Section 11.3 and done between 3 and 5 weeks after completion of chemotherapy and/or chemoradiation therapy.

Variation Acceptable: Post-treatment PET scan done on a different model PET scanner from the pre-treatment PET (but still within the same institution).

Variation Unacceptable: Any of the following will be considered an unacceptable variation (violation):
- Post-treatment PET scan done earlier than 3 weeks after completion of chemotherapy or chemoradiation therapy;
- Post-treatment PET scan done later than 6 weeks after completion of all chemotherapy or chemoradiation therapy;
- Post-treatment PET scan not done according to specifications of Section 11.3 (e.g. incorrect dosage of FDG; incorrect scan times).

11.4.3 Post-treatment PET Imaging: Interpretation and Implications of Qualitative Analysis
11.4.3.1 The post-treatment PET scan should be interpreted together with the pre-treatment PET scan, a post-treatment CT scan, and knowledge of the irradiated volume and other relevant clinical information.

11.4.3.2 With respect to metastatic disease, the post-treatment PET scan will be qualitatively analyzed and categorized using a 5-point scale:
1. Definitely no metastatic disease;
2. Probably no metastatic disease;
3. Indeterminate;
4. Probably metastatic disease;
5. Definitely metastatic disease.

See Section 3.1.3.1 regarding pre-surgical evaluation of suspected metastatic sites.

11.4.3.3 Since it is extremely difficult to quantify the size of a lesion(s) by PET scan, the conventional RECIST criteria will not be used for the qualitative, non-SUV-based PET scan interpretation after chemoradiotherapy. Instead, the qualitative visual criteria from Mac Manus et al.64 will be utilized, as follows:

- mCR: No tumor FDG uptake in the tumor bed, or activity in the tumor bed similar to that in the mediastinum;
- mPR: Appreciable reduction in intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side;*
- mNR: No appreciable change in intensity of tumor FDG uptake or tumor volume between scans and no new sites of disease apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side;*
- mPD: Appreciable increase in the intensity of tumor FDG uptake or volume of the tumor apparent to the nuclear medicine physician when pre- and post-treatment PET scans are displayed side by side.*

* For these determinations, the pre- and post-treatment PET scans must be analyzed using the same display techniques to provide a consistent intensity of background soft-tissue activity. Peak SUV will be determined as for the pre-treatment PET scan (see Section 11.3).

11.5 Reimbursement for PET Data Submission (10/31/05)
The Radiation Therapy Oncology Group will provide reimbursement ($250 per scan) to member institutions to support the digital submission of the pre- and post-treatment PET/CT scans to the PET Core Lab.

11.6 Patient-Reported Functional Status (10/31/05)
11.6.1 Patient-reported functional status will be assessed with the lung cancer subscales of the Functional Assessment of Cancer Therapy-Lung (FACT-L). The FACT-L is a 36-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). This questionnaire can be completed in less than 10 minutes. The Trial Outcome Indices (TOI) also will be utilized to measure the summed functional well-being, physical well-being, and the additional concerns (lung symptom module) subscales of the FACT-L. A five-point deterioration in the FACT-L TOI between pre-treatment and six months post-surgery will be considered clinically significant.

11.7 Comorbidity Data and Rating (10/31/05)
11.7.1 Site CRAs will complete the Comorbidity Recording Sheet and The Charlson Comorbidity Index (CCI) following the instructions in Appendix VI. The Recording Sheet and CCI must include the RTOG study number and case number; institution name and number; name of person completing the form; phone number of that person; and date of completion. The patient-specific label may be used; however, all pages must have a label affixed. Comorbidity data should be sent at the same time point as the initial assessment data (See Section 12.1) but will be submitted to:

Elizabeth Gore, M.D.
Fax 414-805-4369

Comorbidity rating is based on pretreatment history/physical, laboratory results, and pretreatment medications. Dr. Gore, Comorbidity Co-Chair will rate comorbidity based on the comorbidity data received from each institution using The Cumulative Illness Rating Scales for Geriatrics (CIRS-G).

11.7.2 Credit for Comorbidity Data Submission (10/31/05)
Institutions will receive cancer control credit per case for submission of comorbidity data. Credit will be given once valid data are submitted. Dr. Gore will notify RTOG Headquarters by sending a copy of the CIRS-G for each case rated.
### 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 (9/15/05) (10/31/05)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within two weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy (FACT-L) [FA]</td>
<td></td>
</tr>
<tr>
<td>Comorbidity Recording Sheet and</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index (see Section 11.7 for details)</td>
<td></td>
</tr>
</tbody>
</table>

**Initial Dosimetry Information:** (See Section 12.2 for PET)

- RT Prescription (Protocol Treatment) Form (T2) Within 1 week of start of RT
- Films (Simulation and Portal and/or DRRs) (T3)
- Dose Calculation Form (T4)
- Composite Isodose Distribution (T6) [Corrected and Uncorrected for Heterogeneity]

**Final Dosimetry Information:** (See Section 12.2 for PET)

- Complete Daily Treatment Record (T5) Within 1 week of RT end
- Off-Cord Films (Simulation and Portal) (T8)
- Radiotherapy Form (T1)
- Color DVH (DV) [Corrected and Uncorrected for Heterogeneity] (See Section 6.6.1 for details)

- Treatment Form (TF)
- Adverse Event (AE) Within 2 weeks of completing Induction Therapy and within 2 weeks of completing Consolidation Therapy

- Post-Induction Follow-up Form (FO)
- Functional Assessment of Cancer Therapy (FACT-L) [FA] Within 2 weeks of completing post-Induction Re-Evaluation
- Adverse Event (AE)

- Surgical Evaluation Form (S1) 30 days post-surgery
- Surgical Operative Report (S2)
- Surgical Pathology Report (S5)

- Functional Assessment of Cancer Therapy (FACT-L) [FA] At 6 and 12 months post-surgery

- Follow-up Form (F1)
- Adverse Event (AE) At 1 month after surgery; every 3 months for 1 year; every 6 months for 2 years; then annually. Also at progression/relapse and death, if these events occur between planned follow-up intervals.
12.2 Summary of PET Data Submission (6/16/05) (11/18/05)*

Data should be submitted to:

RTOG Headquarters
Attn: PET Core Lab
1818 Market Street, Suite 1600
Philadelphia, PA 19103
http://www.acrin.org/petcorelab.html

*Each institution is required to call or e-mail Anthony Levering at RTOG Headquarters before submitting PET data for the first time:

Anthony Levering
(215) 574-3244
alevering@phila.acr.org

Please provide a contact name and phone number with each PET data submission.

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
</table>
| Pre-treatment PET/CT Scan (Fused, if possible) [C5] | Arm 1: Within 2 weeks of study entry  
Arm 2: Within 1 week of start of RT |
| Pre-treatment PET/CT Scan Report (DR) | |
| PET Technical Assessment Form (TA) | |
| Local PET Semi Quantitative Form (IM) | |
| Post-treatment PET/CT Scan (Fused, if possible) [C6] | Within 12 weeks of study entry |
| Post-treatment PET/CT Scan Report (DR) | |
| PET Technical Assessment Form (TA) | |
| Local PET Semi Quantitative Form (IM) | |

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Comparison of overall survival (death from any cause)

13.1.2 Secondary Endpoints
- Comparison of progression-free survival
- Comparison of median survival time
- Comparison of treatment toxicity rates
- Comparison of clinical and pathologic response rates
- Comparison of overall survival and progression-free survival between patients with and without pCR
- Investigation of any association of molecular markers and overall survival, progression-free survival, and response
- Change in patient-reported functional status

13.2 Sample Size

13.2.1 Stratification
Patients will be stratified before randomization with respect to T stage (T1 vs. T2-3), the number of involved mediastinal nodal stations (1 vs. 2 or more vs. not evaluable), and nodal micrometastases vs. clinically involved nodes. The treatment allocation scheme described by Zelen84 will be used because it balances patient factors other than institution. Patients will be randomized to concurrent chemoradiotherapy followed by surgical resection or chemotherapy followed by surgical resection, with post-surgery chemotherapy in both arms.

13.2.2 Sample Size Derivation
The sample size calculations will address the specific primary hypothesis that the addition of RT to a preoperative chemotherapy treatment regimen delivered to patients with biopsy-proven T1-3, N2 non-small cell lung cancer (NSCLC) will result in an absolute 10% increase in the three-year overall survival rate compared to a preoperative chemotherapy treatment regimen. Secondary endpoints that will also be evaluated are progression-free survival, median survival...
time and treatment toxicity rates. INT 0139 was a phase III study assessing the survival differences between concurrent induction chemoradiation followed by surgery and the same chemoradiation therapy with no surgery. This earlier study showed a three-year overall survival rate of 38% in the surgical arm. The sample size estimate is based on the results from INT 0139.

Conditions to determine the required sample size for the overall survival endpoint are:

- Survival times are exponentially distributed with (at least approximately) constant hazards in both treatment arms;
- Induction chemotherapy without RT before surgery, the control arm, will have a three-year overall survival rate of 28% (translates to monthly hazard \( \lambda = 0.0354 \));
- Three-year overall survival rate of 38% is the expected outcome in the experimental arm (translates to monthly hazard \( \lambda = 0.0269 \));
- Two-sided test at \( \alpha = 0.05 \);
- Statistical power of 80%;
- Four-year accrual with three years of follow-up;
- Two interim significance tests and a final test are planned using O'Brien-Fleming boundary shape parameter of 0.0.

Using a group sequential design, we will require a total sample size of 532 to be accrued uniformly. An eligible/analyzable rate of 93%, achieved in the surgical arm of INT 0139, is assumed. Guarding against up to a 7% loss rate, the final targeted accrual for this study will be 574 cases.

13.3 Patient Accrual

Based on the series by Andre and colleagues, the resectable N2 population delineated by the eligibility requirements in the present trial account for approximately 50% of Stage II/III N2 patients. This accounts for a very frequently encountered clinical scenario for which there are currently no large randomized trials in the U.S. and for which the question of the potential value of radiation therapy in addition to induction chemotherapy alone is a widely noted, open clinical question. While the preceding North American Intergroup trial INT 0139 enrolled at a rate of approximately 5-6 per month, this trial was hindered by a randomization to a surgical versus nonsurgical approach that profoundly limited its acceptance by both patients and physicians. In contrast, the ongoing Southwest Oncology Group trial S0022 that targets patients with unresectable locally advanced disease administers a similar cisplatin-based chemotherapy regimen to that proposed here and without randomization to surgery versus no surgery; accrual for this trial has been in the range of 15-20 patients per month. Several other cooperative groups also have expressed interest in participating in this trial and contributing significantly to projected enrollment. Based on the importance of the clinical question to be answered by this study, the lack of essentially any competing studies for this clinical population at the present time, and the significant support for this trial within the broad thoracic oncology community, a realistic expectation of accrual at a rate of 10-12 patients per month is proposed.

The study design is based on a four-year accrual period with approximately 11 patient entries per month. If the monthly accrual falls below 9 cases after 18 months, the feasibility of continuing the study will be discussed at the RTOG Data Monitoring Committee (DMC).

13.4 Analysis Plan

13.4.1 Statistical Methods

All eligible patients randomized will be included in comparison of treatment arms (intent-to-treat analysis). The major analysis will take place after a positive significance test in either of the first two interim analyses or after all the patients have been entered in the study and followed for a minimum of three years or after 422 deaths have occurred, whichever comes later. Critical values used in the sequential analyses will preserve an overall alpha level of .05 for the study. Overall survival will be estimated by the Kaplan-Meier method. The overall survival estimates between the two arms will be compared using the log-rank test and the Cox proportional hazard regression model. The association between pCR and overall and progression-free survival will be investigated using the Cox proportional hazards model. Time at risk for each patient will be included in the model as a time-dependent variable. Toxicity rates will be tested for equality using a two-sided z-test with a 0.05 significance level after transforming the proportions in each arm to an approximate standard normal random variable.
If more than one toxicity rate is tested, a Bonferroni adjustment to the alpha level of 0.05 will be made to protect the overall significance level.

13.4.2 Interim Analysis to Monitor the Study’s Progress

There were 14 treatment-related deaths on the surgical arm of the INT 0139 study, based on the assessment of the 154 patients who underwent thoracotomy at the time of ASCO 2003 analysis (out of the total of 201 patients eligible and 216 total patients enrolled). Seven out of 14 patients died within 30 days from surgery, and all patients were discharged from the hospital before 30 days. Ten out of 14 patients died within 60 days after surgery. Four patients died later than 60 days (at 68; 315; 380 and 416 days after surgery, respectively).

Using the 154 patients known to have had a thoracotomy at the time of presentation, the treatment-related mortality within 60 days of surgery was 6.5% (10/154). Another analysis of mortality data is pending in October 2004.

Since a novel chemotherapy agent (docetaxel) will be combined with cisplatin and thoracic RT preoperatively in the proposed study, particular care will be taken to monitor the treatment-related mortality in the RT arm, within the same period as on INT 0139. There will be five formal interim analyses of the post-surgical mortality of patients randomized to the preoperative thoracic radiation therapy (RT) with concurrent chemotherapy followed by surgical resection arm. Patient death within 60 days of surgery will be considered post-surgical mortality. Using the following critical values assures 85% statistical power to detect a 10% or higher post-surgical mortality rate:

- 2 post-surgical deaths out of the first 25 patients randomized, or
- 6 post-surgical deaths out of the first 50 patients randomized, or
- 10 post-surgical deaths out of the first 75 patients randomized, or
- 13 post-surgical deaths out of the first 125 patients randomized, or
- 17 post-surgical deaths out of the first 175 patients randomized.

If the number of post-surgical deaths exceeds any of these critical values at any of the five interim analyses or the total percentage of post-surgery deaths exceeds 10% of the number of randomized patients on the preoperative thoracic radiation therapy (RT) with concurrent chemotherapy followed by surgical resection arm during the follow-on monitoring after 175 patients have been randomized, accrual to the trial will be temporarily suspended while the study chairs, the RTOG Lung Cancer Committee Chair, and the RTOG Executive Committee are notified. This group, with others they determine are necessary, will review the deaths to determine which are treatment-related and prepare a report for the RTOG DMC. The RTOG DMC will be asked for a recommendation regarding revising the treatment regimen or closing the trial due to excessive surgical mortality in the preoperative thoracic radiation with concurrent chemotherapy followed by surgical resection arm

Surgical mortality and morbidity will be monitored semi-annually by the RTOG DMC. The criteria for assessing surgical mortality are described in the preceding paragraph. The surgical morbidities of most concern include pneumonitis, ARDS, and bronchopleural fistula. The expected rate of these morbidities in the chemotherapy followed by surgical resection arm are low (under 4%), so a rate of 3 times the rates reported on the non-RT arm, not to exceed 10%, on the RT with concurrent chemotherapy followed by surgical resection arm is acceptable. If these standards are exceeded, the RTOG DMC will be asked for a recommendation regarding revising the treatment regimen or closing the trial due to excessive surgical morbidity.

13.4.3 Significance Testing for Early Termination and Reporting

Two interim treatment comparisons shall be performed when we observe 33% (140 deaths) and 67% (283 deaths) of the 422 required maximum number of deaths. The results will be reported to the RTOG DMC with the treatment blinded.

At each planned interim analysis, the p-value from the test for assessing treatment efficacy, and the conditional power for the alternative hypothesis given the observed data will be reported to the RTOG Data Monitoring Committee (DMC). A low conditional power indicates a small probability of a significant treatment effect if future follow-up events are assumed to follow the same distribution under the alternative hypothesis. The responsible statistician may recommend early reporting of the results and/or stopping the trial if the treatment effect, with
respect to overall survival, is highly significant. That is, the p-value is less than the nominal value specified in a sequential design, or if the conditional power is less than 20%. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study are also taken into consideration with the p-value and conditional power. The DMC will then make a recommendation about the trial to the group chair.

13.4.4 Analysis For Reporting the Initial Treatment Results
The primary hypothesis of this study is whether the addition of radiation therapy will increase the three-year overall survival rate compared to induction chemotherapy alone. The major analysis of the primary endpoint, overall survival, will occur after at least three years of follow up or after 422 deaths, whichever is latest, unless an early stopping rule is satisfied in one of the two interim analyses. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit measured by the three-year overall survival rate will be tested using the log-rank test on Kaplan-Meier estimates and separately in a Cox proportional hazard model with the major stratification factors included as fixed covariates. Additional analyses of treatment effect will include modifying factors such as age, race, and other patient characteristics. These analyses will also use the Cox proportional hazards model. The treatment comparison of progression-free survival will use the log-rank test with either progression or death without progression as the event for the endpoint. A two-sided test of the hypothesis of no difference between toxicity rates in the two arms will be tested using the z-statistic for testing binomial proportions after transforming to approximate standard normal values. Where feasible, treatment comparisons with respect to the primary and secondary endpoints will be compared within each ethnic category.

13.4.5 Clinical Data Update System (CDUS) Monitoring
This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5 Analysis of Molecular Markers by Gene Expression
Baseline gene expression levels will be summarized overall and according to response, using medians, quartiles and ranges — or if a transformation is found to render the data compatible with the normal assumptions, with means, standard deviations and confidence intervals. The association with progression-free survival or overall survival will be assessed by dichotomizing the measures of gene expression at the median (or by previously established cut-points) and constructing Kaplan-Meier plots.

All eligible patients randomized with usable tissue specimens will be included in the analyses of molecular markers. If insufficient tissue is available to perform all of the proposed assays, the ERCC1 expression studies will be the first priority. The XRCC1, TUBB III, and MAP4 molecular markers will be treated as exploratory endpoints, and the median expression level of each will be used as the cutpoint; if there are results published after the activation of this protocol that establish or suggest meaningful cutpoints for this patient population, these cutpoints also will be investigated in the analysis of the molecular markers for this study. We will assume, for planning purposes, that the rate of return of samples will be 50%. This will yield 266 cases evenly divided across treatment arms. Patients will be accrued over four years with an additional three years of follow-up. Assuming a median survival of 22.7 months, statistical tests at the 2-sided .05 level will be powered as follows:93

13.5.1 ERCC1
As found in Lord, et al.,41 we assume a prevalence of 50% for abnormal ERCC1 mRNA, using a median ERCC1 expression relative to the expression of the internal control housekeeping gene β-actin of 6.7 x 10^-3. With these assumptions, the statistical power to test for a hazard ratio for overall survival of 1.59 in favor of ERCC1-normal is 88%. A cutoff value of 5.8 x 10^-3 also will be tested because this value was shown in a previous study to be associated with overall survival for patients with gastric cancer.94 Similarly, assuming a prevalence of 50% for the abnormal ERCC1 polymorphism of interest, the statistical power to test for a hazard ratio for overall survival of 1.59 in favor of ERCC1-normal is 88%.
13.5.2 **XRCC1, TUBB III, and MAP4**

We will use a data-derived median value cutpoint so the prevalence of abnormal expression of these molecular markers in NSCLC patients will be 50%. Thus, the statistical power to test for a hazard ratio for overall survival of 1.59 in favor of normal molecular marker levels is 88%. Assuming a prevalence of 50% for the XRCC1 polymorphism of interest, the statistical power to test for a hazard ratio for overall survival of 1.59 in favor of XRCC1-normal is 88%.

13.5.3 Prior to testing for survival differences among these markers, we will test for a treatment arm by marker interaction, though an interaction is not expected and statistical power for these tests will be poor. For example, if marker prevalence is 50%, the statistical power to detect treatment by marker interactions, when there is no effect of the marker in one treatment arm (patients receiving RT) and a hazard ratio (by marker status) of 1.5 in the other, is under 50%.

13.5.4 An exploratory analysis of shed tumor DNA, including the mutational status of K-RAS and the methylated promoter of p16, will investigate the association of these markers with patient response and outcomes (overall survival, progression-free survival). Analysis will include but not be limited to logistic regression for dichotomized patient response for different levels of response (e.g., CR, yes or no; PR/CR, yes or no) and proportional hazards modeling for time-to-event outcomes. Pre-treatment and post-surgery marker values will be considered individually and as repeated measures in a GEE model (dichotomized patient responses) and as change values adjusting for pre-treatment levels in the proportional hazards modeling (time-to-event outcomes).

13.6 **Proteomic Analysis of Tumor Tissue**

Mass spectrometry technologies make it possible to simultaneously measure hundreds of proteins in a particular tissue. One of the complicating factors of MALDI-TOF mass spectrometry is the alignment of protein spectra across multiple samples. This is a challenge since the peaks shift from spectrum to spectrum in a nonlinear manner. One approach to aligning peaks across spectra is to do it by hand using the human eye. However, this can be very time consuming, especially if the number of spectra is large. In response to this challenge, we have developed a machine learning strategy for the automated alignment of multiple spectra in parallel. This is carried out using an evolutionary computing algorithm that simultaneously determines an optimal set of bins for categorizing each peak as a specific protein. Here, optimal bins are identified as those that maximize the number of single peaks within each bin across the spectra while minimizing the number of bins that have multiple peaks within a spectrum. With the aid of our 300-processor parallel computer cluster, the evolutionary computation search can determine the optimal bins for many spectra in less than an hour. This is in contrast to the several days that it takes a single human to align the spectra by hand. We have demonstrated that this is an effective approach in a recent proteomics study of lung cancer in collaboration with Vanderbilt's Lung Cancer SPORE investigators. This approach will be refined by Jason Moore and his colleagues at Dartmouth and utilized here to bin all protein mass spectrometry data. We will continually improve and evaluate the algorithm and its performance. We will utilize new versions of the algorithm or more powerful approaches as they become available.

The statistical analyses for the primary objective will be focused on the following steps: (a) Apply the MS profile and most significant MS features from our existing study to evaluate and refine the profile and significant MS features on different cohorts. The selection of significant MS features was based on the Kruskal-Wallis test, Fisher’s exact test (dichotomize the expression level as present or not), the permutation t-test, Significance Analysis of Microarrays (SAM), Weighted Gene Analysis (WGA), and the modified information score method, and the cutoff points for each method were p<0.0005, p<0.0005, p<0.0005, 2, 2 and 0 respectively. The feature was included on the final list if it met at least two of these six selection criteria. (b) The Weighted Flexible Compound Covariate Method (WFCCM) will be employed in the class-prediction model based on the selected features to determine whether the proteomic patterns may be used to classify study samples into two classes, e.g., cancer vs. non-cancer. We will estimate the misclassification rate based on the closeness of the distance from the two classes. (c) For some endpoints, e.g., node + vs. node -, we will retrain the refined and existing data sets then apply the results to an independent testing cohort. (d) The agglomerative hierarchical clustering algorithm will be applied to investigate the pattern among the statistically significant discriminator features as well as disease status using M. Eisen’s software. The detailed statistical methods are provided at http://www.vicc.org/biostatistics/lancet/methods.pdf.
We will be testing the following profiles: 1) Prediction of response to chemotherapy or chemo/radiation by pre-treatment serum proteomics; 2) Evaluation of tumor burden and recurrence by serial serum proteomic analysis; 3) Prediction of outcome by proteomic analysis of post-therapy resection tumor samples; and 4) Pilot studies of survival prediction by tumor proteomics in pre-treatment tumor samples.

13.6.1 Power Analysis and Sample Size Calculation

All eligible patients randomized with usable tissue specimens will be included in the proteomic analysis of tumor tissue. Because multiple variable protein expression data has not been well studied, we relied on simulation methods to generate an estimate of power. We simulated a 1,500 variable dataset for a sample size of 200. Each variable represents a certain molecular weight or a protein. The total sample size for this trial is 574 (287 patients in each arm), out of 287 patients in each arm, we need at least 100 patients tumor samples from each arm (approximately 35%) in order to have a meaningful statistical analysis. We will attempt to collect as many fresh frozen tumor samples as possible in this trial, and we believe collecting 35% of tumor sample is an achievable goal. Using 2,000 such simulations, we determined that cluster analysis has greater than 80% power to correctly classify observations into two groups (good prognosis group vs. poor prognosis group) at a misclassification rate of less than 5% per group when there is a 1.5 standard deviation difference in the means of 1% or 15 of the 1,500 variables.

13.6.2 Statistical Analysis of Proteomic Data

The statistical analyses for the proteomic data will focus on the following steps: (1) selecting the important proteins differentially expressed among the good prognosis patients (patients who survive more than 2 years) and poor prognosis patients (patients who live less than 2 years); (2) using the class prediction model based upon the Compound Covariate Method\textsuperscript{99-100} and the Weighted Flexible Compound Covariate Method (WFCCM)\textsuperscript{97-98} to verify if the proteins selected in step one have the statistically significant prediction power on the study patients; and (3) employing the agglomerative hierarchical clustering algorithm\textsuperscript{101} to investigate the pattern among the statistically significant discriminator proteins as well as the biologic status.

The selection of important proteins will be based on Kruskal-Wallis test, Fisher’s exact test (dichotomize the expression level as present or not), permutation t-test, Significance Analysis of Microarrays (SAM),\textsuperscript{95} Weighted Gene Analysis (WGA),\textsuperscript{91} mixed effect model,\textsuperscript{102} and the modified information score method.\textsuperscript{96}

The Weighted Flexible Compound Covariate Method will be employed in the class-prediction model based on the selected proteins. This method was designed to combine the most significant proteins associated with the biologic status from each analysis method, e.g., Kruskal-Wallis test, Fisher’s exact test, permutation t-test, SAM, WGA, Mixed effect model, and modified info score. In other words, the WFCCM is an extension of the compound covariate method that allows considering more than one statistical analysis method into the compound covariate. The WFCCM for tumor sample $i$ is defined as $WFCCM(i) = \sum_{j} \left[ \sum_{k} (ST_{jk}) \right] \left[ W_j \right] x_{ij}$, where $j$ represents statistically significant protein $j$, $x_{ij}$ is the log-ratio measured in tissue sample $i$ for protein $j$, $ST_{jk}$ is the standardized statistic, e.g., t-statistic, for statistical analysis method $k$, $W_j$ is the weight of protein $j$ defined as $W_j = [\sum_{k} I_{jk} / K] \{ 1 – Info Score_j \}$, $I_{jk} = 1$, if the protein $j$ was statistically significant in method $k$ and $I_{jk} = 0$, if the protein $j$ is not statistically significant in method $k$.

The class-prediction model will be applied to determine whether the patterns of protein expression can be used to classify tissue samples into two classes according to the chosen parameter, e.g., good prognosis group vs. poor prognosis group. We will estimate the misclassification rate using leave-one-out cross-validated class prediction method, including re-selection of the significant proteins, based on the WFCCM.\textsuperscript{103} This leave-one-out cross-validated method will be processed in four steps. First, one tissue sample will be selected and removed from the data set, and the significant proteins will be selected as described previously. Second, WFCCM will be applied to calculate the single compound covariate for each remaining tissue sample based on the significant proteins, and the distance between two tissue classes for the remaining tissue samples will be calculated. Third, the removed tissue sample will be classified based on the closeness of the distance of two tissue classes. Fourth, steps 1 through 3 will be repeated for each tissue sample. To determine whether the accuracy for predicting membership of tissue samples into the given classes (as measured by the number of
correct classifications) is better than the accuracy that can be attained for predicting membership into random grouping of the tissue samples, we will create 5,000 random data sets by permuting class labels among the tissue samples. The cross-validated class prediction will be performed on the resulting data sets and the percentage of permutations that result in as few or fewer misclassifications as for the original labeling of samples will be reported. If less than 0.05 of the permutations result in as few or fewer misclassifications, the accuracy of prediction into the given classes will be considered significant.

The agglomerative hierarchical clustering algorithm\textsuperscript{101} will be applied to investigate the pattern among the statistically significant discriminator proteins as well as the biologic status using M. Eisen’s software.\textsuperscript{53}

### 13.7 Imaging Predictors of Outcome: FDG-PET

Assuming 532 eligible and analyzable patients accrued over four years with three years of follow-up, exponential survival, constant hazard rates between groups and a 40-53% FDG-PET adequate response assessment rate (between 213-282 patients with pre- and post-treatment FDG-PET assessments), we can achieve at least 90% statistical power for each hypothetical distribution listed in the table below using a 2-sided 0.05 alpha level log-rank test.

<table>
<thead>
<tr>
<th>3-year survival, CR or PR by FDG-PET</th>
<th>3-year survival, No CR or PR by FDG-PET</th>
<th>% with CR or PR by FDG-PET</th>
<th>% with No CR or PR by FDG-PET</th>
<th>Sample size for 90% statistical power</th>
</tr>
</thead>
<tbody>
<tr>
<td>.48</td>
<td>.25</td>
<td>.60</td>
<td>.40</td>
<td>162</td>
</tr>
<tr>
<td>.48</td>
<td>.25</td>
<td>.50</td>
<td>.50</td>
<td>152</td>
</tr>
<tr>
<td>.46</td>
<td>.25</td>
<td>.40</td>
<td>.60</td>
<td>155</td>
</tr>
<tr>
<td>.46</td>
<td>.25</td>
<td>.60</td>
<td>.40</td>
<td>188</td>
</tr>
<tr>
<td>.46</td>
<td>.25</td>
<td>.50</td>
<td>.50</td>
<td>177</td>
</tr>
<tr>
<td>.46</td>
<td>.25</td>
<td>.40</td>
<td>.60</td>
<td>181</td>
</tr>
<tr>
<td>.44</td>
<td>.25</td>
<td>.60</td>
<td>.40</td>
<td>225</td>
</tr>
<tr>
<td>.44</td>
<td>.25</td>
<td>.50</td>
<td>.50</td>
<td>213</td>
</tr>
<tr>
<td>.44</td>
<td>.25</td>
<td>.40</td>
<td>.60</td>
<td>218</td>
</tr>
<tr>
<td>.42</td>
<td>.25</td>
<td>.60</td>
<td>.40</td>
<td>280</td>
</tr>
<tr>
<td>.42</td>
<td>.25</td>
<td>.50</td>
<td>.50</td>
<td>265</td>
</tr>
<tr>
<td>.42</td>
<td>.25</td>
<td>.40</td>
<td>.60</td>
<td>272</td>
</tr>
</tbody>
</table>

### 13.8 Quality of Life Analysis

The primary patient-reported endpoint will be a difference in the deterioration from the pre-induction FACT-L TOI score to the score at 6 months post-surgery. This score measures functional status and a difference of 5 FACT-L TOI points will be considered clinically significant.\textsuperscript{104} We expect the arm receiving combination induction therapy to show more deterioration. Statistical power is at least 89% to detect a 5-point difference for a total sample size of 531 (assuming a 2-tailed test, alpha = .05, 29% attrition, a standard deviation of 14 at each time point and a test-retest correlation of .50).

The first analysis of change in QOL from baseline to 6 months will only be performed on patients who are still alive at 6 months, which assumes a missing-completely-at-random (MCAR) mechanism. An additional analysis of the six-month change will be based on the linear mixed model, which uses all available data at baseline, 6, and 12 months, and assumes a missing-at-random (MAR) mechanism. A final analysis assuming a missing-not-at-random (MNAR) mechanism will be performed using pattern-mixture models. The difference between treatments in six-month change will be considered significant only if it is significant under all three analyses.

Secondary quality of life outcomes will also be examined: deterioration in the FACT-L TOI score between the pre-induction assessment and the pre-surgery assessment; the rate of deterioration in FACT-L TOI and the FACT-L total scores over the one-year assessment period; the prognostic
value of the pre-induction FACT-L TOI score for clinical outcomes (e.g., SUV, progression-free survival, and overall survival). We will also compare the percentage of patients in each arm with an effect size for the change in FACT-L TOI scores between pre-induction and 6 months of < .2; this will allow us to compare the percentage of patients in each arm whose functional status remains more similar to baseline levels.

13.9 Comorbidity Index
The baseline comorbidity score will be presented descriptively and used to as a prognostic variable.

13.10 Gender and Minorities
13.10.1 Inclusion of Minorities
Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer; however, the RTOG did not show this to be the case. An analysis of race also 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 interactions between gender and treatments and race and treatments. Participation rates of men and women will be examined in the interim analyses. Based on accrual statistics from RTOG 93-09, the following table lists projected accrual by gender and race/ethnicity.

<table>
<thead>
<tr>
<th>Planned Gender and Minority Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Females</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
</tr>
</tbody>
</table>

| **Gender**                        |
| **Females** | **Males** | **Total** |
| American Indian or Alaskan Native  | 2         | 5         | 7         |
| Asian                                                | 2         | 5         | 7         |
| Black or African American                     | 14        | 28        | 42        |
| Native Hawaiian or other Pacific Islander        | 0         | 0         | 0         |
| White                                               | 183       | 335       | 518       |
| **Racial Category: Total of all subjects**         | 201       | 373       | 574       |
REFERENCES


REFERENCES (Continued)


REFERENCES (Continued)


37. Personal communication, SWOG 0022, April 2004.


REFERENCES (Continued)


REFERENCES (Continued)


REFERENCES (Continued)


REFERENCES (Continued)


Informed Consent Template for Cancer Treatment Trials
(English Language)

Study Title

PHASE III RANDOMIZED TRIAL OF PREOPERATIVE CHEMOTHERAPY VERSUS
PREOPERATIVE CONCURRENT CHEMOTHERAPY AND THORACIC RADIOTHERAPY
FOLLOWED BY SURGICAL RESECTION AND CONSOLIDATION
CHEMOTHERAPY IN FAVORABLE PROGNOSIS PATIENTS
WITH STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

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

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of two treatments on you and your lung cancer to find out which is better. The two treatments are:
- Chemotherapy followed by surgery
- Chemotherapy and radiation followed by surgery

In this study, you will get one of the two treatments, not both. However, all patients will receive chemotherapy after surgery.

How many people will take part in the study?

About 574 people will take part in this study.

What will happen if I take part in this research study? (9/15/05) (2/16/06)

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical exam
- Blood tests
- Tests of your lung function
- A PET (Positron Emission Tomography) scan: A computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein and imaging a few hours later
- An MRI (Magnetic Resonance Imaging) of your brain: Imaging using a strong magnetic field to look at one part of your body (or CT [Computed Tomography] scan: A study using x-rays to look at one part of your body, if advised by your doctor)
- A chest x-ray
• A CT scan of your lungs and stomach
• An EKG or echocardiogram (tests of your heart function), if advised by your doctor

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures **weekly during chemotherapy or chemotherapy and radiation therapy**:

- Blood tests

**Three to five weeks after you finish chemotherapy or chemotherapy and radiation therapy**, you will have the following tests. They are part of regular cancer care and are done to see how you and your cancer was affected by the treatment you received:

- A physical exam
- Blood tests
- Tests of your lung function
- An MRI of your brain
- A chest x-ray
- A CT scan of your lungs and stomach

Your study doctor may want you to have this test that is part of regular cancer care. It is being done more often because you are in this study.

- A PET scan 3-5 weeks after you finish chemotherapy or chemotherapy and radiation therapy

You will need these tests and procedures **weekly during chemotherapy** (after surgery). They are being done to see how you and your cancer was affected by the treatment you received.

- Blood tests

You will need these tests and procedures in follow up visits, **every 3 months for 1 year, every 6 months for 2 years, then annually**. They are being done to see how you and your cancer was affected by the treatment you received.

- A physical exam
- A chest x-ray
- A CT scan of your lungs and stomach
- Tests of your lung function

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

**If you are in Group 1** (often called “Arm” 1), you will receive two chemotherapy drugs, cisplatin followed by docetaxel, in your vein on days 1 and 22 of treatment. It will take about 2 hours each time you are given chemotherapy.

**If you are in Group 2** (often called “Arm” 2), you will receive the chemotherapy drug, cisplatin, in your vein on days 1, 8, 22, and 29 of treatment. You also will receive the chemotherapy drug, docetaxel, on days 1, 8, 15, 22, and 29. It will take about an hour each time you are given cisplatin and about one hour each time you are given docetaxel. When you begin receiving chemotherapy, you also receive radiation therapy, once a day, 5 days a week for about 5 weeks. Each radiation therapy treatment will take about 10 minutes.

**All patients** will be re-evaluated 3-5 weeks after completing chemotherapy or a combination of chemotherapy and radiation therapy to see if those treatments are controlling their cancer.
Following this re-evaluation, most patients will have surgery to remove all or most of the lung cancer 4-8 weeks after completing chemotherapy or a combination of chemotherapy and radiation therapy. 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.

Then 4-6 weeks after surgery, these patients will receive the chemotherapy drug, docetaxel, through the vein every 3 weeks x 3 cycles. Patients also will receive a drug, pegfilgrastim or filgrastim, to help their bone marrow make new white blood cells and fight infection. Pegfilgrastim is given 24 hours after each dose of docetaxel by an injection under the skin, while filgrastim is given starting 24 hours after each dose of docetaxel by injection under the skin on a daily basis for 10 days.

Patients whose cancer has progressed or who are too ill after chemotherapy or 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 and what non-surgery treatments you can receive.

When you are finished having treatment, you will be seen in follow-up visits every 3 months for 1 year, every 6 months for 2 years, then annually for your lifetime.

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.
How long will I be in the study?

If you are randomized to Group 1 and have surgery, you will receive chemotherapy for six weeks. About 1-2 months after chemotherapy, you will have surgery. You will receive chemotherapy again beginning about 1-2 months after surgery and will receive it every 3 weeks x 3 cycles. If you are randomized to Group 1 and don’t have surgery, the length of your treatment after six weeks of chemotherapy may vary, depending on your and your doctor’s decisions about your non-surgical treatment.

If you are randomized to Group 2 (chemotherapy and radiation therapy) and have surgery, you will receive treatment for 5-6 weeks. About 1-2 months after chemotherapy and radiation therapy, you will have surgery. You will receive chemotherapy again beginning about 1-2 months after surgery and will receive it every 3 weeks x 3 cycles. If you are randomized to Group 2 and don’t have surgery, the length of your treatment after 5-6 weeks of chemoradiotherapy may vary, depending on your and your doctor’s decisions about your non-surgical treatment.

After you are finished treatment, the study doctor will ask you to visit the office for follow-up exams every 3 months for 1 year, every 6 months for 2 years, then annually for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the chemotherapy, radiation, and/or surgery can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs or stop receiving radiation therapy. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks Associated With Cisplatin

Likely

- Tiredness and/or general weakness;
- Nausea and/or vomiting;
- Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding;
- Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath;
- Loss of appetite and/or weight loss;
- Ringing in the ears and/or hearing loss;
- Loss of muscle or nerve function, which may result in weakness or numbness in the hands or feet;
- Decrease in the kidneys’ ability to handle the body’s waste, which may be permanent

Less Likely

- Changes in electrolytes, which may result in tiredness, cramps, and/or numbness and tingling
• Involuntary movements, restlessness, muscle cramps, and/or loss of coordination;

**Rare**
• Hair loss;
• Loss of taste;
• Seizures;
• Allergic reactions, which can involve flushing, difficulty breathing, irregular heartbeat, low blood pressure, and can even be life threatening;
• Changes in vision;
• Changes in heart function;
• Another cancer called acute leukemia

**Risks Associated With Docetaxel**

**Likely**
• Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding;
• Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath;
• Tiredness and/or general weakness;
• Unusual sleepiness
• Nausea and/or vomiting;
• Mouth sores;
• Diarrhea;
• Loss of appetite, change in taste, and/or weight loss;
• Loss of hair;
• Headache;
• Shortness of breath;
• Muscle or joint pain;
• Changes in the nails;
• Inflammation of the eyes;
• Loss of feeling or numbness and tingling in fingers and toes

**Less Likely**
• Rash, redness and/or swelling of the skin;
• Allergic reactions, which may involve rash, fever, swelling, chills, or low back pain;
• Inflammation of veins;
• Irregular heartbeat;
• Lowered platelet count, which may increase risk of bleeding;
• Seizures;
• Liver inflammation, which may result in yellowing of skin and eyes, tiredness, and/or pain on upper right of the stomach area;
• Swelling of feet;
• Increased fluid around the lung and heart, which may result in shortness of breath;

**Rare but serious**
• Lung inflammation, which may involve shortness of breath, cough, and/or fever
• Death

**Risks Associated With Pegfilgrastim or Filgrastim (9/15/05)**

**Likely**
• Bone pain

**Less Likely**
• Hair loss;
• Nausea and/or vomiting;
• Diarrhea or constipation;
• Loss of appetite, change in taste, and/or weight loss;
• Tiredness and/or general weakness;
• Indigestion and/or stomach pain;
• Mouth sores;
• Fever;
• Headache;
• Difficulty sleeping;
• Muscle and/or joint pain;
• Swelling of legs;
• Dizziness

**Rare**

• Low oxygen levels in the blood

**Risks Associated With Radiation Therapy**

**Radiation To The Chest**

**Likely**

• The skin in the treated area may become reddened and/or dry; you may loose your chest hair, and the chest hair may not grow back;
• Difficulty, pain, or burning sensation when swallowing (this is temporary, usually beginning in the 2\(^\text{nd}\) or 3\(^\text{rd}\) week of treatment and usually ending after treatment is finished);
• Tiredness for no apparent reason, which is temporary;
• Cough;
• Some difficulty breathing

**Less Likely**

• Peeling of the skin in the treated area;
• Shallow skin ulcer (wound due to skin break down) in the treated area;
• Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily;
• Narrowing of the esophagus (swallowing tube), which may require dilation of the esophagus (stretching of the swallowing tube so you can swallow more easily)

**Rare but serious**

• Lung irritation due to treatment with coughing and shortness of breath that could be mild, moderate, or severe; rarely, this can cause death;
• 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

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 radiation therapy that some patients will receive 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/or radiation therapy before surgery. In a previous study of patients with lung cancer who received chemotherapy and radiation before surgery, 13 of 164 patients (about 7%) died within 60 days of surgery.

**Reproductive risks**
You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs and/or the radiation used in the study may make you unable to have children in the future."

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While doctors hope that a combination of chemotherapy and radiation therapy followed by surgery will result in better control of your lung cancer compared to chemotherapy alone followed by surgery, there is no proof of this yet. We do know that the information from this study will help doctors learn more about chemotherapy, radiation, and surgery as a treatment for cancer. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The Radiation Therapy Oncology Group and the Southwestern Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide patients and doctors greater access to cancer trials
- Sanofi Aventis Pharmaceuticals (manufacturers of docetaxel)

**What are the costs of taking part in this study? (2/16/06)**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.
A second PET scan (which may be done after initial chemotherapy/chemoradiotherapy and before surgery in this study) usually is covered by insurance. However, there is a chance that it might not be covered or that your insurer might cover it only partially. You may want to discuss this possible cost with your insurance company and your doctor before participating in this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ [telephone number].

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [Only applies to sites using the CIRB.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.
You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

Quality of Life

We want to know your view of how your life has been affected by cancer and its treatment. This “quality of life” part of the study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 1 questionnaire four times during the study: one before you begin treatment; one after you have completed chemotherapy or chemoradiation therapy; one 6 months after surgery, and the last one 12 months after surgery. It takes about 5 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the four questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life part of the study. I agree to fill out the four Quality of Life Questionnaires.

YES     NO

Health and Hospitalization

We want to know what illnesses other than cancer you have had or currently have and what hospitalizations you may have had. This information will be used to find out if there are factors that can predict recovery or outcome of patients with lung cancer.

If you decide to participate in this part of the study, the only thing you will be asked to do is answer some questions before you begin treatment. It takes about 10 minutes to answer these questions.

If any questions make you feel uncomfortable, you may choose not to answer. You may change your mind about answering these questions at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Health and Hospitalization part of the study. I agree to answer the questions involved.

YES     NO
About Using Tissue and Blood for Research

You are going to have a biopsy (or surgery) to confirm that you have lung cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

We also would like to send a small amount of your blood to a central office for future research. About 3 teaspoons of your blood will be drawn twice, before treatment and after surgery. These samples of your blood will be sent to the central office and may be used to learn more about cancer and other diseases.

Your tissue and blood may be helpful for research. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue or blood. Then any tissue or blood that remains will no longer be used for research and will be returned to (doctor/institution).

In the future, people who do research may need to know more about your health. While the ________ (doctor/institution) may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.
No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes  
   No

2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   
   Yes  
   No

3. Someone may contact me in the future to ask me to take part in more research.
   
   Yes  
   No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

   1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

   • For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
   • For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

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 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 self-care. Totally confined to bed or (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>
APPENDIX III

STAGING SYSTEM

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)
**APPENDIX III (Continued)**

AJCC Staging  

**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>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<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>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</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

<table>
<thead>
<tr>
<th>N2 Nodes – All N2 nodes lie within the mediastinal pleural envelope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Highest mediastinal nodes</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>2. <strong>Upper para-tracheal nodes</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>3. <strong>Prevascular and retro-tracheal nodes</strong></td>
</tr>
<tr>
<td>Prevascular and retro-tracheal nodes may be designated 3A &amp; 3P; midline nodes are considered to be ipsilateral</td>
</tr>
<tr>
<td>4. <strong>Lower para-tracheal nodes</strong></td>
</tr>
<tr>
<td>The lower para-tracheal 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, and contained within the mediastinal pleural envelope; the lower para-tracheal 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</td>
</tr>
<tr>
<td>Researchers may wish to designate the lower para-tracheal 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</td>
</tr>
<tr>
<td>5. <strong>Subaortic (aorto-pulmonary window)</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>6. <strong>Para-aortic nodes (ascending aorta or phrenic)</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>7. <strong>Subcarinal nodes</strong></td>
</tr>
<tr>
<td>Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung</td>
</tr>
<tr>
<td>8. <strong>Paraesophageal nodes (below carina)</strong></td>
</tr>
<tr>
<td>Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes</td>
</tr>
<tr>
<td>9. <strong>Pulmonary ligament nodes</strong></td>
</tr>
<tr>
<td>Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1 nodes - All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. <strong>Hilar nodes</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>11. <strong>Interlobar nodes</strong></td>
</tr>
<tr>
<td>Nodes lying between the lobar bronchi</td>
</tr>
<tr>
<td>12. <strong>Lobar nodes</strong></td>
</tr>
<tr>
<td>Nodes adjacent to the distal lobar bronchi</td>
</tr>
<tr>
<td>13. <strong>Segmental nodes</strong></td>
</tr>
<tr>
<td>Nodes adjacent to the segmental bronchi</td>
</tr>
<tr>
<td>14. <strong>Subsegmental nodes</strong></td>
</tr>
<tr>
<td>Nodes around the subsegmental bronchi</td>
</tr>
</tbody>
</table>
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. Are you willing to provide tissue samples for translational research, as specified in the protocol?

   YES ________ NO ________

   Comments:

4. The surgery arm of this study requires an operation for all patients after chemotherapy or 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:
5. 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

6. Please estimate the number of lobectomies and/or pneumonectomies you perform per year _____

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

8. If there are other surgeons at your institution who will be participating in this program, have they also filled out these forms?

YES  NO  (?)

9. Are you board certified in cardiothoracic surgery and do you have documentation of active certification?

YES  NO

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

Harvey I. Pass, M.D.
Department of Cardiothoracic Surgery
NYU School of Medicine and Comprehensive Cancer Center
530 1st Avenue, 9V
New York, NY 10016
(212) 263-7417
harvey.pass@med.nyu.edu

Signature of Surgeon completing this form  Institution Name

Printed Name of Surgeon  RTOG Institution Number

Telephone number of Surgeon  Physician's Fax Number

Group affiliation (please circle one): RTOG  SWOG  CALGB  ECOG  NCCTG

Return this form to your Research Associate

RTOG Research Associates: Fax the completed form to Dr. Pass, FAX (212) 263-2042.

Dr. Pass: 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

Harvey Pass, M.D. Thoracic Surgery Co-Chair  Date
Instructions for completing THE COMORBIDITY RECORDING SHEET:

1. Complete all patient/institution information or affix RTOG patient-specific label.
2. Extract all comorbidity elements you can identify and note them on the Recording Sheet. Place the elements in the most appropriate category. Be comprehensive. The rater (Dr. Gore) will determine the relevant diseases and modify the category if needed.
3. Include past surgeries, diseases, smoking history, and functional problems, such as incontinence or constipation.
4. For each condition include:
   - When (e.g., 6 months ago, 5 years ago, etc.);
   - Current symptoms;
   - Related treatment (e.g., surgery, stent placement, hearing aides, glasses, etc.);
   - Related laboratory values (e.g., CR, bilirubin);
   - Medications (scheduled/prn).
5. If a functional problem appears to be related to tumor or treatment, place TR after the diagnosis.
6. Specify as much as possible the dose/frequency of medications; the rater may use this information to rate the severity of a disease.
7. Leave the scoring column blank.

Instructions for completing THE CHARLSON COMORBIDITY INDEX:

1. Complete all patient/institution information or affix RTOG patient-specific label.
2. Follow the “Rules for Completing The Charlson Comorbidity Index” in this appendix.
3. Complete the Charlson Comorbidity Index by noting “yes” or “no” for each disease.

Contact Elizabeth Gore, M.D. at 414-805-4465 or bethgore@mcw.edu if you have questions.

Fax completed Comorbidity Recording Sheet and Charlson Comorbidity Index to Dr. Gore at 414-805-4369. Do not submit this data to RTOG Headquarters.
Completing the Comorbidity Recording Sheet

Examples of conditions in each category are listed below. The list is not all-inclusive. Please list other conditions that are present.

| Heart: | MI, Arrhythmia, CHF, Angina, Pericardial disease, Valvular disease |
| Vascular: | Hypertension, Peripheral vascular disease, Aneurysms, Blood abnormalities (anemia, leukopenia, etc.) |
| Respiratory: | Bronchitis, Asthma, COPD, Tobacco history (pack/year) |
| HEENT: | Vision impairment, Sinusitis, Hearing loss, Vertigo |
| Upper GI (esophagus, stomach, duodenum): | Reflux, PUD |
| Lower GI (intestines, hemia): | Constipation/Diarrhea, Hemorrhoids, Diverticulitises |
| Liver/Pancreas/GB: | Cholelithiasis/Cholecystectomy, Hepatitis/pancreatitis |
| Renal: | Creatinine, Stones |
| GU (ureters, bladder, urethra, prostate, genitals, uterus, ovaries): | Incontinence, UTI, BPH, Hysterectomy, Abnormal PAP smear, Bleeding |
| Musculoskeletal/Skin: | Arthritis, Osteoporosis, Skin cancer, Psoriasis |
| Neurological: | Headaches, TIAs/Stroke, Vertigo, Parkinson’s Disease/MS/ALS |
| Endocrine (record height and weight): | Diabetes, Hypo/hyperthyroid, Obesity |
| Psychiatric: | Dementia, Depression |

Rules for Completing the Charlson Comorbidity Index (CCI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>Hx of medically documented myocardial infarction</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Symptomatic CHF w/ response to specific treatment</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Intermittent claudication, periph. arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (&gt;=6cm)</td>
</tr>
<tr>
<td>Cerebrovascular disease (except hemiplegia)</td>
<td>Hx of TIA, or CVA with no or minor sequelae</td>
</tr>
<tr>
<td>Dementia</td>
<td>Chronic cognitive deficit</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>Symptomatic dyspnea due to chronic respiratory conditions (including asthma)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>Patients who have required treatment for PUD</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>Cirrhosis without PHT, chronic hepatitis</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
<td>Diabetes with medication</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td>Retinopathy, neuropathy, nephropathy</td>
</tr>
<tr>
<td>Hemiplegia (or paraplegia)</td>
<td>Hemiplegia or paraplegia</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>Creatinine &gt;3mg% (265 umol/l), dialysis, transplantation, uremic syndrome</td>
</tr>
<tr>
<td>2nd Solid tumor (non metastatic)</td>
<td>Initially treated in the last 5 years exclude non-melanomatous skin cancers and in situ cervical carcinoma</td>
</tr>
<tr>
<td>Leukemia</td>
<td>CML, CLL, AML, ALL, PV</td>
</tr>
<tr>
<td>Lymphoma, MM...</td>
<td>NHL, Hodgkin's, Waldenström, multiple myeloma</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>Cirrhosis with PHT +/- variceal bleeding</td>
</tr>
<tr>
<td>2nd Metastatic solid tumor</td>
<td>Self-explaining</td>
</tr>
<tr>
<td>AIDS</td>
<td>AIDS and AIDS-related complex Suggested: as defined in latest definition</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Score</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Respiratory (include tobacco history)</td>
<td></td>
</tr>
<tr>
<td>Eyes and ENT</td>
<td></td>
</tr>
<tr>
<td>Upper GI</td>
<td></td>
</tr>
<tr>
<td>Lower GI</td>
<td></td>
</tr>
<tr>
<td>Liver and Pancreas</td>
<td></td>
</tr>
<tr>
<td>Renal (Creatinine: )</td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal/Integument</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine/Metabolic and Breast</td>
<td></td>
</tr>
<tr>
<td>(Weight: Height: )</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Myocardial infarct</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Cerebrovascular disease (except hemiplegia)</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
</tr>
<tr>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Ulcer disease</td>
</tr>
<tr>
<td>Mild liver disease</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
</tr>
<tr>
<td>Hemiplegia</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
</tr>
<tr>
<td>2nd Solid tumor (nonmetastatic)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Lymphoma, MM...</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td>2nd Metastatic solid tumor</td>
</tr>
<tr>
<td>AIDS</td>
</tr>
</tbody>
</table>

Total points: _____________
Appendix VII
RTOG 0412/SWOG S0332

A. SPECIMEN PLUG KIT PROCEDURE (9/15/05)

Participating institutions can request specimen plug kits from LDS Hospital by calling or emailing Holly Goold (contact information below). EVERY SPECIMEN MUST BE LABELED WITH THE PROTOCOL NUMBER AND PATIENT CASE NUMBER (or use RTOG labels).

Contents of Specimen Plug Kit:

- 1 Shipping Tube
- 1 Dermal Needle

Instructions for Use of Specimen Plug Kit:

1. Place the dermal needle on the paraffin block over the selected tumor area. (Ask a Pathologist to select area.) Push needle into the paraffin block. Twist the needle once around to separate the plug from the block. Then pull the needle out of the block. The needle should be filled with tissue sample.
2. Label dermal needle with proper specimen ID. DO NOT try to remove specimen from needle.
3. Use a separate dermal needle for every specimen. DO NOT mix specimens.
4. Once the specimen needle is labeled, place it in the shipping tube, and ship to the address below.
5. The RTOG Tissue Bank will remove specimen from the needle, embed it in a cassette, and label it with the specimen ID.

Shipping:
Ship the specimen needle in the shipping tube and all required paper work to the address below:

LDS Hospital
Dept. of Pathology
EM Lab
8th Ave. & C St.
Salt Lake City, UT 84143

For questions, or if you need additional Specimen Plug Kits, please call or email:

Holly Goold
(801)- 408-5626
holly.goold@ihc.com
Appendix VII (Continued)

RTOG 0412/SWOG S0332

B. SPECIMEN COLLECTION/SHIPPING KIT PROCEDURE (9/15/05)

Participating institutions can request initial specimen collection/shipping kits from LDS Hospital by calling or emailing Holly Goold (contact information below). Each site will receive two kits with Fed-Ex shipping attached. When a site ships a kit to the RTOG Tissue Bank, a replacement kit will be sent to the site. EVERY SPECIMEN MUST BE LABELED WITH THE PROTOCOL NUMBER AND PATIENT CASE NUMBER.

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
holly.goold@ihc.com

Instructions for use of frozen tissue kit:

This kit includes:
- Biohazard wipes 4” x 4” (orange)
- Five (5) 5 ml cryovials
- Disposable scalpels
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Fed Ex shipping label

Preparation of Fresh Frozen Tissue:
- On sterile cutting board, lay out underpads.
- Keep biohazard wipes nearby to keep area clean throughout process.
- Label cryovials with RTOG study and case numbers

Process:
- Using provided disposable scalpel, evenly cut tissue into 5 separate pieces.
- Use forceps to place each piece into separate 5 ml cryovials.
- Place cryovials into liquid nitrogen.
- Once frozen, place all the cryovials into biohazard bag
- Use RTOG labels* to label bag.
- Store at –80°C Celsius until ready to mail.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:
- Include all RTOG paperwork in pocket of biohazard bag.
- Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (if appropriate; double-check sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.
- Notify Tissue Bank personnel at LDS Hospital before you send specimens via Fed Ex
- For questions regarding collection/shipping, please contact the Tissue Bank: Call (801) 408-5626 or (801) 408-2035; fax (801) 408-5020; or E-mail holly.goold@ihc.com or jsbryner@ihc.com.
Appendix VII (Continued)

RTOG 0412/SWOG S0332

B. SPECIMEN COLLECTION/SHIPPING KIT PROCEDURE (Continued)

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit:

This kit includes:
- Ten (10) 1 ml cryovials
- Biohazard bags
- Absorbant shipping material
- Styrofoam compartmentalized container (inner)
- Cardboard shipping (outer) box
- Fed Ex shipping label

Preparation of Serum:
- Label four (4) 1 ml cryovials with the RTOG study number, case number, and procedure date, and clearly mark cryovials “serum.”

Process:
- Allow one 5 ml red top tube to clot for 30 minutes at room temperature.
- Spin red top tube in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
- Aliquot serum into the four 1 ml cryovials labeled with the RTOG study and case numbers and procedure date and marked “serum.”
- Place cryovials into biohazard bag.
- Use RTOG labels* to label bag.
- Store at –80°C Celsius until ready to ship.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Preparation of Plasma:
- Label three (3) 1 ml cryovials with the RTOG study number, case number, and procedure date, and clearly mark cryovials "plasma."

Process:
- Spin EDTA (purple top) tube in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes. **Centrifuge within one hour of collection.**
- If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- Aliquot plasma into the 1 ml cryovials labeled with the RTOG study and case numbers and procedure date and marked “plasma.”
- Place cryovials into biohazard bag.
- Use RTOG labels* to label bag.
- Store at a minimum –80°C Celsius until shipped.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.
B. SPECIMEN COLLECTION/SHIPPING KIT PROCEDURES (Continued)

Preparation of Buffy coat:

For a visual explanation of Buffy coat, please refer to diagram below.

- Label three (3) 1 ml cryovials with the RTOG study number, case number, and procedure date, and clearly mark cryovials “buffy coat.”

Process:

- Spin EDTA (purple top) tube in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes. **Centrifuge within one hour of collection.**
- If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- Remove plasma close to the buffy coat and set plasma aside (can be used to send EDTA plasma samples – see above instructions).
- Remove the buffy coat cells carefully and place into the 1 ml cryovials labeled “buffy coat” (it is acceptable for a few packed red cells inadvertently to be collected in the process).
- Place cryovials into biohazard bag.
- Use RTOG labels* to label bag.
- Store buffy coat refrigerated until shipped (ship ambient). Buffy coat samples must be shipped to the Tissue Bank within one (1) week of collection.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:

- Include all RTOG paperwork in pocket of biohazard bag.
- Place frozen specimens and the absorbent shipping material in one compartment of the Styrofoam cooler and fill with dry ice (if appropriate; double-check sample shipping temperature). Place ambient specimens in the other compartment. Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.
- Notify Tissue Bank personnel at LDS Hospital before you send specimens via Fed Ex.
- For questions regarding collection/shipping, please contact the Tissue Bank: Call (801) 408-5626 or (801) 408-2035; Fax (801) 408-5020; or E-mail holly.goold@ihc.com or jsbryner@ihc.com.
A. Gene Expression Analysis in Specimens by Q-RT-PCR: We will use the technique of archival tissue quantitative RT-PCR (Q-RT-PCR) for ERCC1 and XRCC1 expression levels as detailed in our published work.\(^1,2\)

Total RNA is isolated by a single-step guanidinium isothiocyanate method using the QuickPrep Micro mRNA Purification Kit (Amersham Pharmacia Biotech Inc., Piscataway, NJ) according to the manufacturer's instructions. After RNA isolation, cDNA is prepared from each sample, as described previously.\(^2\) Quantitation of cDNAs and an internal reference gene (β-actin) is performed using a fluorescence-based, real-time detection method [ABI PRISM 7700 Sequence Detection System (TaqMan); Perkin-Elmer Applied Biosystems, Foster City, CA.], as previously described.\(^2,4\) The normalized gene expression levels will be correlated with patient clinical data.

Tumor Microdissection: A representative formalin-fixed, paraffin-embedded tumor specimen is selected after examination of the hematoxylin and eosin stained slides. Ten-micron thick sections are stained with neutral fast red to enable visualization of histology for laser capture microdissection (P.A.L.M. Microlaser Technologies AG, Germany), performed to ensure that only tumor cells are studied.

RNA Isolation and cDNA Synthesis: RNA isolation from paraffin embedded specimens is done according to a proprietary procedure (US patent number 6,248,535). Following RNA isolation, cDNA is prepared from each sample as described previously.

Real Time PCR for Measuring mRNA Levels: Quantitation of cDNAs and an internal reference gene (β-actin) is done using a fluorescence based real-time detection method (ABI PRISM 7700 Sequence Detection System [TaqMan\(^{®}\)], Perkin Elmer Applied Biosystems, Foster City, CA.) as previously described. In brief, this method uses a dual-labeled fluorogenic oligonucleotide probe that anneals specifically within the forward and reverse primers. Laser stimulation within the capped wells containing the reaction mixture causes emission of a 3’ quencher dye (TAMRA) until the probe is cleaved by the 5’ to 3’ nuclease activity of the DNA polymerase during PCR extension, causing release of a 5’ reporter dye (FAM). Production of an amplicon thus causes emission of a fluorescent signal that is detected by the TaqMan\(^{®}\)’s CCD (charge-coupled device) detection camera, and the amount of signal produced at a threshold cycle within the purely exponential phase of the PCR reaction reflects the starting copy number of the sequence of interest. Comparison of the starting copy number of the sequence of interest with the starting copy number of the reference gene provides a relative gene expression level. The PCR reaction mixture consists of 600 nM of each primer, 200 nM probe, 5 U AmpliTaq Gold Polymerase, 200 µM each dATP, dCTP, dGTP, 400 µM dUTP, 5.5 mM MgCl\(_2\), and 1 x TaqMan Buffer A containing a reference dye, to a final volume of 25 µl (all reagents Perkin Elmer (PE) Applied Biosystems, Foster City, CA). Cycling conditions are 50 °C for 10 min, 95 °C for 10 min, followed by 42 cycles at 95 °C for 15s and 60 °C for 1 min. TaqMan assays have been established for ERCC-1, XRCC-1, TS, DPD, TP, RR, XPD, and GST-P1.

Quality Control for mRNA Levels in Tumor Tissue: Briefly, ranging studies were performed by processing dilutions of identical specimens multiple times on different days. The range included TaqMan cycle thresholds of 29 to 35. The CV, precision and accuracy were determined in this range by running identical experiments on multiple days. The variation in measurement of the relative gene expression (TS/Actin) was less than 15% on a single day when analyzing more than 50 data points over the usable range of 29 to 35 cycle thresholds. The control variation (CV) between identical samples run on different days was not more than 20%. A series of control RNAs were purchased from Stratagene. These included RNA isolated from diseased colon, lung and breast specimens. The relative gene expression of these standards was determined for a number of targets by averaging twenty measurements. These RNAs are used as PCR plate calibrators. PCR data will not be reported from an experiment when the value of these controls varies more than 15% from the known value. When possible, RNA specific primers are used for quantitation. However, this is not always possible because of the short length of mRNAs isolated from archival tissues. Therefore, a non-reverse transcribed sample of the isolated RNA (no-RT control) is analyzed in order to quantitate the level of contaminating DNA in the specimen. Data from specimens containing more than 25% DNA will not be reported. Data from specimens measured at greater than 37 cTs (cycle thresholds) will likewise not be reported. All specimens are measured in triplicate by the delta cT method and an average value is reported for the ratio of the target gene to the housekeeping gene, β-actin. The cutpoint for abnormally high ERCC1 gene expression has been established to be 5.6 in a previous study.\(^1\)
**APPENDIX VIII (Continued)**

**B. Gene Polymorphism Analyses:** PCR-based approaches to polymorphism analyses of ERCC1 and XRCC1 will be done as has been previously published by our group. DNA is extracted from peripheral blood mononuclear cells (PBMCs) using a standard DNA extraction kit. The DNA is subjected to PCR, and repeat sequence variations are observed as different-sized PCR products migrating in acrylamide gels. DNAs with different from characterized repeat length variations are included in both the PCR and gel analyses as controls. For single nucleotide polymorphisms, PCR is used to amplify the region of interest. These PCR products are then subjected to DNA sequencing to identify the specific base differences and the polymorphic alleles in individual patients.

**C. Immunohistochemistry (IHC) Detection of Basal Levels of TUBB-III and MAP4:** IHC will be used to assess the levels of all three proteins. Staining will follow a similar protocol to what we have published for p53. Five µm paraffin-embedded tissue sections on SuperFrost/Plus slides (Fisher Scientific) are heated overnight at 60°C. Tissue sections are then de-paraffinized. For both tissue section and needle aspirate slides, endogenous peroxidase is quenched by a 30-min exposure to a 1% solution of H₂O₂ in methanol, followed by rehydration. Three plastic Coplin jars, each containing 5 slides immersed in a 10mM, pH 6.0 citrate buffer (Sigma) are centered in a 775 W turntable microwave oven (GE #J E922T001) and irradiated at power level 6 (465 W) for three 4-min cycles. The specimens are then rinsed in Ca++/Mg++-free phosphate-buffered saline (PBS, pH 7.4, Scy-Tek Laboratories, Logan UT). (This PBS solution is used for all rinses and diluents.) Non-specific antibody binding is blocked with a 1:10 dilution of normal goat serum (Gibco Laboratories, Grand Island, NY) for 30 min at room temperature. The samples are then incubated overnight at 4°C in an antibody/PBS solution at 1:200-1:400 final concentrations of primary antibody [TUBB-III: mouse anti-Beta-Tubulin III (Biogene, San Ramon, CA); Map4: anti-Map4 mAb (Transduction Laboratories, USA)]. Duplicate slides are exposed to appropriate concentrations of pre-immune serum: mouse IgG (Organon Teknika, Westchester PA). After rinsing in PBS, a goat anti-mouse biotinylated secondary antibody diluted 1:400 in a 0.5% solution of chicken ovalbumin (Sigma) in PBS is applied for 1 hr at room temperature. After rinsing, the samples are incubated as directed in avidin-biotin horseradish peroxidase complex (Vector Laboratories, Burlingame, CA) prepared in PBS/ovalbumin. The peroxidase reaction is developed with diaminobenzidene/H₂O₂ substrate for 15 min as directed (Scy-Tek). The slides are subsequently rinsed in running water, lightly counterstained with hematoxylin, dehydrated, cleared and mounted. Duplicate sections subjected to all phases of staining except the primary antibody serve as negative controls. Tissues are evaluated by light microscopy and photographed.

**D. IHC Scoring:** Scoring of TUBB-III and MAP4 staining will take into account percentage of positive tumor cells (from 0 to 100%) and intensity of staining (from 0 to 4+). The IHC score is established by multiplying the percentage of cells positive by the intensity, giving scores of 0-400. Two independent observers (Dr. Wilbur Franklin, University of Colorado and Dr. Regina Gandour-Edwards, University of California, Davis) will give scores without knowledge of response or patient outcome and each will be blinded to the reading of the other to provide a measure of inter-observer variability.

**E. K-RAS Mutation Analysis:** This study will be done in a purely exploratory fashion. Tumor cells will be enriched by microdissection, DNA extracted, and subjected to PCR according to standard protocols. DNA from micro-dissected tumor cells will be assessed by a sensitive two-step PCR-RFLP assay that detects all possible 12th codon-activating mutations in K-RAS. Mutations are confirmed by sequencing of the PCR products. If a patient’s tumor is identified to contain a K-RAS mutation, the patient’s plasma will be examined for the presence of the same mutation. The presence or absence of a K-RAS oncogene in the tumors will be correlated with patient clinical data.

**F. Shed Tumor DNA in Patient Plasma:** This study will also be done in a purely exploratory fashion. Assessment of shed tumor DNA K-RAS mutations in plasma of cancer patients has been established in Dr. Gumerlock’s laboratory, and the technical approach has been published. DNA from patient plasma will be assessed by the same two-step PCR-RFLP assay that detects all possible 12th codon-activating mutations in K-RAS. Again, mutations are confirmed by sequencing of the PCR products. The presence or absence of a K-RAS oncogene in plasma will also be correlated with the tumor data and with patient outcomes. As has been previously reported on the specimens from the Southwest Oncology Group S0003 trial, the presence of tumor DNA will be studied in the serial plasma specimens obtained from the patients on this trial.
APPENDIX VIII (Continued)

G. References


Appendix IX (214/07)

CTSU LOGISTICS

ADDRESS AND CONTACT INFORMATION FOR RTOG 0412/SWOG S0332

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the RTOG unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td>CTSU Patient Registration</td>
<td>RTOG Headquarters</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td>Voice Mail – 1-888-462-3009</td>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Phone - 1-888-823-5923</td>
<td>Fax – 1-888-691-8039</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td>Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)</td>
<td>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td></td>
<td>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</td>
<td></td>
</tr>
</tbody>
</table>

For patient eligibility questions:
Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.

For treatment-related questions:
Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at: http://members.ctsu.org

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION
Before recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU Regulatory Office before patient enrollments may proceed. All forms and documents associated with this study can be downloaded from the RTOG 0412/SWOG S0332 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.
Appendix IX (Continued)

Requirements for RTOG 0412/SWOG S0332 site registration (6/16/05):

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Radiation Therapy Facility Inventory Form (Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.)
- Thoracic Surgeon’s Questionnaire (Appendix V) for surgical credentialing. The site must complete and submit form to Dr. Pass within 7-10 days prior to enrollment of their first patient. Dr. Pass will then fax his approval to RTOG and the institution. Status of credentialing review will be posted on the RSS Site Registration Status screen [http://members.ctsu.org/Membrs_RSS_Apps.asp](http://members.ctsu.org/Membrs_RSS_Apps.asp)
- Request specimen collection/shipping kits from LDS Hospital per Appendix VII. Allow 7-10 days for processing of request.

Pre-study requirements for patient enrollment on RTOG 0412/SWOG S0332

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.
- Patient completes baseline QOL forms prior to treatment start.
- CRA completes Comorbidity Recording Sheet and Charlson Comorbidity Index for submission to Dr. Gore within two weeks of study entry.

CTSU Procedures for Patient Enrollment

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG 0412/SWOG S0332 Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and followup with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU registrar will contact RTOG within the confines of RTOG’s registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site via a confirmation e-mail or fax, followed by a data submission calendar and case specific labels with the patient ID number.

Induction therapy (chemotherapy or chemoradiotherapy) will begin within 7 days of randomization.

DATA SUBMISSION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0412/S0332 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

4. Please affix the RTOG study/case label to all source documentation and redact the patient’s name.
SPECIAL MATERIALS OR SUBSTUDIES

Radiation Therapy (section 12.0)
Dosimetry materials and data are to be submitted directly to RTOG Headquarters at the address in Section 12.0 of the protocol. See section 12.0 for a complete inventory of dosimetry items to be submitted.

Chemotherapy (protocol section 7.0):
Chemotherapy modality review will be performed to assess protocol compliance. Sites will receive a listing once a year outlining compliance for each case reviewed during that year.

Tissue/Specimen Submission—optional (section 10.0)
1. With patient’s consent, tumor, serum and plasma samples will be collected.
2. See protocol section 10.0 for detailed instructions on collection kits, preparation, and shipment of samples. Do not send specimens, forms, reports, or transmittals to the CTSU.
3. CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.5 of the protocol. Payments will be made in accordance with RTOG’s pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

PET Evaluations for Analysis of Study Objectives
PET digital data is required for a subset of patients who have both pre-randomization and post-treatment PET scans at the treating institution (or it’s affiliated PET facility).

Quality of Life:
QOL assessments will be performed pre-induction and at 6 months post-surgery. The FACT-L TOI (Form FA) should be submitted to CTSU Data Operations accompanied by a completed CTSU Data Transmittal Form.

Comorbidity Index (10/31/05):
The Comorbidity Recording Sheet and the Charlson Comorbidity Index (CCI) should be completed by the CRA per instructions in protocol section 11.6 and Appendix VI. These forms must be submitted directly to Dr. Gore who will notify RTOG Headquarters that the data have been received. RTOG will, in turn, notify CTSU. The site will receive cancer control credit for submission of valid comorbidity data.

ADVERSE EVENT (AE) REPORTING (6/16/05)
This study will utilize the CTCAE version 3.0 for toxicity and Adverse Event reporting. A hyperlink to the CTEP home page that contains CTCAE information is available on the CTSU website at http://members.ctsu.org/adeers_drug_info.asp. CTSU investigators are responsible for reporting serious adverse events via AdEERS in accordance with RTOG guidelines in section 7.8 of the protocol. Do not copy CTSU Data Operations Center on serious adverse event reports.

Secondary AML/MDS reporting:
CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the CTSU. Once received, the CTSU will send this information to RTOG, and RTOG will forward it on to the NCI.

Your local Investigational Review Board must be informed of all reportable serious adverse events.

DRUG PROCUREMENT (9/15/05):
CTSU investigators should refer to section 7.0 for detailed instructions on drug procurement, formulation, storage, administration, and potential toxicities.

Commercial agents: cisplatin, docetaxel, pegfilgrastim, filgrastim

REGULATORY AND MONITORING

Study Audit
To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site’s primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

**Clinical Data Update System (CDUS) Monitoring**

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.