

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

SCHEMA

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Stereotactic Body Radiation Therapy (SBRT),
20 Gy per fraction for 3 fractions over 1½-2
weeks, for a total of 60 Gy

Patient Population: (See Section 3.0 for Eligibility)

Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 tumors chest wall primary tumors only; no patients with tumors of any T-stage in the *zone of the proximal bronchial tree**. Patients with T3 tumors based on mediastinal invasion or < 2 cm toward carina invasion are not eligible.

*See Section 3.2.2 for details

Required Sample Size: 52

RTOG Institution # _____

RTOG 0236

ELIGIBILITY CHECKLIST (5/26/04) (6/14/05)

Case # _____

(page 1 of 2)

- _____ (Y) 1. Non-small cell lung cancer histologically confirmed by biopsy or cytology?
- _____ 2. TNM Stage:
_____ (Y) If T2 or T3, is primary tumor less than or equal to 5 cm?
_____ (Y) If T3, is primary tumor limited to chest wall?
- _____ (Y/N) 3. Are hilar or mediastinal lymph nodes > 1 cm on CT or demonstrating suspicious uptake on PET scan?
- _____ (Y) If yes, have all lymph nodes > 1 cm on CT or demonstrating suspicious uptake on PET scan been biopsied and are these negative for NSCLC?
- _____ (Y) 4. Based on evaluation by an experienced thoracic cancer clinician, is the primary tumor deemed technically resectable?
- _____ (Y) 5. Is the patient medically inoperable due to presence of severe underlying physiological health problems?
- _____ (Y) 6. Is patient ≥ 18 years of age?
- _____ (Y) 7. Is the patients Zubrod performance status 0-2?
- _____ (Y/NA) 8. Has the patient agreed to use an effective method of contraception?
- _____ (Y) 9. Have the required pretreatment evaluations and staging studies been obtained as specified in Section 3.1.8?
- _____ (N) 10. Is there evidence of distant metastases, or synchronous primary or prior malignancy within the past 2 years?
- _____ (N) 11. Any prior radiotherapy to the lung or mediastinum?
- _____ (N) 12. Are other concomitant cancer therapies planned?
- _____ (N) 13. Is there evidence of active systemic, pulmonary, or pericardial infection?
- _____ (N) 14. If female, is the patient pregnant or lactating?

(Continued on the next page)

RTOG Institution # _____

RTOG 0236

ELIGIBILITY CHECKLIST (5/26/04)

Case # _____

(page 2 of 2)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (above) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date

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 _____

1.0 INTRODUCTION

1.1 Stage I Non-small Cell Lung Cancer

Lung cancer remains the most frequent cause of cancer death in both men and women in North America. There were 173,600 new lung cancer cases in the United States in the year 2003 with an estimated 156,300 deaths due to this highly lethal malignancy. Lung cancer accounts for approximately 13% of all cancers diagnosed but 28% of all cancer deaths.¹ Seventy-five percent of patients with bronchogenic carcinoma will be diagnosed with non-small cell lung cancer (NSCLC). Approximately 15-20% of NSCLC patients present with early or localized disease.² The number of patients diagnosed with stage I NSCLC is expected to rise significantly in the next several decades due to widespread screening with spiral CT scanning.

Surgical resection of stage I (T1-2, NO) NSCLC results in five-year survival rates of approximately 60-70%,³⁻⁵ and remains the treatment of choice for this population. Unfortunately, some patients with early stage NSCLC are unable to tolerate the rigors of surgery or the post-operative recovery period due to lack of adequate respiratory reserve, cardiac dysfunction, diabetes mellitus, vascular disease, general frailty, or other co-morbidities.

Patients deemed medically inoperable have been treated with non-surgical therapies, such as standard fractionated radiotherapy, while many patients have simply been observed without any tumor therapy. While some patients succumb to their comorbid illnesses, many of these patients will die of progressive lung carcinoma. McGarry, et al., reviewed the outcome in 75 medically inoperable patients who received no specific cancer therapy at time of diagnosis for stage I NSCLC, and cause of death was cancer in 53% of cases.⁶

Primary radiotherapy for early stage non-small lung cancer is considered reasonable non-surgical therapy for such patients, with reported five-year survival rates ranging from 10-30%.⁷⁻¹¹ The standard approach involves giving approximately 45-66 Gy total dose in 1.8-2.0 Gy fractions. Several studies have reported a benefit to dose escalation suggesting a dose-response relationship in both survival and local control in these patients.¹⁰⁻¹⁴ For example, a review of 156 medically inoperable stage I NSCLC patients at Duke University between 1980 and 1995 demonstrated a five-year, cause-specific survival of 32% with radiotherapy alone. Improved survival was significantly correlated with achieving local control and approached significance for higher radiotherapy dose ($p=0.07$).¹³ Since early stage non-small cell lung cancer is not inherently a systemic disease from diagnosis and since local control is poor after conventional radiotherapy, research measures aimed at improving survival should put significant emphasis on improving local tumor obliteration.

Historically, radiotherapy fields for early stage NSCLC encompassed the primary tumor and regional lymphatics in the ipsilateral hilum and mediastinum. This "prophylactic" treatment was based on identified risk of occult nodal involvement from surgical series ranging up to 20%, and surgical data indicating better control with more extensive resections.¹⁵ Nonetheless, large radiotherapy fields are potentially poorly tolerated in this population with limited pulmonary reserve.¹⁶ More recent retrospective experience, however, show similar survival results with fields limited to the primary tumor alone¹⁷⁻²⁰ as compared to fields including prophylactic treatment to lymph node chains. In a recent report from the Netherlands, limited "postage stamp" fields were treated using hypofractionated radiotherapy (48 Gy in 4 Gy fractions)¹⁹ with reported three-year overall and disease-specific survival of 42% and 76%, respectively.

The majority of these mostly retrospective reports utilized radiotherapy equipment and techniques from the 1-D and 2-D planning era. With these older techniques, it was difficult to reduce high dose volume due to limitations in visualizing the target, limitations in selection of beam directions, and limitations in computational algorithms describing deposited dose. Newer generation techniques made possible by faster computer processors, software innovation, and hardware improvements have dramatically improved the shortcomings of previous techniques. These newer techniques, including *3-D conformal radiotherapy (3-DCRT)* and *stereotactic body radiation therapy (SBRT)*, allow precise targeting and radiotherapy delivery. 3-DCRT has been proven to allow significant dose escalation of fractionated radiotherapy in locally advanced lung cancer in a Radiation Therapy Oncology Group (RTOG) trial. SBRT, which utilizes elements of 3-DCRT in addition to stereotactic targeting, incorporates a variety of systems for decreasing the effects of lung and other organ motion that would otherwise translate into target motion. These

systems allow even more dramatic reduction of treatment volumes facilitating hypofractionation with markedly increased daily doses and significantly reduced overall treatment time.

RTOG has completed an extensive dose escalation study of conventionally fractionated radiotherapy for NSCLC for stages I, II and III disease as long as all detectable tumor can be encompassed by the radiation therapy fields including both primary tumor and regional lymph nodes. No mechanism for minimizing lung and tumor movements was utilized. Doses escalated as high as 90.3 Gy in the 179 treated patients. . While analysis of study results has not yet been published, results indicate the incidence of grade 3 or higher acute toxicity is less than 10%; however, grade 3 or higher late toxicity was approximately 15%.²¹ Hayman and co-workers at the University of Michigan²² reported on 104 patients with stages I-III treated by 3-D conformal therapy with dose escalation as high as 102.9 Gy with acceptable toxicity. Of note is the fact that despite the dose intensification, 53 patients had disease progression with 52% failing distantly; 8% failing both distantly and in the planning treatment volume (PTV); 2% failing in a distant site, the PTV and a nodal region outside the PTV and 35% failing within the PTV alone. Although the volume of tumor in both of these trials is on average greater than the currently proposed trials, the high rate of failure within the PTV offers justification to maintain high doses even in stage I patients.

Researchers at the Karolinska Hospital in Stockholm, Sweden developed an extracranial stereotactic frame and began treatment with the device in 1992. The results of over 100 patients treated in the extracranial stereotactic frame for metastases in the chest and abdomen have been reported by Dr. Blomgren, et al. from the Swedish group.²³⁻²⁴ In a more recent publication, Blomgren, et al., reported on 17 patients treated with stereotactic radiotherapy for intrathoracic metastases with follow-up of 3.5 to 25 months.²⁵ Tumors ranged in size from 1.8 cm to 7.2 cm. Margin doses ranges from 20 Gy in one fraction to 45 Gy in three fractions. Response was measured by repeat CT scans demonstrating disappearance in 35%, reduction in 41%, stabilization in 18%, and progression in only one patient (the largest tumor treated in the report). All patients received premedication with corticosteroids to potentially decrease acute inflammatory effects prior to treatment. Side effects consisted commonly of fatigue and fever for a few days after the treatments. One patient experienced typical radiation pneumonitis two months posttreatment, with subsequent fibrosis, and another developed chronic cough. There was no severe late pulmonary toxicity or treatment-related deaths.

At Indiana University, a phase I dose escalation protocol has been completed for the treatment of medically inoperable patients with AJCC Stage I lung cancer.²⁶ SBRT (a.k.a. extracranial stereotactic radioablation) with large doses per fraction was delivered in an extracranial stereotactic body frame, which includes a system to decrease respiratory motion. The starting dose was 8 Gy times 3 (24 Gy total), and fraction dose was escalated by 2 Gy per fraction for each cohort. The target lesion was outlined by a physician and designated as the gross tumor volume (GTV). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane was added to the GTV to constitute the PTV based on validation measurements for this commercially available system.²⁷⁻²⁹ Typically, 7-10 non-coplanar beams were used to encompass the PTV. Dose was prescribed to the 80% line; however, higher isodoses (hotspots) occurred within the central core of the target mimicking the heterogenous dose profile common to intracranial stereotactic radiosurgery. The higher dose in the tumor core is intended to give extra dose in areas of presumed greatest tumor hypoxia and radioresistance. The treatment isocenter was identified with 3-D coordinates defined stereotactically and localized on verniers attached to the frame. No skin or bony landmarks were used to set the treatment isocenter, however; orthogonal port films were used on a daily basis for isocenter verification.³⁰ Separate dose escalations were carried out independently for patients with T1 versus T2 small (< 5 cm) versus T2 large (5-7 cm) tumors at diagnosis.

According to the Indiana University protocol guidelines, dose-limiting toxicity (DLT) was any grade 3 cardiac or pulmonary toxicity or any grade 4 toxicity attributed to the therapy. Thirty-seven patients were treated on this protocol using a standard dose escalation protocol with 3 patient cohorts with minimum 1 month between dose levels to assess toxicity. Patients were categorized into separate independent dose escalations according to tumor volume, T1 vs. T2 (≤ 5 cm) vs. T2 (> 5 to ≤ 7 cm). Grade 3 pneumonitis was seen at a dose of $14 \times 3 = 42$ Gy total in one T2 patient with a 7 cm lung tumor and transient grade 3 hypoxia was seen at $16 \times 3 = 48$ Gy

in one T1 patient. Additional patients were treated at each of these levels without further toxicity observed. Twenty-one patients had mild to moderate fibrosis distal to the treated lesion appear on chest x-ray after treatment. Nine of these patients had decline of an element of their pulmonary function tests (FEV1, FVC, DLCO, or PO2) by 10-20% of predicted which returned back to baseline values with follow up in all except two. The timing of onset of this toxicity was generally acute to subacute (< 1 month in most cases). The maximum tolerated dose (MTD) was not reached on this trial for T1 tumor patients and smaller T2 tumors (≤ 5 cm). Dose limiting pneumonitis or pericarditis occurred in 2/5 patients with larger T2 tumors (> 5 to ≤ 7 cm) at a dose of $24 \times 3 = 72$ Gy defining the MTD for this subgroup at $22 \times 3 = 66$ Gy. Patients treated at a dose of 22 Gy per fraction for 3 fractions have had follow up of over 24 months without late toxicity for all T-stage tumor categories. Treatment failure within the PTV has been observed in 8 of 26 patients treated at doses of up to $20 \times 3 = 60$ Gy. However, all but one of these local failures occurred at doses of $16 \times 3 = 48$ Gy or lower.³¹

Similar studies are being performed with respiratory-gated radiotherapy triggering beam-on mode by certain phases of the respiratory cycle or deep inspiration breath-hold techniques.³²⁻³³ Others have used a "tracking" approach in which the radiation source follows the position of the tumor via a surrogate marker.³⁴ Published results on the feasibility of these approaches are available, although no published data on the effectiveness of this approach for dose intensification studies are available yet.

The aforementioned data would imply that stage I NSCLC would be better controlled with hypofractionated radiation to a high biological dose, perhaps resulting in improved survival. In addition, the patient population with medically inoperable stage I NSCLC may have an increased risk of radiation pneumonitis associated with conventional large volume radiotherapy providing further rationale for reduced volume treatments. SBRT is a promising technique for allowing dose escalation through significant reduction in the high dose treatment volume. In the end, it is hoped that the rather large disparity between survivals in radiotherapy treated and surgically treated patients with stage I NSCLC may be narrowed.

1.2 Comorbidity

Patients enrolled in this study will be ineligible for surgery for various reasons, including lack of adequate respiratory reserve, cardiac dysfunction, diabetes mellitus, vascular disease, general frailty, or other comorbidities. They represent a diverse population with varying prognoses.

Comorbid conditions have been shown to affect prognosis in a variety of clinical situations and are independent of functional status.³⁵⁻³⁷ Firat et al. evaluated the effect of comorbidity on survival in 141 patients with stage I NSCLC treated with either surgery or radiation therapy. The presence of significant comorbidity and KPS of < 70 were both found to be important independent prognostic factors in Stage I NSCLC.³⁶ Comorbidity and KPS assessment are recommended when analyzing the prognostic effects of tumor or treatment-related factors on overall survival.

Although comorbid conditions influence a clinician's decision regarding cancer therapy, these judgments are subjective and therefore, vary from physician to physician. In this study, we will objectively evaluate comorbid conditions with the Charlson Comorbidity Index (CCI) and Cumulative Illness Rating Scales for Geriatrics (CIRS-G) and evaluate the effect of comorbidity on survival.

The CCI and the CIRS-G are validated scales³⁸⁻⁴⁰ that will be used to determine the level of comorbidity burden of individual patients. Both scales can be completed from review of detailed past medical history and physical examination.⁴⁰⁻⁴¹ Neither scale correlates with functional status, and each provides independent information.⁴⁰

2.0 OBJECTIVES

2.1 The primary objective of the study is to determine if radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable local control (i.e., $\geq 80\%$) in frail patients with medically inoperable early stage non-small cell lung cancer.

2.2 Secondary Objectives

2.2.1 To determine if radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable treatment-related toxicity;

- 2.2.2 To observe patterns of failure (see definitions in Section 11.3), disease free survival, and overall survival.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (6/14/05)

- 3.1.1 Histological confirmation of non-small cell cancer will be required by either biopsy or cytology. The following primary cancer types are eligible: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchioloalveolar cell carcinoma, or non-small cell carcinoma not otherwise specified.
- 3.1.2 Eligible patients must have appropriate staging studies identifying them as specific subsets of AJCC stage I or II based on only one of the following combinations of TNM staging:
- T1, N0, M0
 - T2 (≤ 5 cm), N0, M0
 - T3 (≤ 5 cm), N0, M0 chest wall primary tumors only
- 3.1.3 Patients with hilar or mediastinal lymph nodes ≤ 1 cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Patients with > 1 cm hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but non-diagnostic uptake) may still be eligible if directed tissue biopsy of all abnormally identified areas are negative for cancer.
- 3.1.4 The primary tumor must be deemed technically resectable by an experienced thoracic cancer clinician, with a reasonable possibility of obtaining a gross total resection with negative margins (defined as a potentially curative resection, PCR). However, the patient should have underlying physiological medical problems that would prohibit a PCR due to a low probability of tolerating general anesthesia, the operation, the postoperative recovery period, or the removal of adjacent functioning lung. These types of patients with severe underlying health problems are deemed "medically inoperable." Standard justification for deeming a patient medically inoperable based on pulmonary function for surgical resection of NSCLC may include any of the following: Baseline FEV1 $< 40\%$ predicted, post-operative predicted FEV1 $< 30\%$ predicted, severely reduced diffusion capacity, baseline hypoxemia and/or hypercapnia, exercise oxygen consumption $< 50\%$ predicted, severe pulmonary hypertension, diabetes mellitus with severe end organ damage, severe cerebral, cardiac, or peripheral vascular disease, or severe chronic heart disease.
- 3.1.5 Patients must be ≥ 18 years of age.
- 3.1.6 The patient's Zubrod performance status must be Zubrod 0-2.
- 3.1.7 Women of childbearing potential and male participants must use an effective contraceptive method such as condom/diaphragm and spermicidal foam, intrauterine device (IUD), or prescription birth control pills.
- 3.1.8 Pretreatment Evaluations Required for Eligibility include:
- A medical history, physical examination, weight, assessment of Zubrod performance status within 4 weeks prior to study entry;
 - Evaluation by an experienced thoracic cancer clinician within 8 weeks prior to study entry;
 - For women of childbearing potential, a serum or urine pregnancy test must be performed within 72 hours prior to the start of protocol treatment;
 - PFTs: Routine spirometry, lung volumes, diffusion capacity, and arterial blood gases within 8 weeks prior to study entry.

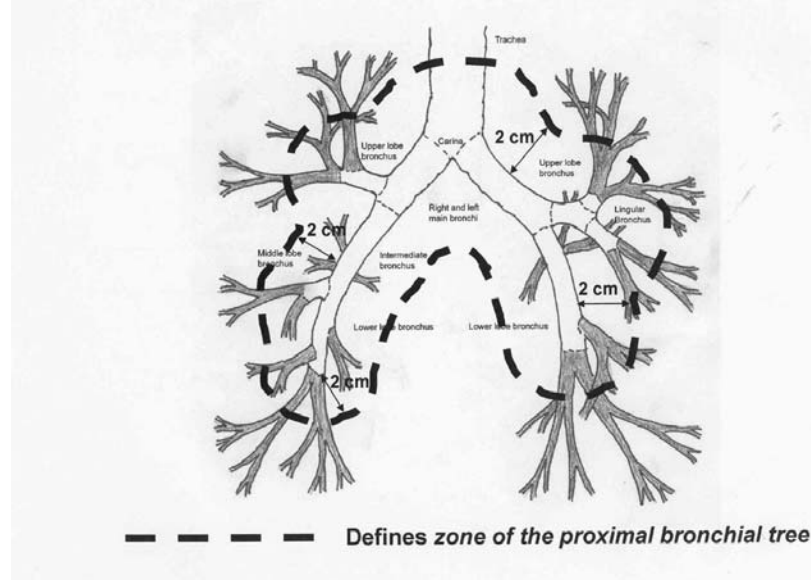
Mandatory staging studies: Must be done 45 days prior to study entry

- Chest radiograph;
 - CT scan (preferably with intravenous contrast, unless medically contraindicated) to include the entirety of both lungs, the mediastinum, liver, and adrenal glands; Primary tumor dimension will be measured on CT;
 - Whole body positron emission tomography (PET) scan using FDG with adequate visualization of the primary tumor and draining lymph node basins in the hilar and mediastinal regions.
- 3.1.9 Patients must sign a study-specific consent form.

3.2 Conditions for Patient Ineligibility (6/14/05)

- 3.2.1 Patients with T2 or T3 primary tumors > 5 cm or patients with T3 primary tumors involving the central chest and structures of the mediastinum;
- 3.2.2 The primary tumor of any T-stage within or touching the *zone of the proximal bronchial tree* defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and

left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi. See figure below:



- 3.2.3 Direct evidence of regional or distant metastases after appropriate staging studies, or synchronous primary or prior malignancy in the past 2 years other than nonmelanomatous skin cancer or in situ cancer;
- 3.2.4 Patients who refuse a PCR due to preference, ideology, emotional or psychological issues, mental illness, or inability to give consent for the PCR and who have no specific accepted medical contraindications for the PCR;
- 3.2.5 Previous lung or mediastinal radiotherapy;
- 3.2.6 Plans for the patient to receive other concomitant antineoplastic therapy (including standard fractionated radiotherapy, chemotherapy, biological therapy, vaccine therapy, and surgery) while on this protocol except at disease progression;
- 3.2.7 Patients with active systemic, pulmonary, or pericardial infection;
- 3.2.8 Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS

- 4.1 Charlson Comorbidity Index (CCI) and hospitalization history (see Section 11.2, Appendix IV)

5.0 REGISTRATION PROCEDURES (10/6/04) (11/21/05) (2/24/06)

NOTE: Institutions will receive 2 case accrual credits for each patient enrolled on this study.

5.1 *Pre-Registration Requirements*

Institutions **must** be credentialed by the Advanced Technology Consortium (ATC) prior to enrolling patients on this study. As it pertains to this study, the ATC includes the Image-Guided Therapy Center (ITC) at Washington University, St. Louis; the Radiological Physics Center (RPC) at MD Anderson Cancer Center; and RTOG RT Quality Assurance. Credentialing includes the following 4 steps (Sections 5.1.1-5.1.4):

- 5.1.1 Each institution must complete the 3D QA Facility Questionnaire for SBRT available on the ATC web site, <http://atc.wustl.edu>. Each institution must submit the completed Facility Questionnaire by email, fax, or mail to:

**Image-Guided Therapy Center (ITC)
 Attn: Roxana Haynes
 4511 Forest Park Avenue, Suite 200
 St. Louis, MO 63108
 E-mail: itc@castor.wustl.edu
 Phone: 314-747-5415
 FAX: 314-747-5423**

The Facility Questionnaire requires the following:

Institutional and/or peer-reviewed documentation of accountability for internal organ motion including compensation for respiratory movement by one of the following methods:

- Inhibition of diaphragmatic movement by abdominal compression or equivalent;
- Active breath holding techniques synchronized to radiation delivery;
- Respiratory gating monitoring consistent breathing patterns synchronized to radiation delivery;
- Dynamic tumor tracking with collimator or machine movement synchronized to radiation delivery.

Institutional and/or peer-reviewed documentation of target position reproducibility (gross tumor volume within planning treatment volume) within the guidelines specified in Section 6.0.

Documented ability to transfer patient specific material and treatment planning parameters including CT-based dose deposition representations, dose-volume matrices and parameters, and stereotactic targeting representations to the ITC.

5.1.2 Each institution must contact the ITC (itc@castor.wustl.edu) and request an FTP account for digital data submission.

5.1.3 Each institution must irradiate a standardized phantom provided by the Radiological Physics Center (RPC) at MD Anderson Cancer Center. Instructions for requesting and irradiating the phantom are available at the RPC web site, <http://rpc.mdanderson.org/rpc/> by selecting "Credentialing" and "RTOG". The phantom simulates a lung tumor within lung tissue equivalent material. The irradiation must be within tolerances specified in Section 6.0. The treatment plan for irradiation of the phantom must be submitted electronically to the ITC (see Section 5.1.2).

5.1.4 Each institution must submit and successfully complete a protocol-specific Dry-Run Test, the treatment plan for the first patient to be treated at the site on this protocol PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The plan will be reviewed centrally at the ITC, and suggestions regarding protocol compliance will be forwarded to the participating institution. The treatment plan for subsequent patients enrolled at a site will not be required to be centrally reviewed prior to treatment, but will be reviewed for protocol compliance at a later date.

5.2 Registration

5.2.1 Online Registration

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

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

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

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

6.0 RADIATION THERAPY **Note: Intensity Modulated RT (IMRT) Is Not Allowed**

6.1 Dose Specifications

6.1.1 Stereotactic Targeting and Treatment

The term “stereotactic” for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks that are indirectly referenced to the tumor. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment). Metallic “seeds” placed within the tumor will not generally be allowed to constitute a fiducial unless the site employing this technique provides satisfactory validation to the Study Chair indicating no seed migration and reproducibility of target positioning from treatment to treatment and obtains permission in writing from the Study Committee (Principal Investigator and Co-Chairs) prior to treatment.

6.1.2 Dose Fractionation

Patients will receive 3 fractions of radiation. A minimum of 40 hours and a maximum of 8 days should separate each treatment. No more than 2 fractions will be delivered per week (7 consecutive days). The dose for all patients will be 20 Gy per fraction to the prescription line at the edge of the PTV. Three such fractions will be delivered as above over 8-14 days for a total of 60 Gy.

6.1.3 Premedications

Unless contraindicated, it is recommended that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the three treatments for the intended purpose of modulating immediate pulmonary inflammatory effects. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

6.2 Technical Factors

6.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies greater than 10 MV but not more than 15 MV will only be allowed for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter.

6.2.2 Minimum Field Aperture (Field Size) Dimension

Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, a minimum field dimension of 3.5 cm is required for any field used for treatment delivery. It is understood that this may exceed the technical requirements listed in Section 6.4 for small lesions (< 2.5 cm axial GTV dimension or < 1.5 cm cranio-caudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined PTV. This minimum field dimension does not apply to centers using tomotherapy or multiple pencil beam delivery systems.

6.2.3 Dose Verification at Treatment

Personal dosimeter measurements (e.g. diode, TLD, etc.) may be obtained for surface dose verification for accessible beams as per institutional preference. This information is not required by the protocol.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patient Positioning

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the

stereotactic coordinate system (see Section 6.1). All positioning systems must be validated and accredited by the Study Committee (Principal Investigator and Co-Chairs) prior to enrolling or treating patients on this trial. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.2 Inhibition of Effects of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (i.e., breathing, etc.) on target positioning and reproducibility. Acceptable maneuvers including reliable abdominal compression, accelerator beam gating with the respiratory cycle, and active breath-holding techniques. All systems used to account for internal organ motion must be validated and accredited by the Study (Principal Investigator and Co-Chairs) prior to enrolling or treating patients on this trial. Internal organ inhibition maneuvers must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.3 Localization

Isocenter port localization films (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study utilizing the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification CT scans and portal films may be taken at the discretion of the participating institution, but are not required for protocol participation. The localization verification films will be submitted for QA purposes to the ITC. Centers with tomographic imaging study capability using the linear accelerator couch should create digitally reconstructed radiograph (DRR) images of the anterior/posterior and lateral alignment to be submitted for QA purposes to the ITC.

6.4 Treatment Planning/Target Volumes

6.4.1 Image Acquisition

Computed Tomography (CT) will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and must be done with IV contrast, unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. **This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, only include abnormal CT signal consistent with gross tumor (i.e., the GTV and the Clinical Target Volume, CTV, are identical).** An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (cranio-caudal) will be added to the GTV to constitute the planning treatment volume (PTV). These margins will be used at all sites, even if a particular site uses equipment or techniques felt to be more accurate.

6.4.2 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, 7-10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional “margin” for dose build up at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal

tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COM_{PTV}). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COM_{PTV} must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. The prescription dose of 60 Gy in three fractions will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hot spot" will exist within the PTV centrally at the COM_{PTV} with a magnitude of 60 Gy times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body, including lung, will be assumed to have unit (water) density (no correction for tissue heterogeneity). However, for QA purposes, each plan should also be calculated with software vendor supplied heterogeneity corrections for density enabled. In order for ITC (the QA center) to make an accurate comparison between these plans, the computation using heterogeneity corrections should have beam weights manipulated such that the number of monitor units is the same for each beam between the plans. Both plans (with and without heterogeneity correction) will be submitted to the ITC for comparison. Again, calculation of the accelerator monitor units for the actual patient treatment should reflect the plan where all tissues are assumed to have unit (water) density.

Successful treatment planning will require accomplishment of all of the following criteria:

- 1) Normalization
The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COM_{PTV}). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.
- 2) Prescription Isodose Surface Coverage
The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (i.e., 20 Gy per fraction = 60 Gy total), and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 18 Gy per fraction = 54 Gy total).
- 3) Target Dose Heterogeneity
The prescription isodose surface selected in number 2 (above) must be $\geq 60\%$ of the dose at the center of mass of the PTV (COM_{PTV}) and $\leq 90\%$ of the dose at the center of mass of the PTV (COM_{PTV}). The COM_{PTV} corresponds to the normalization point (100%) of the plan as noted in 1) above.
- 4) High Dose Spillage
 - a) Location
Any dose greater than 105% of the prescription dose ($> 21\text{Gy}$ per fraction = 63 Gy total) should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose ($> 21\text{Gy}$ per fraction = 63 Gy total) should be no more than 15% of the PTV volume.
 - b) Volume
Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 4) to the volume of the PTV is ideally < 1.2 (See table below). These criteria will *not* be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm cranio-caudal GTV dimension) where the required minimum field size of 3.5 cm (see Section 6.2) results in the inability to meet a conformality ratio of 1.2.
- 5) Low Dose Spillage
The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
 - a) Location

The maximum total dose over all 3 fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction be no greater than D_{2cm} where D_{2cm} is given by the table below.

b) Volume

The ratio of the volume of 50% of the prescription dose (10 Gy per fraction = 30 Gy total) isodose to the volume of the PTV must be no greater than $R_{50\%}$ where $R_{50\%}$ is given by the table below.

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to the PTV		Ratio of 50% Prescription Isodose Volume to the PTV, $R_{50\%}$		Maximum Dose 2 cm from PTV in any Direction, D_{2cm} (Gy)		Percent of Lung receiving 20 Gy total or more, V_{20} (%)		PTV Volume (cc)
	Deviation		Deviation		Deviation		Deviation		
	none	minor	none	Minor	none	minor	none	minor	
2.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	1.8
2.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	3.8
3.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	7.4
3.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	13.2
4.0	<1.2	1.2-1.4	<3.8	3.8-4.0	<30.4	30.4-32.4	<10	10-15	21.9
4.5	<1.2	1.2-1.4	<3.7	3.7-3.9	<32.7	32.7-34.7	<10	10-15	33.8
5.0	<1.2	1.2-1.4	<3.6	3.6-3.8	<35.1	35.1-37.1	<10	10-15	49.6
5.5	<1.2	1.2-1.4	<3.5	3.5-3.7	<37.4	37.4-41.7	<10	10-15	69.9
6.0	<1.2	1.2-1.4	<3.3	3.3-3.5	<39.7	39.7-41.7	<10	10-15	95.1
6.5	<1.2	1.2-1.4	<3.1	3.1-3.3	<42.0	42.0-44.0	<10	10-15	125.8
7.0	<1.2	1.2-1.4	<2.9	2.9-3.1	<44.3	44.3-46.3	<10	10-15	162.6

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

Note 2: Protocol deviations greater than listed here as 'minor' will be classified as 'major' for protocol compliance (See Section 6.7).

6) Respect all critical organ dose-volume limits listed in Section 6.5.1 below.

6.5 Critical Structures

6.5.1 Critical Organ Dose-Volume Limits

The following table lists maximum dose limits to a point or volume within several critical organs. **These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation** (See Section 6.7). The dose is listed as total over 3 fractions and per fraction.

These limits were formulated with the approval of the study committee (Principal Investigators and Co-Chairs) including Dr. Jack Fowler, international authority on radiobiology and radiotolerance, using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers,¹⁶⁻²² and the experience of several years of irradiation using these large fractions at Indiana University^{26,30,31} and centers in Sweden,^{24,25,27} Germany, and Japan. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)
Whole Lung (Right & Left)	(See table in Section 6.4.2)	(See table in Section 6.4.2)

6.5.2 Contouring of Normal Tissue Structures

6.5.2.1 Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.5.2.2 Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.5.2.3 Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib.

6.5.2.4 Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

6.5.2.5 Trachea and Proximal Bronchial Tree

The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumors within 2 cm of the proximal bronchial tree (see section 6.5.2.8 below).

6.5.2.5.1 Proximal Trachea

Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (which ever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree (see diagram in Section 3.2.2 and definitions below).

6.5.2.5.2 Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in Section 3.2.2. The following airways will be included according to standard anatomical relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

- 6.5.2.6** Whole Lung
Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.
- 6.5.2.7** PTV Plus 2 cm
As part of the QA requirements for “low dose spillage” listed in 6.4 above, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning.
- 6.5.2.8** Proximal Bronchial Tree Plus 2 cm
As part of adhering to the ineligibility requirements for not enrolling patients with tumors in the zone of the proximal bronchial tree listed in 3.2.2 above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not be treated with the protocol therapy. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment planning software to ensure protocol compliance.
- 6.6** **Documentation Requirements**
- 6.6.1** In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.
- 6.7** **Compliance Criteria**
- 6.7.1** Accreditation Compliance
All criteria listed in Section 5 must be completed to the satisfaction of the study committee in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions’ PIs informing them of accreditation for the study. No institution will be allowed to enroll patients without accreditation.
- 6.7.2** Dosimetry Compliance
Section 6 describes appropriate conduct for treatment planning dosimetry. The Image-Guided Therapy Center (ITC) will evaluate plans as described in Section 6.8. Criteria for both major and minor deviations are provided in the table in Section 6.4. In addition to the criteria in section 6.4, the table in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.
- 6.7.3** Treatment Delivery Compliance
Set-up films will be compared to digitally reconstructed radiographs from the same beam’s eye view. Deviations of less than 0.5 cm in the transverse plane and 1.0 cm in the cranio-caudal plane will be considered compliant. Deviations from 0.5-1.0 cm in the transverse plane and 1.0-1.25 cm in the craniocaudal plane will be considered minor protocol deviations. Deviations greater than those listed as minor will be considered major protocol deviations.
- 6.8** **R.T. Quality Assurance Reviews**
Treatment planning images and dosimetry planning information in accepted format will be submitted to the Image-Guided Therapy Center (ITC), Washington University, St. Louis, MO for QA purposes in all cases. See Section 12.1 for data submission.

The Principal Investigator, Dr. Timmerman, will perform an RT Quality Assurance Review after complete data for the first 18 cases enrolled has been received at ITC. Dr. Timmerman will perform the next review after complete data for the next 18 cases has been received. 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 ITC, whichever occurs first.

Radiation Toxicity

- 6.9.1** Radiation pneumonitis
Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. **Note:** It is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia with fatigue, fever, shortness of breath, non-productive cough, and a pulmonary infiltrate on chest x-

ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically “geometric” corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis prior to completing therapy, therapy should be put on hold until symptoms resolve. At that point, a clinical decision whether to finish therapy will be made in conjunction with the treating physician and the study committee.

6.9.2 Bronchial Injury

In the Indiana University phase I study, the majority of patients treated at doses of 20 Gy times 3 fractions = 60 Gy or higher ultimately experienced atelectasis (collapse) of lung downstream from the area of treatment. This was felt to be related to bronchial injury of bronchi or bronchioles within or near the treated tumor. By unknown mechanisms over a period of 3-6 months, pulmonary parenchyma distal to the site of bronchial injury results in this focal lung collapse. In the majority of patients, this effect noted on imaging studies was asymptomatic. In others, the injury apparently correlated to a drop in diffusing capacity and arterial oxygen tension on pulmonary function tests. This process of collapse was not reversible in the Indiana University experience. This injury is the justification for excluding central and hilar tumors from this protocol so as to avoid substantial (or total) lung collapse.

This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Since atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. Investigators are referred to the strict criteria for progressive disease in Section 11 of this protocol to avoid such mischaracterization.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.3 Other Significant Toxicity

If other severe toxicity resulting in withholding therapy is encountered, the details will be documented.

6.10 Radiation Adverse Event Reporting — RTOG AE TELEPHONE LINE (215) 717-2762

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). **Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

6.10.1 Life-threatening and Grade 4 Events

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

6.10.2 Fatal Events (Grade 5)

All deaths with the attribution of definitely, possibly, or probably related to protocol radiation therapy must be telephoned to the RTOG Headquarters AE telephone line (215) 717-2762, to the RTOG Group Chair, and to the Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to the RTOG Headquarters AE telephone line at (215) 717-2762. If the event is more than 30 days from completion of radiation treatment, but is felt to be definitely, possibly, or probably resulting from protocol radiation therapy, this event should be telephoned to RTOG Headquarters using the same numbers as listed above.

6.10.3 Documentation

Radiation therapy is the only modality in this protocol; therefore, serious adverse events are reported on the appropriate case report forms with a dictated summary of the event(s) from the Primary Investigator (A MedWatch form is not applicable for radiation therapy alone grade 4 and grade 5 events). These items must be sent to RTOG Headquarters within 10 working days of the telephone report.

6.10.4 Summary of AE Reporting in Protocols Involving Radiation Treatment

- Report Grade 4/Grade5 AEs;
- Telephone report to RTOG within 24 hours of discovery;
- Use appropriate case report forms/dictated summary of events for documentation and send to RTOG HQ within 10days (MedWatch/AdEERS not applicable);
- Institutional reporting as required;
- For **DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT**:
 - Telephone report to RTOG within 24 hours of discovery;
 - Appropriate case report forms and if indicated, dictated summary.
 - Telephone report to RTOG within 24 hours of discovery;
 - Follow guidelines outlined in this section of the protocol for AE reporting.

6.10.5 Special Reporting for This Study

Adverse events should be deemed related to therapy. Any grade 4 or 5 toxicity (per CTCAE, v.3.0) related to therapy and acute or late grade 3 toxicity related to specific symptoms, including:

- Gastrointestinal: dysphagia, esophagitis, esophageal stricture, esophageal ulceration;
- Cardiac: pericarditis, pericardial effusion, cardiomyopathy, ventricular dysfunction;
- Neurologic: myelitis, neuropathy — cranial and motor;
- Hemorrhage: pulmonary or upper respiratory;
- Pulmonary: decline in pulmonary function as measured by pulmonary function tests, pneumonitis, pulmonary fibrosis, hypoxemia, pleural effusion

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Patients must not receive other concomitant antineoplastic therapy (including standard fractionated radiotherapy, chemotherapy, biological therapy, vaccine therapy, and surgery) while on this protocol except at disease progression.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/6/04) (6/14/05) (9/9/09)

Assessments	Pre-Study Entry	Tx Week 1	Tx Week 2	Tx Week 3	6 Wks Post- Tx	12 Wks Post- Tx	Follow Up
History/physical	X	X	X	X	X	X	X ^e
Weight and Zubrod	X	X	X	X	X	X	X ^e
Eval by Thoracic Cancer Clinician	X						
Pregnancy Test	X						
Toxicity Evaluation		X	X	X	X	X	X ^e
Chest X-ray	X				X ^f		X ^c
CT scan	X ^b					X ^d	X ^{bc}
PET scan	X						X ^d
PFTs ^a	X ^g				X	X	X ^c
CCI, CIRS-G, & hospitalization history	X ^h						

- Includes routine spirometry, lung volumes, diffusion capacity, and arterial blood gases;
- CT scan (preferably with IV contrast, unless medically contraindicated) and submitted to the ITC for central review for the first 2 years (see Section 12.1.3).
- Alternate chest x-rays and chest CT scans in follow-up visits, with the initial chest x-ray at 6 weeks post SBRT and the initial chest CT scan at 12 weeks post SBRT. Continue alternating the studies every 3 months for 2 years, followed by chest CT scans every 6 months for 2 years. After 2 years, chest x-rays will be at the investigator's discretion. PFTs every 3 months for the first year, then every 6 months for the second year.
- Strongly encouraged; PET scans within 2 years post-treatment are required only if the criteria for local enlargement on CT is realized (see Section 11.2.1.6). The PET scan should occur within 3 months of the CT that defined local enlargement. Investigators are encouraged to submit the PET scans digitally to the ITC for QA, but this is not required. Post-treatment PET scans done outside of the required criteria for assessment of local progression or after 2 years post-treatment may be done at the investigator's discretion but are not required.
- At week 6 and 12 post SBRT as noted above, then every 3 months for 2 years, every 6 months for the next 2 years, then annually for the patient's lifetime.
- Monitor for signs of radiation pneumonitis (see Section 6.9.1).
- Within 8 weeks prior to study entry.
- Strongly encouraged but not required.

11.2 Criteria For Evaluation

11.2.1 Response Determination

This protocol will use a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See <http://ctep.info.nih.gov/guidelines/recist.html> for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

11.2.2 Baseline documentation of "Target" and "Non-Target" Lesions

Patients enrolled to this protocol should have clinical stage I (T1 or T2, N0, M0) or clinical stage II (T3 chest wall primaries only, N0, M0) non-small cell lung cancer. At time of treatment, they should only have one site of gross disease in the lung with no metastases. The primary lung tumor should be identified as the **target lesion** and recorded and measured at baseline and with each follow-up imaging evaluation.

The longest diameter (LD) for the *target lesion* will be calculated **from the treatment planning CT scan** using pulmonary windowing and reported as the baseline LD. The baseline LD will be used as reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using

pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, chest x-ray determination will be allowed as long as the target lesion is clearly visible. Changes in serum tumor markers will not be allowed for assessment of either local tumor progression or metastatic progression.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases where it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor. In order to make the assessment more objective, a central radiology review for CT response evaluation will be required for this protocol.

All other lesions (or sites of disease) that appear after treatment (e.g., regional lymph nodes and distant metastases) should be identified as **non-target lesions** and should also be recorded at the point of their appearance and with each follow up. Non-target lesions should constitute measurable disease, which by definition requires having an appearance suspicious for carcinoma and having a dimension of at least 1.0 cm. Assessment of regional lymphatic or metastatic progression will be made in comparison to the required pretreatment staging studies or any other pretreatment imaging evaluations available. Only non-target lesions appearing at the margin of the PTV (i.e., within 1.0 cm) will have recorded measurements (see Marginal Failure in the table below). Recorded measurements of all other non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.2.3 Response Criteria

Evaluation of Target Lesions	
Complete Response (CR)	Disappearance of the target lesion; ideally, this determination will be made based on CT image evaluation.
Partial Response (PR)	At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started
Local Enlargement (LE)	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; Ideally, this determination will be made based on CT image evaluation.
Local Failure (LF)	Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. For outcome analysis, Marginal Failures (MF; see below) will also be counted as LF; however, they should be distinguished specifically as MF, not LF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation. ⁴⁶
Local Control (LC)	The absence of Local Failure.

Evaluation of Non-Target Lesions	
Marginal Failure (MF)	Refers to the appearance after protocol therapy of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV (see Section 6.4) and meeting the following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.
Regional Failure (RF)	Refers to the appearance after protocol therapy of measurable tumor within lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease only with dimension of at least 1.0 cm on imaging studies (preferably CT scans) within the lung, bronchial hilum, or the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma.
Metastatic Dissemination (MD)	Refers to the appearance after protocol therapy of cancer deposits characteristic of metastatic dissemination from non-small cell lung cancer. Appropriate evaluations for making this determination include physical examination and imaging studies. PET scan OR biopsy to confirm MD is encouraged but not required.

11.2.4 Criteria for Removal from Protocol Treatment (9/9/09)

All reasons for discontinuation of treatment must be documented. All patients will be followed until death.

- 11.2.4.1 Disease progression at any time during therapy or the follow up period; the patient should be re-staged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.
- 11.2.4.2 Unacceptable toxicity;
- 11.2.4.3 The patient may elect to withdraw from study treatment at any time for any reason.
- 11.2.4.4 Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow up.

11.3 Comorbidity Data and Rating

- 11.3.1 Site CRAs will complete the Comorbidity Recording Sheet and The Charlson Comorbidity Index (CCI) following the instructions in Appendix IV. 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 12.3) 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, Radiation Oncology/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).

11.3.2 Credit for Comorbidity Data Submission

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

12.1 Data Submission to ITC

12.1.1 Digital Data Submission

Digital data submission may be accomplished using magnetic tape or the Internet.

For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:
itc@castor.wustl.edu

For tape submission: Please contact the ITC about acceptable tape types and formats.
Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)
 4511 Forest Park, Suite 200
 St. Louis, MO 63110
 314-747-5415
 FAX 314-747-5423**

12.1.2 Data Submission to ITC Prior to Treatment of First Patient (Also see Section 5.1)

- Study-specific Facility Questionnaire relating to capabilities and QA programs;
- Treatment plan for irradiation of standardized phantom;
- Dry Run Test.

12.1.3 Data Submission to ITC for Patient Treatment (8/6/04)

<u>Item</u>	<u>Due</u>
†Digital Data Submission Form (T2) CT treatment planning images, dosimetry information (in 3-D) according to RTOG guidelines AP and Lateral Isocenter Setup Films Daily Orthogonal Isocenter Localization Films *Radiotherapy Form (T1) Complete Daily Treatment Record (T5)	Within 1 week of RT end
Follow-up CT scans	Week 12 post RT, then every 3 months for 2 years
†Available on the ATC web site, http://atc.wustl.edu/ *Send copy to RTOG Headquarters	

12.2 Summary of Data Submission to RTOG (8/6/04) (9/9/09)

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.

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1)	Within 2 weeks of study entry
<u>Final Dosimetry Information:</u> *Radiotherapy Form (T1) Adverse Event Form (AE)	Within 1 week of RT end
Follow-up Form (F1) Adverse Event Form (AE)	At 6 and 12 weeks from end of RT, then every 3 months for 2 years; q 6 months for 2 years; then annually for the patient's lifetime. Also at progression/relapse and at death if these events occur between planned follow-up intervals.

*Copy of original sent to ITC

12.3 Comorbidity Data Submission

Comorbidity data (Comorbidity Recording Sheet and Charlson Comorbidity Index) should be submitted within 2 weeks of study entry (the same time point as the initial assessment data) but will be submitted to: **Elizabeth Gore, M.D. Fax 414-805-4369**. Do not submit to RTOG Headquarters.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is to estimate local control at two years.

13.1.2 To estimate the rate of acute and late treatment-related grade 3 or 4 toxicity (per CTCAE, v.3.0) related to specific symptoms, including:

- Gastrointestinal: dysphagia, esophagitis, esophageal stricture, esophageal ulceration;
- Cardiac: pericarditis, pericardial effusion, cardiomyopathy, ventricular dysfunction;
- Neurologic: myelitis, neuropathy — cranial and motor;
- Hemorrhage: pulmonary or upper respiratory;
- Pulmonary: decline in pulmonary function as measured by pulmonary function tests, pneumonitis, pulmonary fibrosis, hypoxemia, pleural effusion

Or any grade 4 or 5 toxicity attributed to the therapy;

13.1.3 To estimate the rates of local recurrence, regional recurrence, disseminated recurrence, disease-free and overall survival at two years.

13.2 Sample Size (8/6/04)

This phase II study aims to improve the two-year local control rate from 60% to 80%. Local control is defined as the absence of local progression. Assuming at least an approximately exponential distribution of time to local progression, the hazard rate for the expected local control rate of 80% is 0.0093 per month, and the hazard rate for the unacceptable local control rate of 60% is 0.02128 per month. Using the asymptotic properties of the ratio of the logarithms of the observed and expected hazards, 18 cases of local progression are required for a Type I error rate of 0.05 with 80% statistical power to detect a difference in local control rates at least this large. These figures require 25 months of accrual to 49 patients and two years of follow up. Assuming that 5% of the patients will be ineligible or inevaluable, **a total of 52 patients will be required for this trial.**

13.3 Interim Analyses for Early Stopping Due to Unacceptable Toxicity (11/21/05)

Early stopping of this trial will be based on unacceptable toxicity, defined as acute (within 90 days of the start of treatment) or late (more than 90 days from the start of treatment) grade 3 or 4 toxicity (per CTCAE, v.3.0) related to specific symptoms as detailed in Section 13.1.2 or any grade 4 or 5 toxicity attributed to the therapy. If a patient has more than one unacceptable toxicity, they will only be counted as one unacceptable toxicity for this analysis.

Three interim analyses of toxicity are planned after 25%, 50%, and 75% of the total number of evaluable patients to be accrued. The interim analyses will be performed no earlier than 90 days after the 8th, 16th, 24th, and 33rd patients have completed treatment and will include all acute and late unacceptable toxicities reported at the time of the interim analysis.

The following early stopping rules reject the null hypothesis that the toxicity rate is less than or equal to 25% with an overall Type I error rate of no more than 0.10:⁴²

- 8 or more cases of unacceptable toxicities out of the first 12 evaluable patients, or
- 11 or more cases of unacceptable toxicities out of the first 24 evaluable patients, or
- 14 or more cases of unacceptable toxicities out of the first 36 evaluable patients.

The final analysis will test the same null hypothesis using the rejection rule of 17 or more patients with unacceptable toxicities out of the total sample of 49 evaluable patients. This will insure an overall significance level of 0.10 for the final conclusion. If more than 49 of the 52 accrued patients are evaluable, then the first 49 evaluable patients will be used for this analysis.

If the number of unacceptable toxicities observed falls in the rejection region at any test then the conclusion is that the treatment-related unacceptable toxicity rate is greater than 25%. In this case, the study chairs, RTOG Lung Cancer Committee Chair, and statistician will review the

toxicity data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study. Additionally, the treatment-related unacceptable toxicity rate will continue to be monitored during the four year follow-up period. If the lower limit of a one-sided 95% normal approximation confidence interval for the unacceptable toxicity rate exceeds 25% at any time during the four year follow-up period, the study chairs, RTOG Lung Cancer Committee Chair, and statistician will review the toxicity data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee.

13.4 Patient Accrual

Patient accrual is projected to be two cases per month. At that rate, it will take 26 months to reach the required 52 cases. If the average monthly accrual rate is less than 1 patient, the study will be re-evaluated for feasibility.

13.5 Analysis Plans

13.5.1 *Interim Reporting of Accrual and Toxicity Data*

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

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) accrual by institution;
- c) the distribution of pretreatment characteristics;
- d) the frequency and severity of the toxicities.

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

13.5.2 *Analysis for Reporting Treatment Results*

This analysis will be done when each patient has been potentially followed for a minimum of 24 months. It will include:

- a) tabulation of all cases entered into the trial; exclusions with reasons;
- b) institutional accrual;
- c) distribution of important prognostic baseline variables;
- d) observed results for the endpoints listed in Section 13.1.

The primary analysis will be done when each patient has had at least two years of follow up. Time to local progression is defined as the time from the start of treatment to the date of local progression. If a patient has no local progression at the time of the primary analysis, the patient will be censored. The hazard rate of local control will be estimated using life table estimates with a time span of two years. A one-sided Z-test will be performed to test if the difference between the logarithm of the observed hazard rate and the logarithm of the hypothesized hazard rate of 0.0093 per month is statistically significant. The variance for the Z-statistic will be estimated by the reciprocal of the number of cases with local progression within two years.

Estimates of the duration of control (using only patients attaining control), time to progression and overall survival at two years along with their associated 95% confidence intervals will be estimated using the Kaplan-Meier product limit method.⁴³ Toxicity grade will be summarized using contingency tables.

Further subgroup analyses will be undertaken if the sample sizes involved in each subgroup are adequate to support such analyses. 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

13.6 Inclusion of Women and Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have also considered the possible interaction between race and treatments. 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 in a recent analysis.⁴⁴ Furthermore, an analysis of race did not indicate an association with outcome.⁴⁵ The projected gender and minority accruals are:

Planned Gender and Minority Inclusion

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	1	2	3
Not Hispanic or Latino	21	28	49
Ethnic Category: Total of all subjects	22	30	52
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	0	1	1
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	22	26	48
More than one race	0	0	0
Racial Category: Total of all subjects	23	29	52

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APPENDIX I

RTOG 0236

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

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

You are being asked to take part in this study because you have early stage lung cancer and cannot have surgery.

WHY IS THIS STUDY BEING DONE?

The usual treatment for early stage lung cancer is to remove the cancer with surgery. However, when patients have other serious health problems like emphysema, diabetes, or heart disease, they may not be able to have the standard surgery.

Patients who cannot have surgery can receive radiation therapy. Standard radiation therapy involves several weeks of daily treatment sessions. While this therapy is sometimes successful at killing the cancer, it is not as effective as surgery and may seriously damage normal surrounding lung tissue.

A newer treatment technique using radiation therapy, stereotactic body radiation therapy (SBRT), has been developed and used for patients with metastases to the lungs. Metastases are cancerous tumors that have spread from one organ to another.

This newer treatment gives fewer but higher doses of radiation than standard radiation. It uses special equipment to position the patient and guide focused beams toward the cancer and away from normal surrounding lung tissue. The higher dose technique may work better to kill cancer cells with fewer side effects than standard radiation therapy.

The purpose of this study is to use SBRT with patients with early stage lung cancer and find out what effects (good and bad) SBRT has on you and your cancer. This research is being done because SBRT has not been used very often in patients with early stage lung cancer or in patients with other serious health problems. In addition, this study also will gather information about your health and hospitalization history. This information will be used to find out if there are factors that can predict recovery or outcome of patients with lung cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 52 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

Before treatment:

- A physical exam by several doctors
- A blood test to find out how much oxygen is delivered to the tissues beyond your lung
- For women who are able to have children, a test to see that they are not pregnant
- A chest x-ray
- A CT scan of your lungs and abdominal area
- A PET scan of your body: A small amount of radioactive material is injected into a vein, and a scanner makes a detailed picture of areas inside the body
- Tests of your lung function

In addition, you will be asked questions about your health and hospitalization history. Answering these questions will take approximately 10 minutes.

Before receiving radiation therapy, you will have a treatment planning session. You will lie in a specific position, possibly within a frame device, and undergo a CT scan of your lung and upper stomach. Doctors will check your breathing and see how your organs move. The doctors will try to limit the effect of that movement on the position of your tumor by timing your breathing and placing firm pressure on your stomach area to change the pattern of your breathing.

After this planning session, you will receive a total of three radiation treatments. Each of these radiation treatments will be separated by several days. Each treatment will last about an hour and will be given in a particular position to help guide the beams of radiation toward your cancer. You will be given an anti-inflammatory medication (corticosteroid) before each treatment to decrease possible inflammation and/or swelling that the treatment may cause in the lung. In addition, your doctor may give you pain medication before each treatment to decrease any discomfort you may have due to the one-hour duration of each treatment. You will be examined by several doctors after each of these treatments.

(9/9/09) You also will be seen in follow-up visits 6 and 12 weeks after treatment, every 3 months for 2 years, every 6 months for 2 years, then yearly for your lifetime. You will have the following tests and procedures in follow-up visits:

- A physical exam

- A blood test to find out how much oxygen is delivered to the tissues beyond your lung
- A chest x-ray or CT scan of your lungs and abdominal area (alternating every other visit)
- Tests of your lung function

HOW LONG WILL I BE IN THE STUDY? (9/9/09)

You will receive the 3 radiation treatments over 8-14 days. You will be seen in follow-up visits 6 and 12 weeks after treatment, every 3 months for 2 years, every 6 months for 2 years, then yearly for your lifetime.

Your doctor may decide to take you off this study if side effects become very severe, if new scientific developments occur that indicate the treatment is not in your best interest, if funding for this study is stopped, or your condition worsens.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

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

Stereotactic radiation therapy to the chest

Very Likely and Serious

- A common effect of this treatment in previous studies was eventual collapse of a portion of the treated lung; this collapse generally affects a limited portion of the lung, but the collapse appears to be permanent. Efforts will be made to reduce this risk and limit its effect. If collapse of a portion of the treated lung occurs, the patient will have shortness of breath at rest or during exercise, may need to receive oxygen, and/or may have chest wall pain. A few patients may need oxygen therapy permanently. A collapse of a portion of the lung may be life threatening.

Very Likely

- Fatigue (tiredness) for no apparent reason, which is temporary
- The skin in the treatment area may become reddened and/or dry, and chest hair may not grow back.

Less Likely

- Cough

- Difficulty breathing
- Fever
- Chest wall discomfort

Less Likely, But Serious

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

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 chest pain, shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. Six out of 37 patients treated in a previous study using SBRT had some or all of these symptoms. Treatment for this lung damage involves pain medicines, anti-inflammatory medicines (corticosteroids), and rarely, oxygen therapy, which may be permanent. You should tell your doctors immediately if you have any of these symptoms.

Corticosteroids

These anti-inflammatory medicines are usually well tolerated if used for a short period of time (as in this study). They can irritate the stomach. Less likely, but serious risks (if used for a longer period of time) include swelling due to fluid in the tissues; increased blood sugar; and/or increased blood pressure.

Reproductive Risks

This study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your doctor immediately.

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with early stage lung cancer in the future. The stereotactic body radiation therapy may work better to kill cancer cells with fewer side effects than standard radiation therapy, but this benefit is not guaranteed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) standard radiation therapy; or (2) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

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

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

WHAT ARE THE COSTS?

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

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

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

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

A group of experts in lung cancer from the RTOG Lung Cancer Committee, the study chairs, and the RTOG study statistician will be reviewing the data periodically throughout the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

_____ Name

_____ Telephone Number

For information about this study, you may contact:

_____ Name

_____ Telephone Number

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

_____ Name

_____ Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Visit the NCI's Web sites for comprehensive clinical trials information at
www.cancer.gov/clinicaltrials or for accurate cancer information

including PDQ (Physician Data Query) visit
www.cancer.gov/cancerinfo/pdq

SIGNATURE

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

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

_____ Patient's Name	_____ Signature	_____ Date
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_____ Name of Person Obtaining Consent	_____ Signature	_____ Date
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APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	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).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Death (Karnofsky 0)

APPENDIX III

AJCC Staging Lung, 6th Edition, 2002

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
Lung, 6th Edition, 2002**

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

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

APPENDIX IV

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.

APPENDIX IV (Continued)

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, hernia): 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)

(Charlson et al. *J Chron Dis.* 40:373-383, 1987) Adaptation: Do not count non-melanotic skin cancers or in situ cervical carcinoma.

Myocardial infarct	Hx of medically documented myocardial infarction
Congestive heart failure	Symptomatic CHF w/ response to specific treatment
Peripheral vascular disease	Intermittent claudication, periph. arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (>=6cm)
Cerebrovascular disease (except hemiplegia)	Hx of TIA, or CVA with no or minor sequelae
Dementia	chronic cognitive deficit
Chronic pulmonary disease	symptomatic dyspnea due to chronic respiratory conditions (including asthma)
Connective tissue disease	SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA
Ulcer disease	Patients who have required treatment for PUD
Mild liver disease	cirrhosis without PHT, chronic hepatitis
Diabetes (without complications)	diabetes with medication
Diabetes with end organ damage	retinopathy, neuropathy, nephropathy
Hemiplegia (or paraplegia)	hemiplegia or paraplegia
Moderate or severe renal disease	Creatinine >3mg% (265 umol/l), dialysis, transplantation, uremic syndrome
2nd Solid tumor (non metastatic)	Initially treated in the last 5 years exclude non-melanomatous skin cancers and in situ cervical carcinoma
Leukemia	CML, CLL, AML, ALL, PV
Lymphoma, MM...	NHL, Hodgkin's, Waldenström, multiple myeloma
Moderate or severe liver disease	cirrhosis with PHT +/- variceal bleeding
2nd Metastatic solid tumor	self-explaining
AIDS	AIDS and AIDS-related complex Suggested: as defined in latest definition

APPENDIX IV (Continued)

COMORBIDITY RECORDING SHEET

RTOG 0236

RTOG Institution Name/Number: _____

Patient Initials (First Middle Last): _____ RTOG Patient Case Number: _____

Name of Person Completing Sheet: _____ Phone Number: _____

Date Completed: __-__-__

Comorbidities (Add TR if related to tumor or its treatment)	Score
Heart	
Vascular	
Respiratory (include tobacco history)	
Eyes and ENT	
Upper GI	
Lower GI	
Liver and Pancreas	
Renal (Creatinine:)	
GU	
Musculoskeletal/Integument	
Neurological	
Endocrine/Metabolic and Breast (Weight: Height:)	
Psychiatric	

Medications	

APPENDIX IV (Continued)

**CHARLSON COMORBIDITY INDEX (CCI)
Scoring Sheet**

RTOG 0236

RTOG Institution Name/Number: _____

Patient Initials (First Middle Last): _____ RTOG Patient Case Number: _____

Name of Person Completing Sheet: _____ Phone Number: _____

Date Completed: __-__-____

Comorbidity	Present	Points
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd Solid tumor (nonmetastatic)		2
Leukemia		2
Lymphoma, MM...		2
Moderate or severe liver disease		3
2nd Metastatic solid tumor		6
AIDS		6

Total points: _____