NRG ONCOLOGY

RTOG 0618

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

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Document History (3/6/14)

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RTOG Headquarters/Statistical Unit
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1-800-227-5463, ext. 4189

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UNIVERSITY OF WISCONSIN MADISON

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

SCHEMA (2/4/09. 3/25/10, 10/25/12)

Stereotactic Body Radiation Therapy (SBRT), 20 Gy per fraction for 3 fractions over 1.5-2 weeks, for a total of 60 Gy

Local Enlargement (LE) on CT?  

LE

Perform PET or biopsy

Positive

Surgically Resect Tumor

Tumor in specimen?

Yes

Primary Tumor Failure

No

Follow for primary tumor control, toxicity, and survival

CR, PR, Stable

Follow for primary tumor control, toxicity, and survival

Negative

Follow for primary tumor control, toxicity, and survival
Chemotherapy recommended, see Section 9.0.

1 Total treatment dose is 60 Gy given in 3 fractions of 20 Gy per fractions for all enrolling sites. This dose is to be calculated WITHOUT heterogeneity corrections (i.e., assuming only water density within the patient) as was done in RTOG 0236.

2 Defined as in RTOG 0236: At least a 20% increase in the largest diameter (LD) of target lesion, taking as reference the smallest LD recorded since the treatment started.

3 PET positive defined as SUV levels similar or higher than baseline (95% or greater of baseline SUV) after SBRT. Biopsy positive defined as malignant cells in specimen irrespective of viability.

4 Tumor controlled at this point of follow-up.

5 Salvage anatomical lobectomy or pneumonectomy is preferred when feasible, but sublobar or wedge resections are allowed per local surgeon’s discretion.

6 Simple presence of tumor cells irrespective of viability

7 Continue to follow for SBRT related toxicity and overall survival

8 Choice of PET or biopsy evaluation after local enlargement per local treating physician

**Patient Population:** (See Section 3.0 for Eligibility)
Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 operable non-small cell lung cancer; patients with T3 tumors must have 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:** 33 patients
SBRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

___________(Y) 1. Non-small cell lung cancer (NSCLC) histologically confirmed by biopsy or cytology within 180 days prior to registration?

___________(N) Does the tumor histology show bronchioloalveolar cell carcinoma subtype?

___________(Y) 2. Is patient T1, T2, or T3?

___________(Y) If T2 or T3, is primary tumor less than or equal to 5 cm in greatest diameter?

___________(Y) If T3, is primary tumor limited to chest wall?

___________(Y) 3. Is patient nodal status N0 per definition in Section 3.1.3.?

___________(Y/N) Are there hilar or mediastinal lymph nodes > 1 cm on computed tomography (CT) or any size lymph nodes demonstrating suspicious uptake on positron emission tomography (PET) scan?

___________(Y) If yes, are all lymph nodes > 1 cm on CT or demonstrating suspicious uptake on PET scan negative on biopsy for NSCLC?

___________(Y) 4. Is patient M staging M0?

___________(Y) 5. Is the primary tumor predicted to be technically resectable with high likelihood of negative surgical margins by a thoracic surgeon?

___________(Y) 6. Is the patient medically operable as defined in Section 3.1.4?

___________(Y/N) 7. Is pleural effusion present?

___________(Y) If so, is the effusion too small to tap under CT guidance and not evident on chest x-ray? Pleural effusion that appears on chest x-ray and only after thoracotomy or other invasive thoracic procedure will be permitted.

___________(N) 8. Has the patient had weight loss greater than 5% for any reason within the past 3 months?

___________(Y) 9. Is patient ≥ 18 years of age?

___________(Y) 10. Is the patient’s Zubrod performance status 0-1 within 45 days prior to study entry?

___________(Y/NA) 11. Has the patient agreed to use an effective method of contraception?

(Continued on next page)
12. Have the required pretreatment evaluations and staging studies been obtained as specified in Section 3 and are results compatible with required parameters for registration to this study?

13. Is there evidence of distant metastases, or synchronous primary or prior invasive malignancy within the past 3 years?

14. Any prior radiotherapy for lung cancer?

15. Any prior radiotherapy for any other cancer which would overlap the planned SBRT fields?

16. Any previous chemotherapy or surgical resection for this lung cancer?

17. Are other concomitant local or regional antineoplastic therapies planned (aside from adjuvant systemic platinum-based chemotherapy)?

18. Is there evidence of active systemic, pulmonary, or pericardial infection?

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

20. Is 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?

The following questions will be asked at Study Registration:

1. Institutional person registering case?

2. Has the Eligibility Checklist been completed?

3. In the opinion of the investigator, is the patient eligible?

4. Date informed consent signed

5. Patient’s Initials (First Middle Last)

6. Verifying Physician

7. Patient ID

8. Date of Birth

9. Race

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<td>15. Any care at a VA or military hospital?</td>
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<td>16. Calendar Base Date</td>
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<td>(Y/N) 20. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?</td>
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<td>(Y/N) 21. Specify use of IMRT</td>
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<td>(Y/N) 22. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
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<td>(Y/N) 23. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
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<td>(Y/N) 24. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
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<td>(Y/N) 25. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?</td>
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<td>(Y/N) 26. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?</td>
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<td>(Y/N) 27. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?</td>
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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 172,570 new lung cancer cases in the United States in 2005, with an estimated 163,510 deaths as a result of this highly lethal malignancy. Lung cancer accounts for approximately 13% of all cancers diagnosed but 29% of all cancer deaths. 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. The number of patients diagnosed with stage I NSCLC is expected to rise significantly in the next several decades if widespread screening with spiral computed tomography (CT) scanning is adopted.

Surgical resection of stage I (T1-2, NO) NSCLC results in 5-year survival rates of approximately 60-70% and remains the treatment of choice for this population. Based on a randomized trial, the preferred surgical procedure is an anatomic dissection/resection with lobectomy and hilar/mediastinal lymph node removal. Unfortunately, some patients with early-stage NSCLC are unable to tolerate the rigors of surgery or the postoperative recovery period because of lack of adequate respiratory reserve, cardiac dysfunction, diabetes mellitus, vascular disease, general frailty, or other co-morbidities. Some of these patients are treated with a less extensive or radical surgery (e.g., wedge resection), whereas others receive second-line therapy with conventionally fractionated radiotherapy.

Primary radiotherapy for early-stage NSCLC is considered reasonable nonsurgical therapy for such patients, with reported 5-year survival rates ranging from 10-30%. 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. For example, a review of 156 medically inoperable stage I NSCLC patients at Duke University between 1980 and 1995 demonstrated a 5-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). Because early-stage NSCLC is not inherently a systemic disease from diagnosis and because 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 25% and on surgical data indicating better control with more extensive resections. Nonetheless, large radiotherapy fields are potentially poorly tolerated in this population with limited pulmonary reserve. More recent retrospective experience, however, shows similar survival results with fields limited to the primary tumor alone as compared with 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) with reported 3-year overall and disease-specific survival of 42% and 76%, respectively.

The majority of these mostly retrospective reports used radiotherapy equipment and techniques from the one- and two-dimensional planning era. With these older techniques, it was difficult to reduce high dose volume because of limitations in visualizing the target, in selection of beam directions, and 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 three-dimensional 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 uses 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.

The 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 used. Doses escalated as high as 90.3 Gy in the 179 treated patients. Although analysis of this study has not yet been published, the results indicate that the incidence of grade 3 or higher acute toxicity was 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-DCRT 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 these trials is on average greater than that in the currently proposed trial, the high rate of failure within the PTV offers justification for maintaining high doses even in stage I patients.

1.2 Stereotactic Body Radiation Therapy (SBRT)

Researchers at the Karolinska Hospital in Stockholm, Sweden, developed an extracranial stereotactic frame and began treatment with the device in 1992. The results of more than 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.25 reported on 17 patients treated with stereotactic radiotherapy for intrathoracic metastases with follow-up of 3.5 to 25 months. Tumors ranged in size from 1.8 cm to 7.2 cm. Margin doses ranged from 20 Gy in 1 fraction to 45 Gy in 3 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 2 months post treatment, 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 (also known as extracranial stereotactic radioablation) with large doses per fraction was delivered in an extracranial stereotactic body frame, which included 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 were added to the GTV to constitute the PTV based on validation measurements for this commercially available system.27-29 Typically, seven to ten 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 was intended to give extra dose in areas of presumed greatest tumor hypoxia and radioreistance. 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 study, which used a standard dose escalation protocol with three patient cohorts and a minimum of 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 x 3 = 42 Gy total in one T2 patient with a 7 cm lung tumor, and transient grade 3 hypoxia was seen at 16 x 3
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 that appeared 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 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 two of five patients with larger T2 tumors (> 5 to ≤ 7 cm) at a dose of 24 x 3 = 72 Gy, defining the MTD for this subgroup at 22 x 3 = 66 Gy. Patients treated at a dose of 22 Gy per fraction for 3 fractions have had follow-up of more than 24 months without late toxicity for all T-stage tumor categories. Treatment failure within the PTV has been observed in eight of 26 patients treated at doses of up to 20 x 3 = 60 Gy. However, all but one of these local failures occurred at doses of 16 x 3 = 48 Gy or lower.

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. Others have used a “tracking” approach in which the radiation source follows the position of the tumor via a surrogate marker. 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.

Based on the highest dose levels from the Indiana University phase I study, the same group completed a larger phase II study to confirm toxicity and to attempt to measure efficacy. This 70 patient phase II study included patients with T1 or T2 (up to 7 cm maximum diameter), N0, M0 biopsy-proven NSCLC and was funded by a grant from the US National Institutes of Health. All patients had predefined criteria rendering them “medically inoperable.” All patients had baseline clinical staging with spiral CT and positron emission tomography (PET). Patients were divided into two equal groups, T1 vs. T2. T1 patients were treated at 20 x 3 = 60 Gy, while T2 patients received 22 Gy x 3 = 66 Gy. The primary endpoint of the study was 2-year local control, strictly defined as an enlarging CT abnormality in the region of the treated tumor that either was re-biopsied showing persistent tumor or had PET standardized uptake value (SUV) of the order of the pretreatment PET (EORTC criteria). The final results of this trial have not been published, but a preliminary report was presented at the 2005 ASTRO meeting. With median follow-up of 18 months (maximum 44 months), actuarial local control is 95% at 2 years. Despite the general frailty of the population (a third on home oxygen prior to treatment), only 14 patients experienced grade 3-5 toxicity. Prognostic assessment showed that most of these high-grade toxicities, including most of the toxic deaths, occurred in patients treated for tumors located in the proximal Airways in the vicinity of the pulmonary hilum (called the zone of the proximal bronchial tree).

The RTOG completed the enrollment of 56 patients in a multicenter phase II trial, RTOG 0236, for medically inoperable lung cancer patients using a dose of 20 x 3 = 60 Gy (homogeneous tissue planning). This trial allowed biopsy-proven tumors with maximum diameter up to 5 cm. Multiple treatment platforms and technology were allowed so long as the criteria for immobilization/motion control and dose construction were observed. All institutions underwent an extensive accreditation process including irradiation of a phantom. Treatment planning and follow-up data are being collected centrally. Because of the toxicity observed in the Indiana trials, patients with tumors in the zone of the proximal bronchial tree were excluded from this trial. Several interim toxicity analyses of patient outcome on the RTOG trial did not indicate any prohibitive toxicity. Concurrent with the RTOG trial, a similar prospective trial is ongoing in Japan via a multicenter consortium. That trial includes two groups: operable and medically inoperable patients. It uses a dose of 12 x 4 = 48 Gy based on institutional data from Kyoto University Hospital.

1.3 Wedge Resection Versus Anatomical Resection

Although a complete anatomic lobectomy has long been the preferred surgical procedure for treating resectable NSCLC, data from Rush-Presbyterian published in the late 1970s indicated considerably less surgical pulmonary morbidity with less extensive operations, including segmentectomies and generous wedge resections. Because most people with lung cancer have some underlying cardiopulmonary dysfunction related to tobacco abuse, this concept was encouraging, especially if it did not significantly reduce the control or cure rates over lobectomy. This experience led to a phase III trial carried out in the 1980s (before PET scanning) by the North American Lung Cancer Study Group (LCSG) and reported in 1995 by Ginsberg et al. Two
hundred seventy-six patients were enrolled in this randomized trial, all having medical characteristics predicted to allow a lobectomy. Patients were randomized to lobectomy vs. limited resection (segmentectomy or wedge). Lobectomy was superior to limited resection with respect to time to recurrence and survival. The difference in survival was not apparent until 3 years post treatment on actuarial analysis. Despite the fact that margins were mandated to be negative in both groups, excess tumor recurrence was most likely in the involved lobe not completely resected for the limited resection group, indicating a “marginal” recurrence pattern. Furthermore, there was no statistical difference in the operative morbidity or late pulmonary function. The authors concluded that limited resection is inferior to lobectomy at controlling lung cancer and is not inherently less morbid.

Since these data were presented, wedge resections have been generally considered a compromised operation used only in circumstances in which severe pre-existing pulmonary dysfunction excludes lobectomy. Recurrences with wedge resections occur mostly at the proximal bronchial margin along the suture/staple line. Technically, this is related to difficulties in the positioning of the stapler (or suture line) around the tumor without closing off adjacent branching uninvolved segments, resulting in a close margin in the direction of the pulmonary hilum compared to the margins in the direction of the pleura. Some wedge resection experiences have high local control, however, these are in highly selected patients with small peripheral tumors.

Although some have speculated that SBRT effectively performs a wedge resection via ablation of the same distribution of pulmonary tissue and tumor, there are reasons to argue that the procedures are different. With SBRT, there is no technical hindrance to obtaining adequate “margin” on all sides of the treated tumor. Especially with photon-based SBRT using high target dose, there is a concentric zone of intermediate to high dose (called penumbra) capable of eradicating microscopic deposits of tumor. Indeed, in the Indiana phase II trial, the 2-year local recurrence-free survival was 95%, which is much higher than the limited resection data from similarly selected patients in the LCSG trial and is, in fact, comparable to lobectomy.

1.4 Surgical Versus Clinical Staging

Historically, unsuspected hilar or mediastinal lymph node involvement has been observed in about 20% of clinically evaluated stage I patients at the time of surgery. This discrepancy between surgical and clinical staging, coupled with the notion that surgical lymphadenectomy is therapeutically not necessary, has supported the notion that anatomic dissection and resection are both part of the standard of care. Recent series using modern staging studies including spiral CT and PET have not observed such high rates of staging errors.

For pathologically identified stage II patients, standard treatment is lobectomy, lymph node resection, and cisplatin-based chemotherapy. Regional conventionally fractionated radiotherapy is usually reserved for patients with close or positive margins or with unresected gross disease. For pathologically identified stage III patients, the standard treatment is chemoradiotherapy. Staging errors in clinically staged I patients treated with SBRT (with or without adjuvant chemotherapy) could therefore theoretically compromise overall treatment by omitting an effective local therapy to hilar or mediastinal lymph nodes. However, with modern clinical staging, this risk is considered to be low. Furthermore, should patients have recurrence in the regional lymph nodes after SBRT, they likely would still be candidates for the therapy potentially given to pathologically staged patients as primary treatment.

1.5 Proposed Study (3/25/10)

Surgical resection remains the standard of care for resectable patients with early-stage NSCLC, with high rates of primary tumor control, local control and overall survival. Still, the preferred procedure, lobectomy, is associated with substantial perioperative difficulties, including some operative mortality, severe acute and chronic pain, and loss of functional pulmonary reserve. Lesser resections have neither significantly reduced toxicity nor maintained control and survival in prospective trials. As such, it is reasonable to consider alternate therapies, including nonsurgical therapies, in prospective testing.

SBRT has demonstrated high rates of primary tumor control for medically inoperable patients in series from several centers. Although higher grade toxicity has been described, particularly when treating lesions near the pulmonary hilum, the overall rates of toxicity are low. As an outpatient noninvasive therapy, SBRT allows rapid recovery, minimal discomfort, and cost-effectiveness.
With extremely high rates of primary tumor control in prospective studies treating medically inoperable patients who are poorly tolerant of any therapy, there is ample rationale for testing SBRT in operable patients.

Despite the encouraging results using SBRT in medically inoperable patients, the results published thus far do not have long-term follow-up for the majority of patients. Considerable caution must be exercised to avoid under treating this curable population of patients capable of many years of survival with effective therapy.

Adjuvant chemotherapy after resection of stage II-IIIA non-small-cell lung cancer is now the standard of care based on the results of several international phase III studies using platinum-based regimens. There does not appear to be a benefit for such therapy in stage IA patients. The role of adjuvant chemotherapy for stage IB disease remains controversial, especially since information was released from the updated results from CALGB (Cancer and Leukemia Group B) trial 9633.39 This trial employed a carbo-platinum regimen and focused on stage IB patients. While initial results showed a significant survival advantage with the addition of chemotherapy, the updated results are no longer statistically significant. Furthermore, a recent large phase III trial in multiple stages of non-small cell lung cancer showed that the addition of bevacizumab (an antibody against vascular endothelial growth factor, VEGF) over adjuvant therapy with platinum based chemotherapy alone resulted in a significant survival benefit.40

1.6 Comorbidity Assessment

Although deemed medically “operable,” patients enrolled in this study may have confounding medical problems, 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.41-43 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.42 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 scales44-46 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.46,47 Neither scale correlates with functional status, and each provides independent information.46

1.7 Recent Results of SBRT in Lung cancer (3/25/10)

Recently, updated or new reports of SBRT treatment of lung cancer in stage I patients have been reported. Some of these results, again supporting this protocol, are shown in the Table below. Results in Asia are generally better than in North America or Europe similar to what is observed in surgical series probably related to patient selection.

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Primary Tumor Control</th>
<th>Single Fraction Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America/Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timmerman, 2006</td>
<td>20-22 Gy X 3</td>
<td>95% (2+ years)</td>
<td>56 – 62 Gy</td>
</tr>
<tr>
<td>Bauman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (3 years)</td>
<td>41 Gy</td>
</tr>
<tr>
<td>Fritz, 2006</td>
<td>30 Gy X 1</td>
<td>80% (3 years)</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Nyman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (crude)</td>
<td>41 Gy</td>
</tr>
<tr>
<td>Zimmermann, 2005</td>
<td>12.5 Gy X 3</td>
<td>87% (3 years)</td>
<td>43.5 Gy</td>
</tr>
</tbody>
</table>
Patients with similar stage of disease respond to treatment differently with the chance of tumor control. Although reports have shown that SBRT has generated outstanding tumor control rates, local failures are noted in 0-30% of patients (above table). Similarly, patients are different in their risk of developing treatment-related toxicities. Although severe toxicity is limited in the majority of reports, clinically significant toxicities such as aggravated dyspnea and radiation pneumonitis may occur in 20-40% patients. Who will be cured and or who will develop treatment toxicity are important study questions of translational research.

With advancement in the field, we have recently learned that expression of many specific molecules in the tumor were associated with the prognosis and predictive of responsiveness to certain treatments. Zheng, et al. evaluated the prognostic value of the protein expression of excision repair cross-complementation group 1 (ERCC1) and RRM1 (regulatory subunit of ribonucleotide reductase) in tumors of early stage NSCLC treated with surgical resection alone. High expressions of both of these two specific proteins were significantly associated with improved survival. The tumoral RRM1 expression was a major predictor of tumor response to gemcitabine/platinum chemotherapy. Most interestingly, changes in blood nucleosomal DNA fragments, cytokeratin-19 fragments (CYFRA 21-1), ERCC1 protein polymorphisms, or serum carcinoembryonic antigens specifically identify a subgroup of patients with insufficient therapy response at the early treatment phase and were shown to be valuable for disease management. The EGFR mutation status in the blood was consistent with that in the tumor tissue, suggesting the potential value of studying biomarkers in the blood.

To predict normal tissue toxicities, transforming growth factor beta 1 (TGFβ) has been most extensively studied for pneumonitis and non-lung toxicities. Researchers from Duke University reported that the plasma TGFβ level at the end of radiation correlated with symptomatic lung toxicity in patients treated with definitive radiation therapy. Kong, et al. further demonstrated that the loss of a tumor suppressor gene, mannose 6-phosphate insulin-like growth factor-2 receptor, contributed to increased TGFβ levels and subsequent radiation-induced pneumonitis in patients with NSCLC. In patients with lung cancer treated with an escalated dose of radiation, Anscher, et al. found a significant correlation between TGFβ levels and late non-pulmonary grade 3 and radiation toxicity. A recent study from the University of Michigan has shown that radiation-induced elevation during the course of external beam conformal radiation therapy is highly correlated with occurrence of greater than grade 2 radiation pneumonitis. Other cytokines also are involved in lung toxicity. Interleukin-6 (IL-6), a major mediator of the acute-phase inflammatory response, synthesized by a variety of cells in the lung parenchyma including the alveolar macrophages, type II pneumocytes, T lymphocytes, and lung fibroblast, also has increased mRNA expression in macrophages and a trend toward increased plasma concentrations after thoracic RT. IL-6 actively participates in the inflammatory process of lymphocytic alveolitis (radiation pneumonitis) both in experimental models and in human lung diseases by stimulating inflammatory cells, particularly lymphocytes and macrophages. Others reported that pretreatment IL-6 level may serve as a predictor for radiation pneumonitis. Serial plasma IL-6 was consistently higher for the pneumonitis group. A recent study also showed promising results concerning the association of single nucleotide polymorphisms (SNP) of several specific genes of white blood cells with radiation induced acute and late toxicities. There are many other molecules involved in the processes of tumor response and radiation normal tissue toxicity. The advances in cytokine arrays and proteomic and genomic techniques have now made it possible to evaluate many of these proteins and genes together for their association with treatment outcome.
The proposed translational research aims to examine if proteomic or genomic markers in the blood before completion of the last dose of SBRT are predictive of primary tumor control and grade 2 and above radiation toxicity.

2.0 OBJECTIVES

2.1 Primary Objective (3/25/10)
The primary objective of the study is to determine whether radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable primary tumor control (i.e., \( \geq 90\% \) at 2 years) in operable patients with early-stage NSCLC.

2.2 Secondary Objectives (3/25/10)
2.2.1 To determine whether radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable treatment-related toxicity;
2.2.2 To estimate the disease-free survival and the overall survival rate at two years and to observe patterns of failure (see definitions in Section 11.2.3) during first two years;
2.2.3 To assess level of comorbidity burden on morbidity and efficacy.
2.2.4 To study if blood markers prior to, during the course of treatment (between the second and the last dose of SBRT), and at the first follow-up after SBRT predict 2 year primary tumor control and predict for grade \( \geq 2 \) treatment-related toxicities.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (9/3/08, 2/4/09, 8/20/09)
3.1.1 Histological confirmation of NSCLC is required by either biopsy or cytology within 180 days prior to registration. The following primary cancer types are eligible: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, large cell neuroendocrine, and non-small cell carcinoma not otherwise specified. Although bronchioloalveolar cell carcinoma is a subtype of NSCLC, patients with the pure type of this malignancy are excluded from this protocol because this cancer’s spread between adjacent airways is difficult to target on CT.

3.1.2 Eligible patients must have appropriate staging studies identifying them as specific subsets of AJCC Lung 6th Edition, 2002 stage I or II based on only one of the following combinations of TNM staging:
- T1, N0, M0
- T2 (\( \leq 5 \) cm), N0, M0
- T3 (\( \leq 5 \) cm), N0, M0 chest wall primary tumors only

3.1.3 Patients with hilar or mediastinal lymph nodes \( \leq 1 \) cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Mediastinal lymph node sampling by any technique is allowed but not required. Patients with > 1 cm hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but nondiagnostic uptake) will still be eligible if directed tissue biopsies of all abnormally identified areas are negative for cancer.

3.1.4 (3/25/10) The patient must be considered a reasonable candidate for surgical resection of the primary tumor according to the following criteria:
- A qualified thoracic surgeon should make the determination prior to registration that there would be a high likelihood of negative surgical margins.
- baseline FEV1 \( > 35\% \) predicted,
- postoperative predicted FEV1 \( > 30\% \) predicted,
- diffusion capacity \( > 35\% \) predicted,
- absent baseline hypoxemia (hypoxemia defined as PaO2 of \( \leq 60 \) mm Hg on room air) and/or hypercapnia (hypercapnia defined as PaCO2 > 50 mm Hg),
- absent severe pulmonary hypertension,
- absent severe cerebral, cardiac, or peripheral vascular disease,
- absent severe chronic heart disease.
3.1.5 Pleural effusion, if present, must be deemed too small to tap under CT guidance and must not be evident on chest x-ray. Pleural effusion that appears on chest x-ray will be permitted only after thoracotomy or other invasive procedure.

3.1.6 Age ≥ 18 years.

3.1.7 Zubrod performance status 0-1 within 45 days prior to study entry.

3.1.8 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.

3.1.9 Pretreatment Evaluations Required for Eligibility include:
3.1.9.1 A medical history, physical examination, weight within 45 days prior to study entry;
3.1.9.2 Evaluation by an experienced thoracic cancer clinician within 56 days prior to study entry;
3.1.9.3 For women of childbearing potential, a serum or urine pregnancy test must be performed within 72 hours before the start of protocol treatment;
3.1.9.4 PFTs: Routine spirometry, lung volumes, diffusion capacity, and arterial blood gases within 56 days prior to study entry.

3.1.10 Mandatory staging studies: Must be done 45 or fewer days prior to study entry
3.1.10.1 Chest radiograph;
3.1.10.2 CT scan (preferably with intravenous contrast, unless medically contraindicated) to include the entirety of both lungs, the mediastinum, liver, and adrenal glands. If the enrolling center has a combined PET/CT scanner and both aspects are of diagnostic quality and read by a trained radiologist, the images will meet the staging requirements for both CT and PET; (9/3/08)
3.1.10.3 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.

3.1.11 CBC/differential obtained within 28 days prior to registration on study, with adequate bone marrow function defined as follows:
3.1.11.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm³
3.1.11.2 Platelets ≥ 100,000 cells/mm³
3.1.11.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.12 Patient must provide study-specific consent prior to study entry.

3.2 Conditions for Patient Ineligibility
3.2.1 T2 or T3 primary tumors > 5 cm or 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 3 years other than non-melanomatosus skin cancer or in situ cancer;
3.2.4 Previous radiotherapy for the treatment of lung cancer. Previous radiotherapy as part of a treatment for head and neck, breast cancer, or other non-lung cancer is allowed so long as there will not be significantly overlap with the SBRT fields. Previous chemotherapy or surgical resection for the lung cancer being treated on this protocol is NOT permitted.
3.2.5 Plans for the patient to receive other concomitant local or regional therapy per Section 9.2 (including standard fractionated radiotherapy and surgery) while on this protocol except according to protocol requirements or at disease progression;
3.2.6 Active systemic, pulmonary, or pericardial infection;
3.2.7 Pregnant or lactating women or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
3.2.8 Pure type of bronchioloalveolar carcinoma subtype of non-small cell lung cancer.
3.2.9 Weight loss > 5% for any reason within 3 months of study entry.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (2/4/09, 8/20/09)

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management
See Section Appendix II; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements for SBRT Treatment Approach (2/4/09, 8/20/09)
Institutions must be credentialed for stereotactic body radiation therapy 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 four steps (Sections 5.1.1-5.1.4): Centers previously credentialed for these technologies/procedures will not have to be re-credentialed. Institutions that change the technology/procedures previously credentialed (i.e., fundamentally change methods like changing from tracking to abdominal compression for motion control) must be re-credentialed with their new systems. Please refer to the RPC web site for details.

5.1.1 Each institution must complete the New Facility Questionnaire for SBRT available on the ATC web site, http://atc.wustl.edu. Each institution must submit the completed Facility Questionnaire to RTOG Headquarters. (2/4/09)

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.

Each institution must demonstrate its 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 (3/25/10) Each institution must contact the ITC (itc@wustl.edu) and request an SFTP (The ITC is now using Secure FTP (SFTP) and this should now be the term used in all cases of electronic submission to the ITC.) 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. The phantom can be irradiated in a stationary position or placed on a moving platform. 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. This protocol allows dose painting delivery techniques including IMRT, and the phantom irradiation requirements vary according to the combination of delivery technique and respiratory control methodology. In general, institutions using conformal techniques and abdominal compression for respiratory motion control together with the recommended margins (see 6.4.1) will irradiate the stationary version of the phantom. The exception is for institutions intending to use either tracking or gating techniques when lesions do not remain within the stated margins. These institutions will be required to irradiate the moving phantom for credentialing. Additionally, institutions using dose painting or IMRT delivery techniques will be required to irradiate the moving phantom for all methods of respiratory control. 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). It is recognized that some treatment planning systems are only partially able to submit required data to the ITC. As a minimum requirement, the dry run protocol submission. (2/4/09)

5.1.4 Each institution must successfully complete and submit 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 Pre-Registration Requirements for IMRT Treatment Approach (2/4/09, 8/20/09)
In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc/ and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT Lung study). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.1 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://itc.wustl.edu. Upon review and successful completion of the “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Regulatory Pre-Registration Requirements (9/3/08, 8/20/09, 10/25/12)

5.3.1 U.S. sites and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/readfile.aspx?fname=public/CTSU-IRBcertif_Final.PDF, prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to RTOG Headquarters.
- IRB/REB assurance number
5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.3.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.3.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.3.3.1 For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.3.3.2 For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.4 Registration
5.4.1 Online Registration
Patients can be registered only after eligibility criteria are met.
Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:
- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

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

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

(8/20/09) Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (2/4/09)
Note: Dose painting delivery techniques including IMRT are allowed in this protocol.
6.1 **Dose Specifications**

6.1.1 **Stereotactic Targeting and Treatment**

SBRT has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology. This protocol will respect that guideline. 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. The coordinate system is defined by reliable “fiducial” markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). 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 radiopaque 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 be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

6.1.2 **Dose Fractionation (8/20/09)**

Patients will receive 3 fractions of radiation. The dose for all patients will be 20 Gy per fraction to the prescription line at the edge of the PTV. All treatment must be completed within 16 days. The time between fractions is at the discretion of the investigator, but 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).**

6.1.3 **Premedications**

Although not mandatory, it is recommended that patients receive corticosteroid premedication (e.g., Dexamethasone 4 mg p.o. in a single dose, or equivalent) 15-60 minutes before 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 (2/4/09)**

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but not > 15 MV will be allowed only 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 (2/4/09)**

Because of 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 for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements listed in Section 6.4 for small lesions (< 2.5 cm axial gross tumor volume (GTV) dimension or < 1.5 cm craniocaudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques (e.g., Cyberknife, Tomotherapy, etc) where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed.

6.2.3 **Dose Verification at Treatment**

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

6.2.4 **Treatment Platforms (2/4/09)**

The protocol allows most commercially available photon producing treatment units except the exclusion of units described in Section 6.2.1 (e.g., cobalt units and charge particle accelerators). As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used...
with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., the Cyberknife, or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol and are used in a fashion that passes the accreditation tests 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 used, 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) before 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 (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques. All systems used to account for internal organ motion must be validated and accredited by the Study Committee (Principal Investigator and Co-Chairs) before enrolling or treating patients on this trial. Internal organ inhibition maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.3 Localization
Isocenter or reference point 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 using 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 quality assurance (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 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. 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, include only 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 (craniocaudal) will be added to the GTV to constitute the 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, ≥ 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 seven 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 buildup 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 the more traditional 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 3 fractions will be delivered to the margin of the PTV and fulfill the requirements below. As such, a “hotspot” 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 of 60 Gy and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (i.e., 54 Gy).

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 number 1 above.

4) High Dose Spillage
   a) Location
   Any dose $> 105\%$ of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose $> 105\%$ of prescription dose 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 craniocaudal GTV dimension) in which 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) **Intermediate 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 must be no greater than \( D_{2\text{cm}} \) where \( D_{2\text{cm}} \) is given by the table below.

b) **Volume**

The ratio of the volume of the 30 Gy isodose volume to the volume of the PTV must be no greater than \( R_{30\text{ Gy}} \) where \( R_{30\text{ Gy}} \) is given by the table below. This table is used for all prescription requirement in Section 6.4.2 irrespective of calculation algorithm and total treatment dose.

<table>
<thead>
<tr>
<th>Maximum PTV Dimension (cm)</th>
<th>Ratio of Prescription Isodose Volume to the PTV</th>
<th>Ratio of 30 Gy Isodose Volume to the PTV, ( R_{30\text{ Gy}} )</th>
<th>Maximum Dose 2 cm from PTV in any Direction, ( D_{2\text{cm}} ) (Gy)</th>
<th>Percent of Lung receiving 20 Gy total or more, ( V_{20%} ) (%)</th>
<th>PTV Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation</td>
<td>Deviation</td>
<td>Deviation</td>
<td>Deviation</td>
<td>Deviation</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>minor</td>
<td>none</td>
<td>minor</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9</td>
<td>3.9-4.1</td>
<td>&lt;28.1</td>
</tr>
<tr>
<td>2.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9</td>
<td>3.9-4.1</td>
<td>&lt;28.1</td>
</tr>
<tr>
<td>3.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9</td>
<td>3.9-4.1</td>
<td>&lt;28.1</td>
</tr>
<tr>
<td>3.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9</td>
<td>3.9-4.1</td>
<td>&lt;28.1</td>
</tr>
<tr>
<td>4.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.8</td>
<td>3.8-4.0</td>
<td>&lt;30.4</td>
</tr>
<tr>
<td>4.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.7</td>
<td>3.7-3.9</td>
<td>&lt;32.7</td>
</tr>
<tr>
<td>5.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.6</td>
<td>3.6-3.8</td>
<td>&lt;35.1</td>
</tr>
<tr>
<td>5.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.5</td>
<td>3.5-3.7</td>
<td>&lt;37.4</td>
</tr>
<tr>
<td>6.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.3</td>
<td>3.3-3.5</td>
<td>&lt;39.7</td>
</tr>
<tr>
<td>6.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.1</td>
<td>3.1-3.3</td>
<td>&lt;42.0</td>
</tr>
<tr>
<td>7.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;2.9</td>
<td>2.9-3.1</td>
<td>&lt;44.3</td>
</tr>
</tbody>
</table>

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) using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers, and the experience of several years of irradiation using these large fractions at Indiana University and centers in Sweden, 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. Instructions for the contouring of these organs are as follows:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Any point</td>
<td>18 Gy (6 Gy per fraction)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Any point</td>
<td>27 Gy (9 Gy per fraction)</td>
</tr>
<tr>
<td>Ipsilateral Brachial Plexus</td>
<td>Any point</td>
<td>24 Gy (8 Gy per fraction)</td>
</tr>
<tr>
<td>Heart/Pericardium</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Trachea and Ipsilateral Bronchus</td>
<td>Any point</td>
<td>30 Gy (10 Gy per fraction)</td>
</tr>
<tr>
<td>Whole Lung (Right &amp; Left)</td>
<td>(See table in Section 6.4.2)</td>
<td>(See table in Section 6.4.2)</td>
</tr>
<tr>
<td>Skin</td>
<td>Any point</td>
<td>24 Gy (8 Gy per fraction)</td>
</tr>
</tbody>
</table>

### 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 second 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 (aortopulmonary 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 (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree (see the diagram in Section 3.2.2 and the 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 anatomic 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 Section 6.4, 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.

6.5.2.9 Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

6.6 Documentation Requirements
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
Setup 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 craniocaudal 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 Radiation Therapy Quality Assurance Reviews (9/3/08)
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 Remote Review after complete data for the first 15 cases enrolled have been received at ITC. Dr. Timmerman will perform the next remote review after complete data for the next 15 cases have 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 have been received at ITC, whichever occurs first.

6.9 (8/20/09) Radiation Therapy Adverse Events

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, nonproductive 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 nonsteroidal 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 before completing therapy, therapy will 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 in conjunction with Dr. Timmerman, study Principal Investigator. When symptomatic pneumonitis resolves to grade 0, CTCAE, v. 3.0, the treating physician will contact Dr. Timmerman for a decision to continue or terminate protocol therapy.

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 (prescribed without tissue heterogeneity correction) or higher ultimately experienced some degree of 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. Because 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), will all be graded according to the Common Terminology Criteria for Adverse Events v.3.0 (CTCAE).

6.9.3 Changes in Pulmonary Function Tests

Patients enrolled to this study are allowed to have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV₁), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). The Common Toxicity Criteria (CTCAE) version 3 includes specified criteria for grading adverse events related to these PFT parameters under the category of
pulmonary/upper respiratory. The grading criteria for these PFT changes use the “percent predicted” values from 0-100% which are recorded on the patient’s PFT report. A percent predicted of 90% conveys that the patient is able to perform the PFT test to a result that is 90% of what would be expected for the normal general population of the same height, age, and sex. The CTCAE version 3 specified grading criteria for PFTs assumes that all patients have normal baseline pulmonary function. This assumption is not appropriate for this protocol enrolling patients with abnormal baseline function.

As a remedy to monitor treatment effects on PFTs, we will define a protocol specific toxicity classification for PFTs that adjusts for baseline abnormalities. Changes that occur after therapy will be referenced to the baseline for a given patient, which will be abnormal for most patients. We have defined a proportional decline from the baseline. Grade 1 toxicity will be a decline from baseline to a level 0.90 times the baseline, grade 2 will be a decline to a level 0.75 of baseline, grade 3 will be a decline to a level 0.5 of baseline, grade 4 will be a decline to a level 0.25 of baseline, and grade 5 will be death. This scheme is depicted in the table below and graphically represented in the figure below.

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 3 event in the original CTCAE version 3 criteria; however, under this modified PFT toxicity classification for patients with abnormal baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV-1 Decline</td>
<td>0.90-0.75 times the patient’s baseline value</td>
<td>&lt;0.75-0.50 times the patient’s baseline value</td>
<td>&lt;0.50-0.25 times the patient’s baseline value</td>
<td>&lt;0.25 times the patient’s baseline value</td>
<td>Death</td>
</tr>
<tr>
<td>Forced Vital Capacity Decline</td>
<td>0.90-0.75 times the patient’s baseline value</td>
<td>&lt;0.75-0.50 times the patient’s baseline value</td>
<td>&lt;0.50-0.25 times the patient’s baseline value</td>
<td>&lt;0.25 times the patient’s baseline value</td>
<td>Death</td>
</tr>
<tr>
<td>DLCO Decline</td>
<td>0.90-0.75 times the patient’s baseline value</td>
<td>&lt;0.75-0.50 times the patient’s baseline value</td>
<td>&lt;0.50-0.25 times the patient’s baseline value</td>
<td>&lt;0.25 times the patient’s baseline value</td>
<td>Death</td>
</tr>
</tbody>
</table>

**PFT (FEV-1, FVC, DLCO) Decline**

![Graph showing the decline in Percent Predicted for different grades of pulmonary toxicity](image-url)
6.9.4 Other Significant Adverse Events
If other severe adverse events result in withholding therapy, the details will be documented.

6.10 Radiation Adverse Event Reporting (3/6/14)

6.10.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements
(2/4/09, 10/25/12)

Adverse events (AEs) as defined in the tables below and all serious adverse events
(SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the CTEP
Adverse Event Reporting System (CTEP-AERS) as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory
finding), symptom, or disease temporally associated with the use of a medical treatment or
procedure regardless of whether it is considered related to the medical treatment or procedure

Definition of an SAE: Any adverse experience occurring at any dose that results in any of the
following outcomes:
- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require
hospitalization may be considered an SAE experience, when, based upon medical judgment,
they may jeopardize the patient and may require medical or surgical intervention to prevent one
of the outcomes listed in the definition. Any pregnancy occurring on study, including a male
patient’s impregnation of his partner, must be reported via CTEP-AERS as a medically
significant event.

(8/20/09) Pharmaceutically supported studies will require additional reporting over and above
that which is required by CTEP.

(8/20/09) SAEs (more than 30 days after last treatment) attributed to the protocol treatment
(possible, probable, or definite) should be reported via CTEP-AERS.

Note: All deaths on study require both routine and expedited reporting regardless of
causality. Attribution to treatment or other cause must be provided. “On study” is
defined as during or within 30 days of completing protocol treatment.

CTEP-AERS REPORTING REQUIREMENTS (3/6/14)

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced involving
RT only, both with and without a drug component arm. Events that occur on the RT-only arm of
a study with a drug component must be reported for purposes of comparison. Events that occur
on an RT-only study without a drug component also must be reported. Events involving RT-only
must be reported via the CTEP-AERS RT-only pathway.

As of January 1, 2011, this study will utilize the Common Terminology Criteria for Adverse
Events (CTCAE) version 4 for grading of all adverse events. A copy of the CTCAE v. 4 can be
downloaded from the Cancer Therapy Evaluation Program (CTEP) web site at:
Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported as indicated in the following tables using the CTEP-AERS. CTEP-AERS can be accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613). Use the patient’s case number as the patient ID when reporting via CTEP-AERS. AEs and SAEs reported using CTEP-AERS must also be reported to RTOG on the AE case report form (see Section 12.1). In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour CTEP-AERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by CTEP-AERS as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. CTEP-AERS allows submission of all reports regardless of the results of the assessment.

**Phase 1 and Early Phase 2 Studies:** Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of the Intervention

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**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

All serious adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 and Grade 2 Timeframes</th>
<th>Grade 3-5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</table>
NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- **"24-Hour; 5 Calendar Days"** - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **"10 Calendar Days"** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

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**RTOG REPORTING REQUIREMENTS (3/6/14)**

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the CTEP-AERS RT-only pathway.

As of January 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4 for grading of all adverse events reported via CTEP-AERS; all RTOG case report forms will continue to use CTCAE v. 3.0. A copy of the CTCAE v. 4 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page [http://ctep.cancer.gov](http://ctep.cancer.gov) or the RTOG web site [http://www.rtog.org/members/toxicity/main.html](http://www.rtog.org/members/toxicity/main.html).

**Adverse Events (AEs) and Serious Adverse Events (SAEs)** that meet the criteria defined above experienced by patients accrued to this protocol must be reported via CTEP-AERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. CTEP-AERS Reports are forwarded to RTOG electronically via the CTEP-AERS system. Use the patient’s case number as the patient ID when reporting via CTEP-AERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via CTEP-AERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

**6.10.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [3/6/14]**

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis. If the site is reporting in CTCAE, v. 4, the event(s) maybe reported as 1)
Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy.

7.0 DRUG THERAPY
SEE SECTION 9.0.

8.0 SURGERY
8.1 Surgical resection will be considered as a salvage local therapy for all patients at documented disease progression according to Section 11.2.3 irrespective of timing from initial therapy. Surgical salvage could be considered in the case of local failure, marginal failure, and regional failure as defined. There is no required timing in relation to initial therapy to perform such surgical salvage.

8.2 Data collection for a review of surgical salvage, will include operative and pathology reports. Surgical salvage reviews will not be done by sampling; data on all patients will be reviewed.

8.3 A major surgical deviation from protocol therapy will constitute surgical resection of the treated tumor outside of the stated indications of Sections 8.1 and 8.2 (for example, surgical resection in patients without positive tumor biopsy or radiographic evidence of progression).

9.0 OTHER THERAPY
Adjuvant systemic therapy using platinum-based chemotherapy is now considered standard for several stages of early-stage lung cancer. There is universal acceptance that adjuvant therapy is indicated for resected Stages IIA, IIB and IIIA NSCLC. The role of chemotherapy in resected Stage Ib is controversial based upon the recent update of CALGB 9633. Patients with Stages IIA, IIB and IIIA should be offered adjuvant chemotherapy as part of this trial, although chemotherapy-related endpoints will not be primary for this trial. Patients with Stage Ib can be offered chemotherapy at the discretion of the treating physician. Strong consideration for adjuvant therapy should be given for patients with T2N0 tumors whose tumor exceeds 4 cm. All patients with Stage Ib, IIb and IIIA should be offered chemotherapy as part of this trial. The regimen chosen will be at the discretion of the treating oncologist from the following options: carboplatin/paclitaxel, cisplatin/docetaxel, cisplatin/vinorelbine, cisplatin/gemcitabine, or similar combinations approved in advance by Dr. Edelman. The addition of bevacizumab is not permitted unless in the setting of a clinical trial. Patients may be entered on appropriate trials of adjuvant therapy. If a patient is not treated with adjuvant chemotherapy (including patients with Stage Ib), the reason must be documented in the patient’s hospital/clinic chart.

Chemotherapy should be administered to these patients as an adjuvant therapy in conjunction with the protocol (but not concurrently) as the initial management of the patient's lung cancer. If adjuvant therapy is to be administered, it should commence within 4 months (120 days) of SBRT.

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

9.2 Other Cancer Therapy
Aside from the therapy outlined in Sections 6.0 and 9.1, patients must not receive other concomitant local or regional antineoplastic therapy (including standard fractionated radiotherapy, non-approved systemic therapy, and surgery except as in Section 8.0) while on this protocol except at disease progression.

10.0 TISSUE/SPECIMEN SUBMISSION (9/3/08) (2/4/09)
NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.

- If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens as specified in Section 10 of the protocol. Note: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.
For patients who have consented to participate in the submission of tissue, urine, and blood for the study (See Appendix I).

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue and urine will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking, and blood will be submitted for specific hypothesis based translational research.

10.1 Tissue/Urine Submission for Banking (Optional)

10.1.1 Sites may submit the following specimens for banking:

10.1.1.1 [5/7/09] A paraffin-embedded tissue block of the tumor (preferred) or a 2-mm diameter core of tissue punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource (see Appendix VI). Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.1.1.2 10 ml of clean-catch urine collected at the following time points:
- Within 3 days of delivering the first dose of SBRT;
- At the last day, before delivery of the last dose of SBRT;
- At the 6 week follow-up visit.

10.1.2 The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.1.2.1 One H&E stained slide

10.1.2.2 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.1.2.3 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient’s case number.

10.1.2.4 (5/7/09) A Specimen Transmittal Form documenting the date of collection of the urine; the RTOG protocol number and the patient’s case number. **Note:** The method of storage, (for example, stored at -80° C) must be included.

10.1.3 (5/7/09, 10/25/12) Submit materials for banking to:

**Shipping Address (FedEx, UPS, Courier):** For all Frozen, Overnight, or Trackable Shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St., Room S341
San Francisco, CA 94115

**U.S. Postal Service Address:** For all non-urgent, ambient specimens-FFPEs, slides, blocks
RTOG Biospecimen Resource
University of California San Francisco
UCSF Box 1800
(2340 Sutter St., Room S341)
San Francisco, CA 94143-1800

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu
10.2 **Rationale/Hypotheses for Blood Collection for Translational Research**

As discussed in Section 1.8 recent studies have shown correlations of genomic mutations (such as EGFR) between blood and tumor tissue and between expression of certain genes/proteins (such as ERCC1) and tumor responses to chemotherapeutic regimens. For radiation toxicity prediction, the levels of cytokine/proteomic markers and presence of certain specific gene polymorphisms in the blood as well as the changes of the levels during and after treatment were correlated with radiation induced lung toxicity after completion of conventional fractionated 3D-CRT. These levels may also be predictive of treatment outcomes in tumor control and treatment toxicity after SBRT. We hypothesize that changes in the expression of blood markers will reflect tumor response and normal tissue damage at the molecular level, and thus, predict 2-year tumor control and post-treatment toxicity.

10.3 **Blood Collection for Translational Research** (Highly recommended, but not required)

10.3.1 (5/7/09) Blood samples for translational research will be collected per protocol requirements (see Appendix VI). **Note:** A blood collection kit including materials, instructions, and a pre-paid return label can be obtained from the Biospecimen Resource, rtog@ucsf.edu. Plasma, serum and buffy coat (platelets, lymphocytes and white cells) will be collected at the following time points:
- Within 3 days before the first dose of SBRT;
- At the last day, before delivery of the last dose of SBRT;
- At the 6 week follow-up visit.

10.3.2 (5/7/09) The following materials must be provided in order for the case to be evaluable: A Specimen Transmittal Form documenting the date of collection of the plasma, serum, and buffy coat; the RTOG protocol number and the patient’s case number. **Note:** The method of storage, (for example, stored at -80° C) must be included.

10.3.3 Submit blood samples for translational research to: (5/7/09, 10/25/12)

**Shipping Address (FedEx, UPS, Courier): For all Frozen, Overnight, or Trackable Shipments**

RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter St., Room S341  
San Francisco, CA 94115

For questions regarding specimen shipments, contact RTOG@ucsf.edu/415-476-7864/FAX 415-476-5271

For any study-specific questions regarding the blood sample handling process, contact the Translational Research Co-Chair, Dr. Kong at 734-936-7810 or by e-mail: fengkong@umich.edu or RTOGTRP@umich.edu

10.4 **Specimen Collection Summary** (5/7/09)

<table>
<thead>
<tr>
<th>Specimens taken from</th>
<th>Specimens collected</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient:</td>
<td>when:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A paraffin-embedded</td>
<td>From pre-treatment</td>
<td>Paraffin-embedded tissue block or punch biopsy</td>
<td>Block or punch shipped ambient</td>
</tr>
<tr>
<td>tissue block of the</td>
<td>biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary tumor taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before initiation of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment or a 2 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diameter core of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tissue, punched from</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the tissue block with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a skin punch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mL clean-catch</td>
<td>Within 3 days before</td>
<td>A minimum of 10 mL unpreserved urine in a sterile collection container</td>
<td>Urine sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>urine</td>
<td>the first dose of SBRT; at the last day before the last dose of SBRT; at the 6 week follow-up visit.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens for Translational Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>20mL blood</td>
</tr>
<tr>
<td>Within 3 days before the first dose of SBRT; at the</td>
</tr>
</tbody>
</table>

Specimens for Tissue Banking
10.5 Reimbursement (5/7/09, 10/25/12)
RTOG will reimburse submitting institutions $200 per case for a block or core of material. Urine is reimbursed at $50 per specimen. Blood specimens are reimbursed $100 per blood sample. **Note:** If the institution submits all three blood samples, collected at the specified time points, the institution will receive an additional $1000 reimbursement and .5 credit.

In the event of patient death before all samples have been collected, institutions will receive reimbursement on a pro-rated basis, and institutions that have submitted at least one blood sample will receive the .5 case credit.

For tissue, blood specimens, and urine sent to the RTOG Biospecimen Resource: When the Biospecimen Resource confirms that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG website ([http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323](http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323)).

10.6 Confidentiality/Storage (9/3/08, 10/25/12)

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

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

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters
See Appendix II.

11.2 Criteria for Evaluation
11.2.1 **Response Determination** (3/25/10)
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](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 primary tumor 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) NSCLC. At time of treatment, they should have only 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 a 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 in which 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 (3/25/10)

<table>
<thead>
<tr>
<th>Evaluation of Target and Involved Lobe Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
</tr>
<tr>
<td><strong>Local Enlargement (LE)</strong></td>
</tr>
<tr>
<td><strong>Primary Tumor Failure (PTF)</strong></td>
</tr>
<tr>
<td><strong>Marginal Failure (MF)</strong></td>
</tr>
<tr>
<td><strong>Primary Tumor Control (PTC)</strong></td>
</tr>
</tbody>
</table>
Involved Lobe Failure

Refers to the appearance of lung cancer after protocol therapy within the anatomical boundaries of the lobe in which the primary tumor arose (involved lobe). The measurable tumor apart from the primary tumor but within the involved lobe should meet criteria for LE should be avid on Positron Emission Tomography (PET) imaging with uptake highly suspicious for cancer (e.g., SUV>3-5), OR the measurable tumor should be biopsied confirming viable carcinoma. Failure outside of the involved lobe (uninvolved lobes) will be considered metastatic disseminated (distant) failures.

Local Failure

Refers to either primary tumor failure or involved lobe failure or both.

Local Control (LC)

The absence of Local Failure

Evaluation of Non-Target Lesions

<table>
<thead>
<tr>
<th>Regional Failure (RF)</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Dissemination (MD)</td>
<td>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.</td>
</tr>
</tbody>
</table>

11.2.4 Criteria for Removal from Protocol Treatment (3/25/10)

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 restaged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.

11.2.4.2 Unacceptable toxicity.

11.2.4.3 A delay in protocol treatment, as specified in Sections 6.0.

11.2.4.4 Development of intercurrent, non–cancer-related illnesses that prevent either continuation of therapy or regular follow-up.

11.2.4.5 If protocol treatment is discontinued for any reason other death, follow up and data collection will continue as specified in the protocol.

11.3 Comorbidity Data and Rating

The Charlson Comorbidity index will be used to assess pretreatment comorbidity status per Appendix V.

12.0 DATA COLLECTION

Attach patient labels from RTOG to each case report form. Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (3/25/10)

Data should be submitted to:

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

*Please note that RTOG Headquarters address is for administrative purposes only and not for patient care.
* If a data form is available for web entry, it must be submitted electronically.

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks after registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>COMORBIDITY DATA SUBMISSION:</td>
<td>Within 2 weeks after registration</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (CN) and</td>
<td></td>
</tr>
<tr>
<td>Comorbidity Recording Sheet</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1) (Copy to HQ and ITC)</td>
<td>Within 1 week of SBRT end</td>
</tr>
<tr>
<td>Daily treatment Record (T5) Copy to HQ and ITC</td>
<td></td>
</tr>
<tr>
<td>Treatment Summary Form (TF)</td>
<td>At the completion of recommended chemotherapy</td>
</tr>
<tr>
<td>Surgical operative form (S2)</td>
<td>4 weeks post protocol surgery, if applicable</td>
</tr>
<tr>
<td>Surgical pathology report (S5)</td>
<td>4 weeks post protocol surgery, if applicable</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from the start of treatment until the end of year two, every 6 months until year 5, then annually</td>
</tr>
</tbody>
</table>

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1) (9/3/08, 3/25/10)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD) †</td>
<td>Within 1 week of start of SBRT</td>
</tr>
</tbody>
</table>

†Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist.

Digital data submission includes the following:
- CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3)
- Digital beam geometry for initial and boost beam sets
- Doses for initial and boost sets of concurrently treated beams
- Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)

Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html)

Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)

NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.
12.2.1 Digital Data Submission to ITC (3/25/10)
Digital data submission may be accomplished using media or the Internet.
For network submission: The secure 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:
itr@wustl.edu
For media submission: Please contact the ITC about acceptable media 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)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints
13.1.1 Primary endpoint (3/25/10)
2-year primary tumor control (see Section 11.2.3 for definition of failure): Time to primary tumor control is measured form the start of treatment. Patients, who develop distant metastases from original lung cancer or a second primary tumor prior to 2 years, will remain at risk for primary tumor failure. Patients, dying with lung cancer but no documented local failure, will be considered a non-failure and will be censored on the day of their death. Patients, dying without progressive lung disease and no documented primary tumor failure, will be considered a non-failure and will be censored on the day of their death.

13.1.2 Secondary endpoints (3/25/10)
• Rates of treatment-related (definitely and probably, but not possibly related to treatment*) grade 3 or 4 adverse events (per CTCAE, v.3.0, with the exception of pulmonary function tests as noted in Section 6.9.3) related to the following specific symptoms, including:
  ➢ Gastrointestinal: dysphagia, esophagitis, esophageal stricture/stenosis, esophageal ulceration;
  ➢ Cardiac: pericarditis, pericardial effusion, restrictive cardiomyopathy, ventricular dysfunction (left ventricular diastolic dysfunction, left ventricular systolic dysfunction, right ventricular dysfunction);
  ➢ Neurologic: myelitis, neuropathy (cranial and motor);
  ➢ Hemorrhage: pulmonary or upper respiratory;
  ➢ Pulmonary: decline in pulmonary function as measured by pulmonary function tests per Section 6.9.3 (DLco, FEV1, FVC), pneumonitis, pulmonary fibrosis, hypoxia, pleural effusion, cough, and dyspnea
  ➢ Any grade 4 or 5 adverse event attributed to the therapy (definitely and probably, but not possibly related to treatment)

*Patients enrolled on this study are highly likely to have associated tobacco related cardiopulmonary co-morbidities that would result in adverse events (e.g., hospitalizations) irrespective of any cancer treatment. In RTOG 0236 as well as the Indiana University trials referenced in the introduction, adverse event analysis was confounded by problems distinguishing whether adverse events were treatment related versus part of the natural
As such, in this protocol only adverse events deemed probably and definitely related to treatment are considered for formal adverse event assessment. Adverse events deemed possibly related will be collected and reviewed but not used in adverse event analysis (e.g., for stopping rules).

- Rates of grade 3-5 adverse events other than those specified in 13.1.2 which are definitely or possibly related to treatment.
- 2-year rates for primary tumor failure, marginal failure, regional failure, metastatic dissemination, disease-free and overall survival. (See Section 11.2.3 for definitions of failure.)
- Assess level of comorbidity burden on morbidity and efficacy.
- Assess if blood markers prior to, during the course of treatment (between the second and the last dose of SBRT), and at the first follow-up after SBRT predict 2 year primary tumor control and predict for grade ≥ 2 treatment-related adverse events.

### 13.2 Sample Size

#### 13.2.1 Sample Size Derivation (3/25/10)

This phase II study aims to target a 2-year primary tumor control rate of 90%. Primary tumor control at 2 years of 70% is considered unacceptable. Primary tumor control is simply defined as the absence of primary tumor progression. (See Section 13.1.1 for further details). Assuming at least an approximately exponential distribution of time to primary tumor progression, the hazard rate for the expected primary tumor control rate of 90% is 0.00439 per month, and the hazard rate for the unacceptable primary tumor control rate of 70% is 0.01486 per month. The sample size was calculated under following conditions; uniform accrual rate of 1.5 evaluable cases per month for 18 months with additional 24 months of follow-up and a one-sided Type I error rate of 0.05 with 90% statistical power to detect a difference in primary tumor control rates at least this large. Assuming that two (7%) patients may be found ineligible retrospectively and another 4 patients (15%) may die without any evidence of primary tumor progression prior to two years, a total of 33 patients will be required for this trial.

#### 13.2.2 Patient Accrual

Patient accrual is projected to be two cases per month. At this rate, it will take approximately 24 months to reach the target accrual, assuming that there will be very little accrual during first 6 months while institutions are obtaining IRB approval and possibly SBRT approval by the RTOG QA center. If fewer than 6 patients are entered into the trial between 7 and 18 months, it will be re-evaluated for feasibility.

### 13.3 Analysis Plans

#### 13.3.1 Interim Reporting of Accrual and Adverse Event 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 adverse events.

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.

#### 13.3.2 Analysis for Reporting Treatment Results (3/25/10)

This analysis will be done after 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 after each patient has had potentially at least 2 years of follow-up. Time events, such as time to local progression, are measured from the start of treatment to the date of event of interest or last date of follow-up if it did not occur. The hazard rate for primary tumor control will be estimated using life table estimates within a time span of 2 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 0.014886 per month is statistically significant. [Note: a negative difference indicates a reduction in the failure
rate. The variance for the Z-statistic will be estimated by the reciprocal of the number of cases with local progression within 2 years.

The two year rates along with their associated 95% confidence intervals for primary tumor failure, marginal failure, involved lobe failure, local failure, regional failure, local-regional failure, metastatic dissemination, disease-free and overall survival will be estimated using the Kaplan-Meier product limit method. Grades of adverse events will be summarized using contingency tables.

The incidence rate of “unacceptable” adverse events and the primary tumor failure rate will be analyzed with respect to the patient's baseline comorbidity scores.

The incidence rate of grade ≥ 2 treatment-related adverse events at 2 years and the primary tumor failure rate at 2 years will be analyzed with respect to blood markers.

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 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

### 13.4 Gender and Minorities (9/3/08)

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities 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 NSCLC. However, the RTOG did not show this to be the case in a recent analysis. Furthermore, an analysis of race did not indicate an association with outcome. The projected gender and minority accruals are:

<table>
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<th></th>
<th></th>
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</thead>
<tbody>
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REFERENCES


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

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

You are being asked to take part in this study because you have stage I or II (early stage) lung cancer.

Why is this study being done?
The purpose of this study is to use stereotactic body radiation therapy (SBRT) with patients with early-stage lung cancer and find out what effects (good and bad) SBRT has on you and your early stage lung cancer. SBRT is a treatment where treated tumors are carefully assessed to understand how they move prior to treatment. This allows your doctors to decrease the typical margins (extra uninvolved tissue) compared to what is done in conventional radiation therapy. Very focused radiation is given to the tumor in a few outpatient treatment sessions. SBRT is non-invasive and requires no hospital stay to undergo the procedure. Patients too frail for surgery have been studied extensively using SBRT in trials in the United States and around the world. These patients with multiple medical problems have tolerated SBRT well and have had low rates of cancer recurrence. This research is being done because SBRT has not been used very often in patients able to have surgery with early-stage lung cancer.

Participants in this trial should be aware that this is an experimental therapy. The established standard treatment for your kind of cancer is surgery. At this time, there is no strong evidence that the study therapy is as effective as surgery. While tests will be done to assess the effectiveness of the experimental therapy used in this study, it is possible that this treatment will not be as effective as surgery and your outcome might be worse due to tumor recurrence.

How many people will take part in the study?
A maximum total of about 33 people will take part in this study.
What will happen if I take part in this research study?

Before you begin the study …

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

- Physical exam
- A blood test to find out how much oxygen is delivered to the tissues beyond your lung
- Pregnancy test, for women who are able to have children to insure that they are not pregnant
- Chest x-ray
- CT scan of your lungs and abdominal area
- 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

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Assessment of other (comorbid) illness: You will be asked questions about your health and hospitalization history. Answering these questions will take approximately 10 minutes.
- Simulation for radiation therapy delivery: Before receiving radiation therapy, you will have a treatment planning session (also called simulation). You will lie in a specific position, possibly within a frame device, and undergo a CT scan of your lung and upper stomach. Your breathing will be checked to see how your organs move. In order to try to limit the effect of that movement on the position of your tumor your breathing will be timed and firm pressure may be placed on your stomach area to change the pattern of your breathing. There may be other methods to control breathing motion used at your institution.
- Radiation treatments: After the treatment planning session, you will receive a total of three outpatient 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. Your study doctor may give you pain medication before or after each treatment to decrease any discomfort you may have due to the one-hour length of each treatment.
When I am finished taking SBRT… (3/25/10)

You will be seen in follow-up visits 6 and 12 weeks after treatment, every 3 months for 2 years, then 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

- If the CT scan for your lungs is suspicious for tumor growth, your doctor will either order a PET scan or biopsy. If the post treatment PET or biopsy shows cancer recurrence, you will be referred for restaging and for consideration for surgical resection. If post treatment PET or biopsy does not show recurrence, you will continue to be followed on the study.

How long will I be in the study? (3/25/10)

You will receive the three 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.

Can I stop being in the study?

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

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

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

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

This is an experimental therapy. While the therapy has been used extensively in patients who cannot have surgery because of medical problems, it has been used and studied much less often in patients able to have surgery. Surgery is the standard treatment for your kind of lung cancer. Non-surgical therapies, like SBRT, may be less effective at curing the cancer than surgery.

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

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

**Stereotactic body radiation therapy (SBRT)** to the chest may cause the following side effects:

**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 may 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. All or portions of the collapsed lung may show up on your chest x-ray or chest CT scan.

**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/or death
- Irritation and/or damage to the muscle of the heart; rarely, this may cause a heart attack, heart failure, and/or death
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which may 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) causing difficulty swallowing meals
- Irritation of the large blood vessels surrounding the heart; rarely, this can cause bleeding (coughing up blood) and/or death

Chest radiotherapy may cause changes in normal lungs. These changes may be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy may cause lung damage that leads to symptoms such as chest pain, shortness of breath, cough, or fever. Rarely, these symptoms may be severe or life threatening. Six out of 37 patients treated in a previous study using SBRT had some or all of
these symptoms. You should tell your doctors immediately if you have any of these symptoms. Treatment for this lung damage involves pain medicines, anti-inflammatory medicines (corticosteroids), and rarely, oxygen therapy. Some patients are required to be on oxygen therapy for the rest of their lives.

**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), and 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, and if you are unwilling to use adequate birth control measures as approved by your doctor 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.

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

**Are there benefits to taking part in the study?**
Taking part in this study may or may not make your health better. While researchers hope SBRT will be as effective at avoiding recurrence from early-stage lung cancer compared to surgery, there is no proof of this yet. We do know that the information from this study will help researchers learn more about SBRT as a treatment for cancer. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**
Your other choices may include:
- Surgical removal of the tumor
- Standard radiation therapy
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment except medications to make you feel better. Your tumor would continue to grow and your disease would spread.

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

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

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

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- Local Institutional Review Board or research personnel
What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

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

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

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

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

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

What are my rights if I take part in this study? (3/25/10)

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

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

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.
Who can answer my questions about the study?

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

For questions about your rights while taking part in this study, call the ________________________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at ________________________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

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

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to the following study. Below, please mark your choice.

Consent Form for Use of Tissue, Urine, and Blood for Research

About Using Tissue, Urine, and Blood for Research (10/25/12)

You are going to have or have had a biopsy to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research.

In addition to the tumor tissue, we would like to collect some blood and urine for research. You will be asked to provide about four teaspoons of blood and about two teaspoons of urine at the following time points: within three days of the first radiation treatment, on the last day before the last radiation treatment, and at the six week follow-up visit.

If you agree, this tissue, urine, and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called “How is Tissue Used for Research” to learn more about tissue research. This information sheet is available to all at the following web site: http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm.

The research that may be done with your tissue, urine, and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.
Reports about research done with your tissue, urine, or blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us keep the left over tissue and to use your urine and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

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

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

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

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

**Benefits**

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

**Risks**

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

**Making Your Choice (8/20/09)**

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue: □ Yes □ No
   - Urine: □ Yes □ No
   - Blood: □ Yes □ No
2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease), as follows:
   - Tissue ☐ Yes ☐ No
   - Urine ☐ Yes ☐ No
   - Blood ☐ Yes ☐ No

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

Where can I get more information? (3/25/10, 10/25/12)

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

1-800-4-CANCER (1-800-422-6237)

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

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://www.cancer.gov/cancertopics/

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

Signature

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

Participant ______________________________

Date ________________________________
## APPENDIX II

### STUDY PARAMETER TABLE (2/4/09, 8/20/09, 3/25/10, 10/25/12)

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<td></td>
</tr>
<tr>
<td>Tissue, urine, blood for banking &amp; trans. Research</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. central review not required;  
2. preferably with IV contrast unless medically contraindicated  
3. includes routine spirometry, lung volumes, diffusion capacity, and arterial blood gases  
4. post treatment PET should be done using same unit/platform and technique for pretreatment PET to allow comparison of SUV values  
5. only required if CT-based tumor response evaluation indicates local tumor enlargement (per Section 11.2.3) and must occur within 3 months of the CT which detected local tumor enlargement;  
*as needed based on reporting requirements.
ZUBROD PERFORMANCE SCALE

0  Fully active; able to carry on all predisease activities without restriction
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
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
3  Capable of only limited self-care; confined to bed or chair 50% or more of waking hours
4  Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5  Death
APPENDIX IV

AJCC Staging

Primary Tumor (T)

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

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

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

Regional Lymph Nodes (N)

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

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

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

### Stage Grouping

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>T, N, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1, N1, M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1, N2, M0</td>
</tr>
<tr>
<td></td>
<td>T2, N2, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N2, M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td></td>
<td>Any T, Any N, M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
APPENDIX V:
Comorbidity Scoring

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.
4. Disease that are “no” get zero points. Diseases marked “yes” score the number of points designated in the far right column. Total the points at the bottom of the scoring sheet.
5. The completed form will be submitted to RTOG Headquarters

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, Hgb);
   - 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.

Contact Elizabeth Gore, M.D. at 414-805-4465 or egore@radonc.mcw.edu if you have questions.
### Rules for Completing the Charlson Comorbidity Index (CCI)

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

### Scoring Sheet

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

Total points: ____________


**APPENDIX V (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. All conditions, including ab values, are before the start of therapy.

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

### COMORBIDITY RECORDING SHEET

**RTOG 0618**

<table>
<thead>
<tr>
<th>RTOG Institution Name/Number:</th>
<th>________________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Initials (First Middle Last):</td>
<td>________________________________</td>
</tr>
<tr>
<td>RTOG Patient Case Number:</td>
<td>________________________________</td>
</tr>
<tr>
<td>Name of Person Completing Sheet:</td>
<td>________________________________</td>
</tr>
<tr>
<td>Phone Number:</td>
<td>________________________________</td>
</tr>
<tr>
<td>Date Completed:</td>
<td><strong>-</strong>_-_____</td>
</tr>
</tbody>
</table>

### Comorbidities

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Vascular (Hemoglobin:_____)</td>
<td></td>
</tr>
<tr>
<td>Respiratory (include tobacco history)</td>
<td></td>
</tr>
<tr>
<td>Eyes and ENT</td>
<td></td>
</tr>
<tr>
<td>Upper Gi</td>
<td></td>
</tr>
<tr>
<td>Lower GI</td>
<td></td>
</tr>
<tr>
<td>Liver and Pancreas</td>
<td></td>
</tr>
<tr>
<td>Renal (Creatinine: )</td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal/Integument</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine/Metabolic and Breast (Weight: Height: )</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
</tbody>
</table>

### Medications (PRN/scheduled)

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
APPENDIX VI (5/7/09, 10/25/12)  
SPECIMEN COLLECTION INSTRUCTIONS

Specimen Plug Kit* and Instructions

The Specimen Plug Kit contains a shipping tube and a dermal needle.

Step 1
Place the dermal needle on the paraffin block over the selected tumor area. 
*(Ask a Pathologist to select area with tumor.)* Push the needle into the 
paraffin block. Twist the needle once around to separate the plug from the 
block. Then pull the needle out of the block. The needle should be filled 
with tissue sample.

Step 2
Label dermal needle with the pathology accession number, RTOG study and 
case numbers. **Do not try to remove specimen from needle.**

Use a separate dermal needle for every specimen. **Do not mix specimens.**
Call or e-mail the RTOG Biospecimen Resource for questions or for 
additional specimen Plug Kits.

Step 3
Once specimen needle is labeled, place it in the shipping tube and mail to 
the address below.

The RTOG Biospecimen Resource will remove the specimen from the needle 
and embed it in a cassette, labeled with the specimen ID.

*NOTE: If an institution is uncomfortable obtaining the plug but wants to 
retain the tissue block, the institution should send the entire block to the RTOG Biospecimen Resource. The 
Biospecimen Resource will sample a plug from the block and will return the remaining block to the institution. 
Institutions should indicate their request to perform the plug procedure and to return the block on the submission 
form.

Ship: Specimen Plug Kit, specimen in dermal needle, and all paper work to:

**U.S. Postal Service Address:** For all non-urgent, ambient specimens-FFPEs, slides, 
blocks  
RTOG Biospecimen Resource  
University of California San Francisco  
UCSF Box 1800  
(2340 Sutter St., Room S341)  
San Francisco, CA 94143-1800

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu
Urine Collection Kit Instructions*

This Kit contains:
- One (1) Sterile Urine collection cup
- Biohazard bags

Preparation for collecting Urine:
- A clean catch urine specimen will be collected.

Process
- To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
  - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark specimen as "urine".
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag.
- Immediately freeze urine sample at -20°C.
- Store specimens frozen at -20°C until ready to ship.

Shipping Instructions for urine specimens:
Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 kg minimum). Seal the box with plastic tape. All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box “biohazard”.

(5/7/09) Send specimens by overnight express to the address below. Specimens should be shipped only Monday through Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.

Notes: (5/7/09, 10/25/12)
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and there is sufficient ice for shipment.
- Sites must submit the required documentation with specimens. All specimens will be shipped to:

  Shipping Address (FedEx, UPS, Courier): For all Frozen, Overnight, or Trackable Shipments
  RTOG Biospecimen Resource
  University of California San Francisco
  2340 Sutter St., Room S341
  San Francisco, CA 94115
  Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu
APPENDIX VI (Continued)

Blood Collection Instructions

Blood Sample Drawing and Handling

Samples for TGFβ and other cytokine measurement and proteomic analysis need to be handled gently and carefully to avoid platelet degradation or contamination.

(5/7/09) Blood should be drawn in a standard fashion from each individual within 3 days before treatment, at the last day of treatment (before the delivery of the last dose of SBRT), and at the 6 week follow-up visit after completion of SBRT. Needles of large gauge (19-21G) should be used to minimize platelet-contamination from hemolysis. Blood will be collected in two standard blood collection tubes (one purple top and one red top). Blood samples can be drawn in the clinic or blood lab, and temporarily placed vertically at 4°C until plasma/serum are prepared within 2 hours of collection.

Collection of Plasma and Buffy Coat Samples

a. Collect one 10 ml tube of blood using one EDTA (purple top) tube, and invert gently one to two times to mix with anticoagulant.
b. Store the blood at 4°C or ice as soon as possible (the time of samples setting in room temperature should be less than 5 minutes).
c. Centrifuge under ~ 2500xG at 4°C for 30 minutes.
d. Carefully pipette and transfer ~1 ml aliquots of plasma into 4-5 CRYOVIAL® Polypropylene Tubes, keeping the pipette tip at least 5 mm above the buffy coat (at the level of the thickest arrow) to avoid platelets contamination.
e. Remove the buffy coat cells carefully and place into one 1 ml CRYOVIAL® Polypropylene Tubes labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process).
f. Place tops on CRYOVIAL® Polypropylene Tubes and make sure tops of CRYOVIAL® Polypropylene Tubes are on securely.
g. Tubes should be clearly labeled as indicated.
h. Place tubes in a Styrofoam holder and then place into a zip lock bag.
i. Store samples at -80°C until packed and shipped in dry ice.
APPENDIX VI (Continued)

Blood Collection Instructions (Continued)

Serum Sample Preparation
a. Collect one 5-10 ml tube of blood without coagulants (Red-topped tube).
b. Sit at room temperature for 30 min to allow clot formation.
c. Centrifuge in a standard clinical centrifuge ~ 2500xG at 4°C for 30 minutes.
d. Transfer ~1ml aliquots of separated serum into 4-5 CRYOVIAL® Polypropylene Tubes.
e. Place tops on CRYOVIAL® Polypropylene Tubes and make sure tops are secured.
f. Tube should be clearly labeled as serum as indicated.
g. Place tubes in a Styrofoam holder and then place into a zip lock bag.
h. Store samples at -80°C until packed and shipped in dry ice.

Sample Labeling
Each label will contain the following:
- RTOG Protocol Number;
- Patient ID number (Case number);
- Date of Sampling: (mm/dd/yy);
- Time of blood collection;
- Time of sample (plasma, serum, or buffy coat) collection;
- Sample Type;
- Site ID Number.

When serum/plasma/lymphocytes are collected: The following materials must be provided to the translational research co-chair: A Specimen Transmittal Form documenting the date of collection of the serum; the RTOG protocol number and the patient’s case number. Note: The method of storage, for example, stored at -80°C, must be included.

Blood Sample Shipping Instructions (9/16/2008)
Ship by express overnight service, Monday through Wednesday; avoid a weekend or holiday arrival date, and DO NOT ship on Friday. Samples of one patient are encouraged to ship at once, after the completion of the 6 week follow up visit.

(5/7/09) All tubes and CRYOVIAL® Polypropylene Tubes (plasma samples, serum, and buffy coat) should be shipped in Styrofoam holders to prevent glass tubes from breaking. Tubes should be placed within Styrofoam containers into gallon sized zip lock bags. Use separate zip lock bags for each patient’s samples. Use an adequate amount of dry ice for delivery; sample biohazard labels, etc. as required by carrier. Do not put sample shipment log on top of dry ice unless it is in a zip lock bag. Blood collection kits with instructions and pre-paid return labels can be requested from the Biospecimen Resource at rtog@ucsf.edu

(5/7/09, 10/25/12) Submit plasma, serum, and buffy coat for translational research to:

Shipping Address (FedEx, UPS, Courier): For all Frozen, Overnight, or Trackable Shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St., Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu