RADIATION THERAPY ONCOLOGY GROUP

RTOG 0813

SEAMLESS PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOTHERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED, NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS

Limited Participation Study: See Section 5.0

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RTOG 0813

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

SCHEMA

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks									
Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

See Section 5.0 for pre-registration requirements; see Section 6.0 for details of radiation therapy planning and delivery.

ALL SITES NOTE: (2/2/09)

- **Immediately upon identification of a serious adverse event (SAE) as defined in Section 13.1.1, the site will telephone the 24-hour RTOG AE Report Line: 215-717-2762.** The site will provide details of the SAE to RTOG Headquarters and will be instructed to fax the completed lung adverse event form (AE), FAX: 215-940-8830, within 24 hours of discovery of the adverse event. The AE form is available on the RTOG web site, with all of the 0813-specific forms (will be on web site prior to activation of study). The site also will report the adverse event via AdEERS (see Section 6.10).
- **All sites must fax the Treatment Chart (T5) to RTOG Headquarters (215-940-8831; Attn: RTQA) on the last day of the patient's treatment or by the end of the next business day** (see Section 12.1).

Patient Population: (See Section 3.0 for Eligibility)

Patients with stage T1-2, N0, M0, non-small cell lung cancer, tumor size ≤ 5 cm, who are not candidates for a complete surgical resection in the opinion of a thoracic surgeon; **only patients with tumors within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura** (see Section 3.1.5 for details).

Required Sample Size: 94

RTOG Institution # _____

RTOG 0813 **ELIGIBILITY CHECKLIST (8/20/10)**

Case # _____ (page 1 of 3)

_____(Y) 1. Does the patient have a pathologically (histologically or cytologically) proven diagnosis of non-small cell lung cancer (NSCLC)?

_____(Y) 2. Is the patient AJCC stage T1-2, N0, M0, tumor size ≤ 5 cm, prior to registration, based upon the minimum diagnostic workup specified in Section 3.1?

_____(Y) 3. Was a history/physical examination performed within 4 weeks prior to registration?

_____(Y) 4. Was the patient evaluated by an experienced thoracic cancer surgeon within 12 weeks prior to registration?

_____(Y) 5. Was the pre-treatment imaging (CT scan with contrast; PET using FDG) done within 8 weeks prior to registration?

_____(Y) 6. Was the Zubrod performance status 0-2 within 4 weeks prior to registration?

_____(Y) 7. Is the patient at least 18 years of age?

_____(Y) 8. Is the tumor within or touching the zone of the proximal bronchial tree (as defined in Section 3.1.5)? [Note: Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol.]

_____(Y) 9. Does the patient have measurable disease?

_____(Y) 10. Was pleural effusion absent, or, if present, was pleural effusion deemed too small to tap under CT guidance and not evident on chest x-ray? [Note: pleural effusion that appears on chest x-ray will be permitted only after thoracotomy or other invasive procedure(s).]

_____(Y/NA) 11. If female, was there a negative serum or urine pregnancy test performed within 72 hours prior to registration for women of childbearing potential?

_____(Y/NA) 12. If the patient is a woman of childbearing potential or a male participant, did the patient agree to use a medically effective means of birth control throughout the patient's participation in the treatment phase of the study and until at least 60 days following the last study treatment?

_____(Y) 13. Did the patient provide study-specific informed consent prior to any protocol-specified procedure(s)?

_____(N) 14. Has the patient had prior invasive malignancy within the past 2 years (other than non-melanomatous skin cancer) (e.g., carcinomas in situ of the breast, oral cavity, or cervix are permissible)? [Note: previous lung cancer, if the patient is disease-free for a minimum of 2 years is also permitted.]

_____(N) 15. Has the patient received prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

(Continued on next page)

_____(N) 16. Does the patient plan to receive other local therapy (including standard fractionated radiotherapy and/or surgery) while on this study, except at disease progression?

_____(N) 17. Does the patient plan to receive systemic therapy (including standard chemotherapy or biologic-targeted agents) while on this study, except at disease progression?

The following questions will be asked at Study Registration:

SBRT (and IMRT, if used) CREDENTIALING ARE REQUIRED BEFORE REGISTRATION.

_____ 1. Name of institutional person registering this case?

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

_____(Y) 3. Is the patient eligible for this study?

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

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

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

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

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

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

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)

_____(Y/N) 18. 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?

_____(Y/N) 19. 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?

_____(Y/N) 20. 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?

_____(Y/N) 21. 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)?

_____(Y/N) 22. 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: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. 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)?

_____(Y/N) 24. 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?

_____(Y/N) 25. Specify use of IMRT

The Eligibility Checklist must be completed in its entirety prior to registering the patient by phone. 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 _____

_____ **Assigned SBRT dose NOTE: If the patient does not received the assigned dose, the institution must contact RTOG RTQA as quickly as possible, 215-574-3219.**

1.0 INTRODUCTION

1.1 Early Stage Non-Small Cell Lung Cancer

Lung cancer is one of the most common cancers, and the leading cause of cancer deaths in men and women in North America and other developed countries, as well as many developing nations.

In 2005 in the United States there were 172,570 new lung cancer cases diagnosed, and an estimated 163,510 deaths as a result of lung cancer. The most common types of lung cancer, affecting 75-80% of patients with lung cancer, are grouped under the term "non-small cell lung cancer (NSCLC)". Approximately 15-20% of NSCLC patients present with early or localized disease, with the primary tumor in the lung, and no nodal involvement, or metastases elsewhere.[1] With increasing evidence that screening with computed tomography (CT) can detect lung cancers at an earlier stage, the number of patients diagnosed with stage I NSCLC is expected to rise significantly in the next several decades.

Surgical resection of centrally located stage I (T1-2, N0) NSCLC, specifically a lobectomy or pneumonectomy, results in 5-year survival rates of approximately 60-70%[2-3] and is the treatment of choice for this stage of lung cancer. However, some patients with early-stage NSCLC are not suitable surgical candidates for a number of reasons: poor pulmonary reserve, cardiac dysfunction, diabetes mellitus, vascular disease, general frailty, or other co-morbidities. In the case of poor pulmonary reserve, less extensive surgical resection (e.g., wedge or segmental resection) are not usually options for patients with centrally located tumors.[4] Many of the co-morbidities impact on the anesthetic and peri-operative risk, and thus, preclude any surgical procedure. These patients are typically considered for radiotherapy, with the aim of eradicating the primary tumor.

(2/9/11) Reports of conventional radiation describe inferior results when compared to surgical series, with 5-year survival rates ranging from 10-30%.[5-6] This is partially due to lower rates of tumor eradication and resultant higher rates of local failures with RT, and partially due to less rigorous staging and selection of less fit patients for RT treatment, when compared to surgically treated patients. Conventional RT typically consists of 50-66 Gy total dose in 1.8-2.0-2.5 Gy per fraction, or occasionally higher fraction size. Some studies demonstrate a benefit to dose escalation;[7] other studies suggest that draining lymph nodes not known to contain tumor need not be included in the RT field.[8] These uncontrolled RT series provide the rationale for increasing the RT dose and confining the fields to the primary tumor only, thus reducing the side-effects and toxicity of RT. However, even with significant dose escalation of conventionally fractionated RT, such as in the University of Michigan study,[9] in which dose was escalated to as high as 103 Gy, local failures within the irradiated area represented more than 70% of all failures. Therefore, novel technological and clinical approaches are required, to increase the RT dose to tumors.

1.2 Stereotactic Body Radiation Therapy (SBRT) for Lung Cancer **(8/20/10)**

Stereotactic body radiation therapy (SBRT) is a technique that allows delivery of very high doses of radiation, usually in several large fractions (hypofractionated), by multiple co-planar and non-coplanar beams and guided by a set of coordinates ("stereotactic"). These coordinates are set in relationship to the precise location of the tumor, rather than a set of external marks (tattoos) or anatomical landmarks (such as bony structures). The principles of SBRT are an adaptation of the principles and experience gained from stereotactic brain radiation therapy. SBRT requires a precise definition of the target, assessment and/or management of target motion (i.e., the respiratory excursion of the target), identification of a relatively tight planning target volume (PTV), conformal RT planning, and daily high quality set-up verification prior to each treatment. It was developed in the early 1990s in the Karolinska Institute in Stockholm, Sweden,[10] and is used as an accepted alternative treatment for patients with early stage lung cancer in many centers in Japan[11] and a number of centers in Germany, the U.S.,[12] and elsewhere, where it is typically employed for patients who are not candidates for surgery. A number of fractionation schedules have been employed, including single fractions of 20-26 Gy (currently used particularly in centers in Germany) and various hypofractionated, regimens (commonly 3, 5, or more fractions).

In addition to the heterogeneity of dose-fractionation schedules of SBRT, there are also significant differences in the important technical aspects of SBRT planning and delivery, that make it challenging to compare the results across different protocols, as these technical factors clearly influence the dose delivered, particularly to the periphery of the tumor, and to organs at risk (OAR), and thus, may impact both primary tumor control and toxicity of SBRT. The important

aspects of SBRT planning that differ among institutions and protocols and limit comparison of results include: a) selection of patients (often not clearly described); b) how patients are simulated (and particularly how respiratory motion is assessed, accounted for and/or controlled); c) how the target volumes are outlined (GTV alone or with a margin for CTV); d) how the plan is generated (only co-planar beams or also non-co-planar, lung heterogeneity correction or not; if yes, what correction algorithm is being used); e) where the prescribed dose is defined (which isodose is chosen and how, what amount of GTV is covered by the prescription dose); and f) what doses are allowed for the organs at risk. Just as important and just as much a source of variability, are the different aspects of SBRT delivery process: how are the patients immobilized; how are the stereotactic coordinates defined and assured; what quality of image guidance is used; and how to assure that patients will not move during the (often long) treatment time of large fraction SBRT treatment.

In addition to these technical aspects, another critical factor in being able to confidently apply the information from the literature is whether patients have been followed rigorously and for long enough, as both primary tumor control and toxicity are expected to, and indeed have been demonstrated to get worse with longer follow up. Therefore, formal prospective studies, particularly with an independent data safety monitoring committee, are more reliable than a single institution retrospective review of that institution's SBRT experience. This is especially true for studies that include patients who are frail or have significant co-morbidities, as these patients may be more likely to be lost to follow up or to have their symptoms attributed to their other illnesses. Thus, despite emerging reports in the literature on the results of SBRT for early stage NSCLC, it is still not clear which schedules are best in terms of tolerable toxicity and highest rates of primary tumor control.

The only dose finding study of SBRT for lung tumors was reported by Timmerman, et al. from Indiana.[13] They conducted a phase I study of dose escalation of a three fraction regiment, starting with 8 Gy x 3, and escalating to 10, 12, 14, 16, 18, 20 and 22 Gy x 3 fractions, in patients with potentially resectable NSCLC but who were not surgical candidates for medical reasons ("medically inoperable"). Doses were calculated without correction for tissue inhomogeneity. Patients were enrolled into three separate dose escalation groups based on tumor size. While dose-limiting toxicity (DLT) was observed in one or two patents at several dose levels, the protocol-defined maximum tolerated dose (MTD) was only observed in patients with large T2 tumors (5-7 cm in size) at 22 Gy x 3. In other tumor size groups, dose escalation was stopped prior to reaching the MTD (20-22 Gy x 3). Greater than 90% primary tumor control was observed with 20 Gy x 3; this total dose of 60 Gy corresponds to a biologically equivalent dose (BED) [if expressed in 2 Gy/fraction] of 180 Gy if using the formula BED = nd (1+d/alpha/beta), where n = number of fractions; d = dose per fraction; and alpha/beta = 10 for acute reacting tissue), although it is not clear how applicable this conversion is to highly hypofractionated treatments.

In a subsequent single institution phase II study of this SBRT regiment, Timmerman and colleagues treated 70 patients with early stage (T1-2, N0) inoperable NSCLC with 60 Gy in 3 fractions for T1 and 66 Gy in 3 fractions for T2.[14] That study allowed enrollment of patients with tumors located anywhere within the lung, and confirmed high rates of primary tumor control: 95% at 2 years. After median follow up of 17.5 months, three patients demonstrated a local recurrence. The study was particularly instructive in terms of local toxicity: 8 patients were deemed by the data safety monitoring board to have grade 3 or 4 adverse events resulting from SBRT; the adverse events were primarily respiratory (decline in pulmonary function, pneumonia, pleural effusion, apnea) and/or skin reaction; they occurred a median of 7.6 months after completion of SBRT. Six patients may potentially have had grade 5 (i.e., fatal) toxicity. In five patients, these grade 5 adverse events were respiratory: one fatal hemoptysis (associated with a local recurrence) and four infectious pneumonias; the sixth patient died of complications from a pericardial effusion. These deaths occurred a median of 10.4 months after SBRT (range 0.6-19.5 mo). Tumor location was a strong predictor of toxicity, with hilar or pericentral tumors showing an 11-fold increased risk in grade 3-5 adverse events when compared to more peripheral tumors (p=0.004). 2-year freedom from severe adverse events was 54% for these central tumors, as compared to 83% for the peripheral tumors, defined as outside the "zone of the proximal bronchial tree", which is a 2 cm radius around the main tracheo-bronchial tree: trachea; left and right main stem bronchi; right upper, middle, and lower lobe bronchus; and left upper, lingular, and lower lobe bronchus. The only other variable that was a predictor of toxicity, although not as

strong as tumor location, was the size of gross tumor volume (GTV), with > 10 cc tumors showing greater toxicity than smaller GTVs.

On the basis of these two studies, 60 Gy in 3 fractions was chosen as the dose for the RTOG-led phase II multicenter study, RTOG 0236, but patients with tumors within the above-described zone of proximal bronchial tree were excluded from the study. As in the prior phase I and II studies, the doses were calculated without correction for tissue inhomogeneity. The study was activated in May 2004 and opened in 8 sites, after those sites had completed the credentialing process. RTOG 0236 was closed October 2006. Of 55 evaluable patients, 44 had T1 and 11 had T2 tumors. With median follow up of 8.7 months, there was one (2%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment. Two of the 7 patients reported pulmonary function test decreased, 1 patient reported cough/dyspnea, 1 patient reported hypoxia, 1 patient reported pneumonitis, 1 patient reported cough/forced expiratory volume, and 1 patient reported pneumothorax. There also was a grade 3 dermatitis and a grade 3 syncope reported as related to protocol treatment. No treatment related deaths have been reported.[15] An analysis was done to determine the actual dose delivered using inhomogeneity corrections. Therefore, the treatment-related morbidity with SBRT using an ablative total dose of 54 Gy in 3 fractions, corrected for tissue inhomogeneity, appears to be acceptable in a population of frail patients.

The RTOG Lung Committee will be further exploring lung SBRT as it offers potentially curable treatment for patients with localized lung cancer. A phase II trial of the SBRT schedule of 60 Gy in 3 fractions for peripheral tumors, in potentially resectable patients (RTOG 0618) will explore SBRT as a potential alternative to surgery. However, the tumors within the zone of proximal bronchial tree continue to be excluded from these SBRT schedules, both on trial and off trial. Thus, it is not known what SBRT dose and fractionation schedule would be most efficacious while still safe in patients with these more centrally located tumors. This seamless phase I/II study aims to answer that clinical question and to establish the maximum tolerated dose of SBRT for centrally located NSCLC in patients who are not operative candidates.

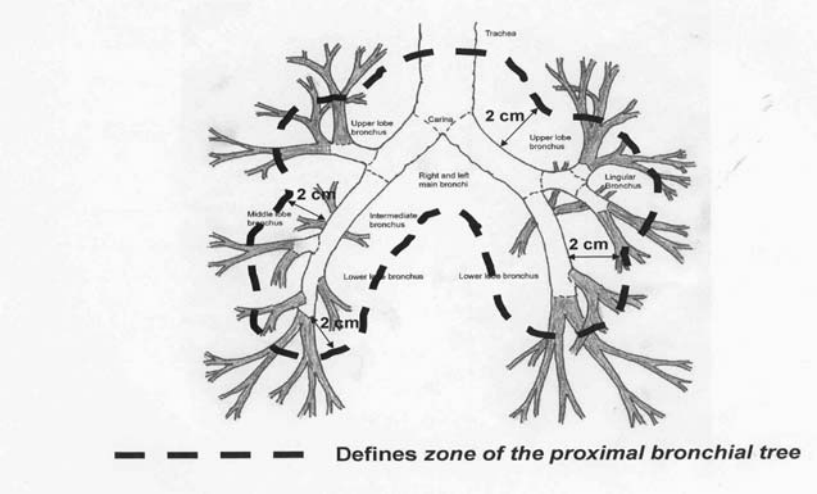
1.3 Justification for Proposed Study Design

Phase I/II oncology trials are intended to determine the maximum tolerable dose (MTD) of a single or combined modality and to make a preliminary assessment of the efficacy of that treatment. The design of a phase I/II trial is acceptable if it: a) does not expose participants in the trial to unacceptable risk; b) has a reasonable probability of identifying a dose that is close to that which is associated with the highest clinically tolerable probability of dose-limiting toxicity; and c) has at least modest statistical power to demonstrate that the efficacy of the treatment under study maybe superior to standard therapy, if the experimental therapy does in fact have a significant clinical advantage.

The proposed study employs a relatively new but advantageous statistical approach: continuous reassessment methodology (CRM).[16-18] rather than the conventional phase I design of 3 patients per each dose level. Utilizing CRM, the dose level for the next patient will be determined based on any dose-limiting toxicities experienced in the previous patients. In that way, more patients will be spared dose-limiting toxicities and more patients will be entered on the dose level that eventually will be chosen as the most appropriate one. Therefore, rather than a classical phase I study proceeding to a phase II study, this will be a seamless phase I/II study, in which all patients will contribute to finding the dose level that is most appropriate and all will contribute to the information about the efficacy of that dose level, within one trial. Statistics for this phase I/II study, and the RT dose level for each patient, is based on the Time-to-Event Continual Reassessment (TITE-CRM)[19-20] methodology. TITE-CRM is a refinement of the CRM design that allows for continual accrual of patients when delayed adverse events may be observed. Details of this methodology are provided in Section 13.3.

The primary endpoint of the study is the maximal tolerated dose (MTD) of a SBRT schedule of 5 fractions, administered on alternate days, over 1½ - 2 weeks, for stage I NSCLC tumors that are touching or within the zone of the proximal bronchial tree (Figure 1 below) or are adjacent to mediastinal or pericardial pleura (as these are also dose-limiting organs for high dose SBRT).

Figure 1



Five fractions were chosen because this short, practical schedule is suitable for patients with co-morbidities and/or patients traveling from a distance to an SBRT center, as well as being within the definition of SBRT as accepted by regulatory bodies;[21] it has potential radio-biological advantages of the 3 fraction schedule as repair of sub-lethal damage occurs after each fraction. Thus, more repair and greater tolerance of normal structures would be expected, particularly in the penumbra region of the high dose with 5 rather than with 3 fractions.[22]

The MTD for this schedule will be assessed by the adverse events within the first 12 months following study entry. This was felt to be more clinically relevant than the classical 90 day toxicity, as the dose-limiting toxicity of SBRT to central thoracic structures may be acute (within a month of SBRT) but is more likely to be sub-acute (1-6 months post SBRT) and chronic (more than 6 months post SBRT).

The starting RT dose for the study will be 10 Gy x 5 fractions every 2 days, over 1½ - 2 weeks (total dose [TD] of 50 Gy). The subsequent dose levels will escalate dose by 0.5 Gy per fraction (i.e., a 2.5 Gy total dose) to a maximum dose of 12 Gy x 5 fractions (TD 60 Gy in 5 fractions). Several lower dose levels will be employed if unacceptable dose-limiting toxicity (DLT) is seen with the planned starting dose of 10 Gy. All treatment plans will have to respect the organ-at-risk doses as outlined in the protocol and discussed below.

1.3.1 *Critical Organ Dose-Volume Limits*

The aim of this study is to determine the toxicity (i.e., the MTD) of SBRT for centrally located lung tumors. The thoracic organs that are at risk for RT injury (i.e., organs at risk [OARs]) from high SBRT doses and are expected to be determinants of dose-limiting toxicity are lung, central airway/bronchi, esophagus, heart, great vessels, spinal cord, and nerves (as detailed in Section 6.5). If the RT dose-volume limits of these critical organs exposed to high dose per fraction RT were known, there would be no need to perform this dose-seeking study. There is a large body of knowledge on the RT tolerance of those organs to conventionally fractionated RT (1.8-2 Gy per fraction), describing the RT tolerance in terms of volume of the organ irradiated to a certain dose (e.g., V20, volume irradiated to 20 Gy or more) or as mean RT dose to the entire organ.[23] There are clinical studies reporting experience with somewhat hypofractionated RT (e.g., 2.5-3 Gy per fraction),[24] but it is not clear how those dose-volume limits can be converted into limits suitable for this study in which much smaller volumes are irradiated to much higher doses per fraction. Although BED formulas are used to compare different RT dose-fractionation schedules, these formulas may not be appropriate for the extreme hypofractionation (in conjunction with very small volumes irradiated).[25-26] Of more relevance, particularly in terms of airway tolerance, is the longstanding experience with endobronchial brachytherapy,[27] which demonstrated the safety of large doses per fraction (in the range of 10-15 Gy) to the airway and surrounding structures, with low incidence of radiation bronchitis and/or bronchial stenosis (6% -12%)[28-29] and isolated cases of fatal hemoptysis in patients with associated progression of their cancer in the airway.

There are several SBRT trials specifically for centrally located tumors; a phase I SBRT study for centrally located tumors is actively accruing at the Washington University School of Medicine, St Louis, MO (PI: Jeffrey Bradley, MD). As of September 2007, five patients had completed the first dose level of 9 Gy x 5 fractions, with a minimum follow up of 5 months, and no observed toxicities. The only OAR dose limits in this study are spinal cord (20 Gy) esophagus (30Gy), brachial plexus (25 Gy) and heart (30 Gy). It did not prove to be possible to respect these OAR limits for bronchus in 1 patient (of the 5) who had a tumor immediately adjacent to a central structure, and the protocol was amended so that these dose constraints are now guidelines rather than actual limits (with the exception of the spinal cord). Dr. Bradley's study is now accruing patients at 10 Gy x 5 fractions. Another SBRT center, VU University Medical Center in Amsterdam, treats patients with central tumors with 60 Gy in 8 fractions (PI: Frank J. Lagerwaard, MD). As of May 2007, 25 lesions were treated with the dose prescribed at the PTV encompassing 80% isodose and with no upper limit on dose allowed to bronchus or pericardium but avoidance of hot spots and limitation to volume irradiated (for esophagus and spinal cord, a limit of 18 Gy). At Fox Chase Cancer Center in Philadelphia, PA, 10 patients were treated with 12 Gy x 4 fractions, with a median follow up of 1 year, and no dose-limiting toxicity (PI: Benjamin Movsas, MD)[30]

Given that volumes of critical organs being irradiated in SBRT are smaller than for conventionally planned RT, the conventionally used metrics to express dose-volume limits (such as mean dose or volume receiving a certain "threshold" dose, such as V20) are not as useful in determining allowable dose limits.[31] Since fraction size is large, the relevant dose limits for critical organs, such as cord and brachial plexus derived from conventionally fractionated schedules, do not apply; the dose limits are considerably lower. Building on the experience from RTOG 0236, this study will require careful contouring of the OAR, respecting strict limits of dose on the most critical organs (spinal cord, brachial plexus) and limiting the volume of normal structures receiving high doses.[31]

A variable that will influence the dose to the organs at risk is the location of the tumor. Even though all the tumors need to be within a 2 cm radius around airway or mediastinal pleura, there will nevertheless be some tumors that are in more immediate proximity to a critical organ (typically, only one or two organs, not all of the organs listed above). For example, a tumor may be within millimeters of proximal airway and/or esophagus, but far away from the spinal cord and brachial plexus. In that case, the PTV will include a portion of that critical structure, and it is not technically possible to give the full dose to the PTV and not give the same dose to the (small) part of the critical organ that is so close to the tumor. For other tumors that are further away from critical organs, conformal planning techniques, use of non-coplanar beams, and if necessary, IMRT, will ensure that critical organs receive a far lower dose than the prescription dose. Thus, rather than dose limits, we are proposing volume limits and dose guidelines in the protocol, which we expect to be observed for cases in which the tumor is not in the immediate vicinity of a critical organ. For tumors that involve a critical organ, we expect that the volume of that organ that gets a higher dose than limits suggest will be limited to the wall of the organ that is in immediate vicinity of the tumor and that the contralateral wall of the organ will not exceed the proposed limit. The only organ for which the limit is required is the spinal cord, as RT complications can lead to paralysis, a devastating consequence.

Given that some of the tumors may be so close to OAR, there is a strong rationale to utilize IMRT (Intensity Modulated RT) in order to allow for better sparing of normal tissues in close vicinity of the target. IMRT is an acceptable technology in other current RTOG lung studies (specifically RTOG 0617, the study of 60 Gy vs. 74 Gy RT with concurrent chemotherapy in locally advanced, unresected NSCLC); centers will be required to have appropriate credentialing (see Section 5.3). IMRT cannot be planned without the plans being corrected for tissue heterogeneity, i.e., correcting for lower density of lung tissue. There are now several algorithms for dose calculation that provide much more accurate dose calculations and allow for better determination of dose to OAR. As this is the fundamental question in this trial, it is required that all dose calculations be done with correction for tissue heterogeneity, as in RTOG 0617. This is not being done in the other SBRT lung study, RTOG 0618, but that study treats peripheral tumors, where the dose to OAR is less of a concern and for which IMRT is not being

used. Thus the argument for the use of heterogeneity corrections is much stronger for the current study.

1.4 Comorbidity

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

Comorbid conditions have been shown to affect prognosis in a variety of clinical situations and are independent of functional status.[32-34] 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.[33] 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 scales[35-37] 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.[37-38] Neither scale correlates with functional status, and each provides independent information.[37]

1.5 Translational Research **(8/20/10)**

Patients with similar stage of disease respond to treatment differently in tumor control and normal tissue toxicity. Although historical comparisons have shown that SBRT has generated a much better tumor control rate than traditional 3D-CRT, local failures are noted in 10-30% of patients. 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.[14,39] Also, due to the large fraction size used in SBRT, late normal tissue toxicities such radiation pneumonitis and lung fibrosis are worth studying.

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. Zhang, 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.[40] 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.[41] 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.[41-44] 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.[45-46]

To predict normal tissue toxicities, transforming growth factor beta 1 (TGFβı) has been most extensively studied for pneumonitis[47] and non-lung toxicities.[48] Researchers from Duke University reported that the plasma TGFβı level at the end of radiation correlated with symptomatic lung toxicity in patients treated with definitive radiation therapy.[48-49] 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 TGFβı levels and subsequent radiation-induced pneumonitis in patients with NSCLC.[50] In patients with lung cancer treated with an escalated dose of radiation, Anscher, et al. found a significant correlation between TGFβı levels and late non-pulmonary grade 3 radiation toxicity.[51] 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 grade 2 or above radiation pneumonitis.[52] 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.[51-53] 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.[53-54] Serial plasma IL-6 was consistently higher for the pneumonitis group. A recent study also showed promising results concerning the associated of single nucleotide polymorphisms (SNP) of several specific genes of white blood cells with radiation induced acute and late toxicities.[55-56] 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 associations with treatment outcome.

The primary goal of this correlative translational analysis is to examine if any proteomic or genomic markers in the blood before completion of the last dose of SBRT are predictive of primary tumor control outcome or late radiation toxicity. Specifically, we will: 1) explore the correlation of cytokine array, proteomic analysis, and genomic analysis of blood samples with 2-year local control; 2) explore the correlation of TGFβ1, IL-6 (and many other cytokines), proteomic profile, and yet-to-be identified proteins, genomic profiles, and molecular specific SNPs in the blood prior to and during the course of SBRT with the occurrence of grade ≥ 2 pulmonary adverse events and with occurrence of grade ≥ 2 non-pulmonary adverse events after completion of SBRT. The data will be analyzed in conjunction with other lung SBRT studies, including operable and inoperable patients.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 Phase I Portion

To determine the maximal tolerated dose (MTD) of SBRT for centrally-located NSCLC and the efficacy of that dose in patients who are not operative candidates

2.1.2 Phase II Portion **(8/20/10)**

To estimate the primary tumor control rate at the MTD of SBRT

2.2 Secondary Objectives **(8/20/10)**

2.2.1 To estimate rates of ≥ grade 3 CTCAE, v. 4 adverse events other than a dose-limiting toxicity (DLT) which is possibly, probably, or definitely related to treatment and which occurs within 1 year from the start of SBRT;

2.2.2 To estimate rates of late (> 1 year from start of SBRT) adverse events;

2.2.3 To estimate the primary tumor control and progression-free and overall survival rates for patients treated with this regimen;

2.3 Tertiary Objectives (Exploratory) **[8/20/10]**

2.3.1 To study if molecular markers (proteomic or genomic) in the blood circulation prior to, during the course of treatment (between the third and fourth dose of SBRT), and at the first follow-up after SBRT predict 2-year primary tumor control, the occurrence of treatment-related grade ≥ 2 pulmonary adverse events, or the occurrence of treatment-related grade ≥ 2 non-pulmonary adverse events; data will be analyzed in conjunction with other lung SBRT studies, including operable and inoperable patients.

2.3.2 To analyze the prognostic significance of comorbidity status; data will be analyzed in conjunction with other SBRT studies, including operable and inoperable patients;

2.3.3 To document tumor motion and inter-fraction (setup) errors.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility **(8/20/10)**

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of non-small cell lung cancer (NSCLC);

3.1.2 Stage T1-2, N0, M0 (AJCC Staging, 6th Ed.), tumor size ≤ 5 cm, prior to registration, based upon the following minimum diagnostic workup:

3.1.2.1 History/physical examination within 4 weeks prior to registration;

3.1.2.2 Evaluation by an experienced thoracic cancer surgeon within 12 weeks prior to registration; the primary tumor must be deemed technically resectable by an experienced thoracic cancer clinician, with a reasonable possibility of obtaining a gross total resection with negative margins, defined as a potentially curative resection (PCR). However, the patient must have underlying physiological medical problems that would prohibit a PCR due to a low probability of tolerating general anesthesia, the operation, the post-operative recovery period, or the removal of adjacent functioning lung. These types of patients with severe underlying health problems are deemed "medically inoperable." Standard justification for deeming a patient medically inoperable based on pulmonary function for surgical resection of NSCLC will include any of the following: Baseline FEV1 < 40% predicted, post-operative FEV1 < 30% predicted; severely reduced diffusion capacity; baseline hypoxemia and/or hypercapnia; exercise oxygen consumption < 50% predicted; severe pulmonary hypertension; diabetes mellitus with severe end organ damage; severe cerebral, cardiac, or peripheral vascular disease; or severe chronic heart disease.

3.1.2.3 Imaging as follows:

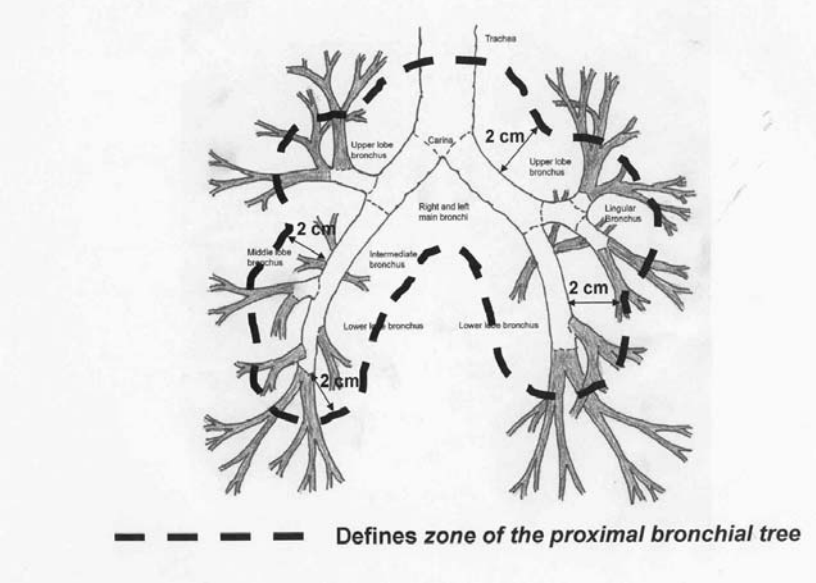
- CT scan with contrast (unless medically contraindicated) within 8 weeks of registration. The CT scan will include the entirety of both lungs, the mediastinum, liver and adrenal glands; the primary tumor dimensions will be measured on CT. **Note**: Patients with lesions that cannot be visualized by CT scan are not eligible for the study.
- Whole body positron emission tomography (PET) scan within 8 weeks of registration, using FDG with adequate visualization of the primary tumor and draining lymph node basins in the hilar and mediastinal regions.

Patients with hilar or mediastinal lymph nodes ≤ 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) may still be eligible if directed tissue biopsies of all abnormally identified areas are negative for cancer.

3.1.3 Zubrod Performance Status 0-2 within 4 weeks prior to registration;

3.1.4 Age ≥ 18;

3.1.5 **(2/16/10)** Tumor 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] Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol.



3.1.6 Patients must have measurable disease.

3.1.7 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(s).

3.1.8 **(2/16/10)** Negative serum or urine pregnancy test within 72 hours prior to registration for women of childbearing potential;

3.1.9 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment);

3.1.10 Patients must provide study-specific informed consent prior to any protocol specified procedures.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 2 years (e.g., carcinomas *in situ* of the breast, oral cavity, or cervix are permissible); previous lung cancer, if the patient is disease-free for a minimum of 2 years is permitted.

3.2.2 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.3 Prior chemotherapy for the study cancer;

3.2.4 Plans for the patient to receive other local therapy (including standard fractionated radiotherapy and/or surgery) while on this study, except at disease progression;

3.2.5 Plans for the patient to receive systemic therapy (including standard chemotherapy or biologic targeted agents), while on this study, except at disease progression.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

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

4.1 Required Evaluations/Management (2/16/10)

4.1.1 Collection of weight and documentation of extent of weight loss in previous 3 months, to be done within 4 weeks prior to treatment;

4.1.2 Chest x-ray within 2 weeks prior to treatment;

4.1.3 Routine spirometry, lung volumes, diffusion capacity, and arterial blood gases within 12 weeks prior to treatment;

4.1.4 CBC/differential obtained within 8 weeks prior to treatment;

4.1.5 Charlson Comorbidity Index (CCI) and hospitalization history (see Section 11.4 and Appendix V) within 12 weeks prior to start of treatment.

5.0 REGISTRATION PROCEDURES

This is a limited institution study; see the pre-registration criteria below.

5.1 Pre-registration Requirements for Data Quality This study is designed so that there is no suspension of patient accrual to assess a dose level. Each new patient is assigned a dose based on the information received for all patients previously entered on study. This assumes that all critical data, such as the occurrence of a dose-limiting toxicity (DLT), are reported to RTOG Headquarters in a very timely manner. If these critical data are delinquent, a patient may be assigned to a potentially toxic dose.

5.1.1 Due to the importance of timely data quality with regards to assigning doses to new cases, institutions must receive approval for participation from RTOG Headquarters. Approval will be based upon the data quality score generated regularly by RTOG Headquarters for the RTOG Membership Evaluation Committee. Institutions with a data quality score ≥ 80% will be permitted to participate. Participation by institutions with data quality scores < 80% will be determined by the RTOG Headquarters Lung Team and the RTOG Group Statistician.

5.1.1.1 Sites will fill out the 0813 Application to Participate, found on the RTOG web site, http://www.rtog.org, next to the protocol, prior to submitting the protocol to their IRB/REB and fax the form to RTOG Headquarters, 215-574-0300. RTOG Headquarters will respond to the site's application within 2 business days.

Sites must receive written approval of submitted applications from RTOG Headquarters prior to registering patients on study.

5.1.2 Institutions that are approved to participate will have their data quality continuously monitored. Participation privileges for an institution will be suspended whenever the institution has two violations at any time based on the following criteria:

1. Treatment chart **(T5)** must be received < 1 week from the completion of RT;
2. Adverse Event form **(AE)** must be received either a) +/- 2 weeks from 1 year from the start of RT if no adverse event was experienced or b) within 24 hours of discovery of the adverse event.

After the delinquent data are submitted and judged to be complete, the institution may have its participation privileges restored depending upon the site's prior history with data submission.

5.2 Regulatory Pre-Registration Requirements **(2/9/11)**

5.2.1 **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, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.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 translations to RTOG Headquarters.
- IRB/REB assurance number

5.2.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved, RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual IRB/REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.2.2 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

5.2.2.1 **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

5.2.2.2 **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.

5.3 Pre-registration Requirements for SBRT

Participating Institutions must be credentialed for stereotactic body radiation therapy and heterogeneity corrections by the Advanced Technology Consortium (ATC) prior to enrolling patients on this study. Institutions wishing to submit IMRT plans must also be credentialed for intensity modulated radiotherapy (IMRT) by the Advanced Technology Consortium (ATC) prior to enrolling patients on this study. Sites using CyberKnife™ equipment must be credentialed for dose painting IMRT prior to enrolling patients on 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 5 steps (Sections 5.3.1-5.3.5): Centers previously credentialed for some of the technologies/procedures involved may be absolved from re-credentialing. However, institutions previously credentialed to use Clarkson or pencil beam algorithms for SBRT on RTOG 0236 by the ATC will be required to be re-credentialed for heterogeneity corrections. In addition, 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.

5.3.1 **(2/16/10)**Each participating institution must complete the 3D QA Facility Questionnaire for SBRT available on the ATC web site, http://itc.wustl.edu. Each institution must submit the completed Facility Questionnaire by e-mail, fax, or mail to:

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

The Facility Questionnaire requires the following:

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

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

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

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.

5.3.2 Each institution must perform a verification study demonstrating their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the gross tumor volume falls within the CT simulation defined PTV). The patient used for this study must have a target in the lung that is similar to the lesions that will be treated for patients entered on this study. The information submitted must include 3 IGRT datasets (from 3 different fractions) for a single anonymized patient and must employ the method that will be used for respiratory control for patients entered from a particular institution. This information with a spreadsheet (the spreadsheet is available on the see ATC web site, http://itc.wustl.edu) will be reviewed by the Medical Physics Co-Chair, Dr. Lech Papiez. Upon approval of the images and spreadsheet by Dr. Papiez, RTOG Headquarters will notify the institution that it is credentialed.

5.3.3 **(2/16/10)** Each participating 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.

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

5.3.5 Each participating 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.

5.4 Dial-in Registration Only

Note: Patients cannot be web registered for this study.

Patients can be registered only after eligibility criteria are met. 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.

Patients can be registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. EST. Patients will be assigned to an SBRT dose level based on the data available through the previous day. For further details, see Section 13.3.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) is allowed, but sites that wish to use IMRT must be credentialed for heterogeneity corrections and IMRT for RTOG lung studies (see Section 5.3).

Protocol treatment must begin within 1-3 weeks after registration.

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.[22] 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*

Patients will receive 5 fractions of radiation, on an every 2-day basis i.e., 2-3 treatments per week, so that the SBRT schedule is completed within 1.5-2 weeks. There should be a minimum of 40 hours between treatments.

The starting dose level will be dose level 5: **10 Gy x 5 fractions, i.e., 50 Gy/5 fractions**. The dose per fraction for each patient will be provided at the time of registration based on the toxicity experience of the previous patients on study.

The dose per fraction is to be prescribed to the prescription line at the edge of the PTV.

Dose Level	Dose per Fraction	Total Dose
1	8 Gy	40 Gy
2	8.5 Gy	42.5 Gy
3	9 Gy	45 Gy
4	9.5 Gy	47.5 Gy
5	**10 Gy†**	**50 Gy**
6	10.5 Gy	52.5 Gy
7	11 Gy	55 Gy
8	11.5 Gy	57.5 Gy
9	12 Gy	60 Gy

†Protocol treatment begins at Level 5, 10 Gy. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) dose.

6.1.3 *Premedications*

Corticosteroid premedication will not be mandated, although it can be used at the discretion of the treating oncologist (in which case, its use needs to be reported). Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate.

6.2 Technical Factors

6.2.1 *Physical Factors*

Only photon (x-ray) beams with photon energies 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 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*

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. It is understood that this may exceed the technical requirements listed in Section 6.4 for small lesions (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined PTV. This minimum field dimension does not apply to centers using tomotherapy or multiple pencil beam delivery systems.

6.2.3 *Dose Verification at Treatment*

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

6.3 Localization, Simulation, and Immobilization

6.3.1 *Patient Positioning*

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be 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). Patient immobilization must be reliable enough to ensure 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 Principal Investigator and Study 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 images (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 images 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 in the region of the tumor. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

Helical and four-dimensional CT (4DCT) is permitted for the study. Using either approach, 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 for centers acquiring image datasets using helical scanning. The methodology employed for centers incorporating 4DCT image datasets into target definition and treatment planning must first be approved through the process described in Section 5.3.2. Institutions using 4DCT must provide on a per-person basis the following information: method of image acquisition, utilization of the 4DCT image datasets, and the expansion margin to define the PTV. In addition, for each plan the target motion measured from 4DCT must be submitted.

There are many valid approaches to defining target volumes and margins using multiple datasets representing different phases of the breathing cycle. These include but not limited to:

a. the ITV (Internal Target Volume) concept from ICRU 62 with an appropriate margin accounting for geometric uncertainties (uniform 5 mm recommended) to define the PTV;
b. the mean target position with an appropriate margin to account for target motion and geometric uncertainties to define the PTV;
c. two helical scans, one scan with the patient at inhale breath-hold and the second scan with patient at exhale breath-hold.

The following will be required in terms of documenting target motion:

1. For particular method of target motion suppression (abdominal compression, breath hold, etc.), keep a tally of target motion range for each patient treated. Describe clearly the method utilized in the measurement of range of target motion and provide estimated error of measurement. Justify the estimation of error.
2. It is preferable to have information on range of motion along each axis of pt body (sup-inf, ap-pa, lt-rt). In case such information is not available, provide range of motion in 1 or 2 directions with clear indication of the orientation of the axis along which the motion range is evaluated.
3. In case of multiple measurements of ranges of motion (at simulations and/or at treatments, possibly pre- and post-treatments) provide information about the day and time when the data have been collected.
4. When data for some patients/treatment fractions is not collected the record of the missing measurement has to be kept and reported. If there is a clinical reason for not collecting data, it needs to be reported as well.
5. The reported range of motion has to be separated from setup errors.

6.4.2 *Dosimetry*

6.4.2.1 3D Conformal Planning

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 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 in the case of volumetric imaging) 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 (COMPTV). 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 COMPTV 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 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 COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

6.4.2.2 Intensity Modulated Radiation Therapy (IMRT)

IMRT is allowed in this study, provided that the participating institution is credentialed by the RTOG for intra-thoracic IMRT treatments. The NCI Guidelines for the Use of IMRT can be found on the RTOG homepage, http://www.rtog.org/.

The use of IMRT in this study is at the discretion of the participating institution. However, IMRT should be considered only when target coverage, OAR dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized (2-3 segments per beam should be adequate), and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam’s eye view).

6.4.2.3 Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction (RTOG 0236 did not allow heterogeneity correction). The particular algorithm used for such correction must be approved by the RTOG Physics Committee in advance.

For purposes of this protocol, superposition/convolution dose calculation algorithms demonstrate agreement between planned versus delivered dose. Institutions with treatment planning software utilizing superposition/convolution dose calculation algorithms will need to complete a questionnaire and submit a digital "dry-run" test to the ITC. Institutions using alternative algorithms (i.e., Clarkson or pencil beam) will need to credential their treatment planning system by irradiating the Radiation Physics Center (RPC) lung phantom. Doses falling within criteria established by the Medical Physics Committee will be deemed acceptable. The criteria for acceptable agreement between measured doses in the RPC lung phantom and calculated doses using older algorithms are: Across the PTV, the agreement shall be within 5% or 5 mm.

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 (COMPTV). 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 and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
3. Target Dose Heterogeneity: The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COMPTV) and ≤

90% of the dose at the center of mass of the PTV (COMPTV). The COMPTV 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. Low Dose Spillage: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
   a. *Location*: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below.
   b. *Volume*: The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given. See Table 1 below.
6. Respect all critical organ dose-volume limits listed in Section 6.5.1 below.

Table 1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

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).

6.5 Critical Structures

6.5.1 *Critical Organ Dose-Volume Limits* **(2/16/10)**

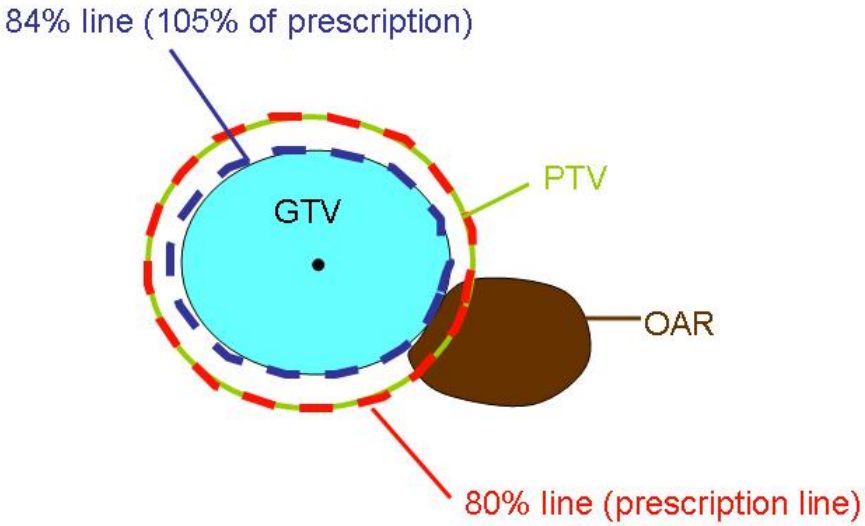
Table 2 lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (See Section 6.7). The dose is listed as total over 5 fractions and per fraction.

The esophagus, trachea, bronchi and heart may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to any of the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning needs to be done so that there

is no hot spot within that organ, even if that organ is part of the PTV, i.e., that no part of any OAR receives more than 105% of the prescribed dose (see Figure 2 below). In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. In Table 3, suggested volume limits are listed for these organs to be used for treatment planning purposes. Since the tumor and normal tissue may not allow strict avoidance, the volume limits (columns 2 and 3) will not be scored as protocol violations if exceeded. However, the maximum point dose limits (column 4) must be respected.

For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 6 Gy/fraction).

Figure 2



1. Prescription dose 50 Gy
2. Prescription isodose 80%
3. 105% of prescription dose 52.5 Gy (corresponds to 84% isodose line)
4. Maximum dose (normalization) at isocenter is 62.5 Gy

Table 2

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.25 cc <0.5 cc	22.5 Gy (4.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

Table 3

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	aneurysm
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	stenosis/fistula

*The volume maximum column shows suggested limits for these structures for planning purposes. Exceeded these limits is not a protocol violation. However, exceeding the Maximum Point Dose column is a violation per Section 6.7.2.

6.5.2 *Contouring of Normal Tissue Structures*

In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

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 cm 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 neuroforamine 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 (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

6.5.2.5 Trachea and Proximal Bronchial Tree

The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

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.

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 Figure 1 in Section 3.1.7. 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. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as "proximal bronchial tree GTV", not as part of the "proximal bronchial tree".

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 eligibility requirements for enrolling patients with tumors in the zone of the proximal bronchial tree, the RTOG SBRT protocols defined an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this structure, the patient is eligible for this protocol. 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).

6.5.2.10 Great Vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel 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 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

6.5.2.11 Non-adjacent Wall of a Structure

For the esophagus, trachea and proximal bronchial tree, and great vessels, the non-adjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV, These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

6.6 Documentation Requirements (2/2/09)

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.

NOTE: **If for any reason the assigned course of treatment cannot be completed, RTOG RTQA must be notified at 215-574-3219 on the day the patient stops radiation. The treatment record must be submitted to RTOG via FAX (215-940-8831, Attn: RTQA) on the last day of the patient's treatment.**

6.7 Compliance Criteria

6.7.1 *Accreditation Compliance*

All criteria listed in Sections 5.1-5.1.4 must be completed to the satisfaction of the Principal Investigators and Study Co-Chairs in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions 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 *Intra-fraction Setup Errors Reports*

1. For particular platform of patient setup utilized at any given center (pre-treatment CT matching with anatomy from planning stage; KV OBI-DRR matching in one or two filmed directions; 2D CBCT-DRR matching; 3D CBCT-TPS CT matching, etc.) keep a tally of target setup adjustment before each treatment. Describe the method used to correlate anatomy in predefined setup position with actual anatomy as observed before treatment, describe criteria for shifts/rotations of the anatomy to achieve no error matching and estimate the error after final matching (justify the estimates).
2. Report all values for shifts/rotations for all patients treated, including days of treatment.
3. When data for some patients/treatment fractions is not collected the record of the missing measurement has to be kept and reported. If there is a clinical reason for not collecting data, it needs to be reported as well.
4. It is preferable to have information on shifts/rotations before and after each treatment if possible.

6.8 R.T. Quality Assurance Reviews

Treatment planning images and dosimetry planning information in accepted format will be submitted to the Image-Guided Therapy Center (ITC), Washington University, St. Louis, MO, for QA purposes in all cases. See Section 12.1 for data submission.

The Principal Investigator, Dr. Bezjak, assisted by Radiation Oncology Co-Chairs Drs. Bradley and Gaspar, will perform an RT Quality Assurance Remote Review after complete data for the first 18 cases enrolled have been received at ITC. Drs. Bezjak, Bradley, and Gaspar will perform the next review after complete data for the next 18 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 (2/16/10) Radiation Therapy Adverse Events

The rationale for this phase I/II study is to determine the safe SBRT dose schedule for centrally-located NSCLC, i.e., within the proximal bronchial tree. There is concern about RT effects on organs at risk, most notably central airway, esophagus and heart/pericardium, as these organs

will be in immediate proximity to the centrally-located tumors. **See Section 13.1.1 for definitions of dose-limiting toxicities for this study.**

6.9.1 *Cardiac and Pericardial Injury*

Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of SBRT a number of possible side-effects can be seen.

6.9.2 *Gastrointestinal/Esophageal Injury*

The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases.

6.9.3 *Central Airway/Bronchial Injury*

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 mis-characterization.

(7/27/10) The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 4; MedDRA, v. 12.0.

6.9.4 *Lung Injury*

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. **Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has not been as dose-limiting as in conventionally fractionated large field RT, but it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence.** 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.

6.9.5 *Changes in Pulmonary Function Tests* **(7/27/10)**

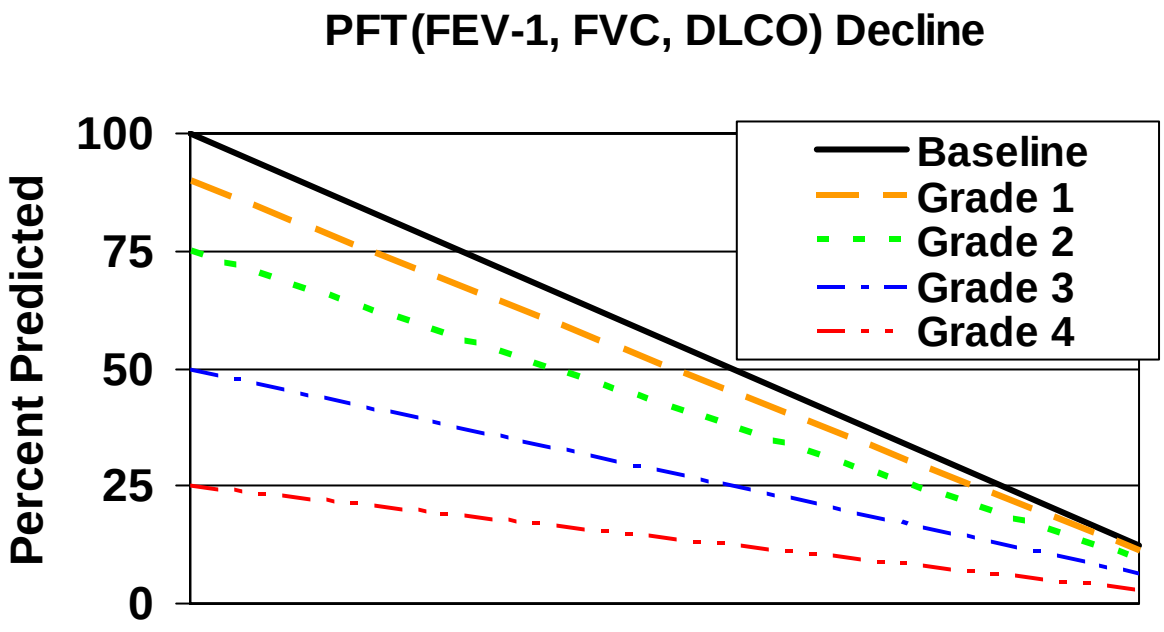
Patients enrolled to this study are allowed to have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). The Common Toxicity Criteria (CTCAE), v. 4 includes specified criteria for grading adverse events related to these PFT parameters under the system organ class of Investigations. 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 4 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 4 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.

The SBRT Pulmonary Toxicity Scale					
	Grade				
Adverse Event	1	2	3	4	5
FEV-1 Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
Forced Vital Capacity Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
DLCO Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death



6.10 Radiation Therapy Adverse Event Reporting

6.10.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

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 Adverse Event Expedited Reporting System (AdEERS) application 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 (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after 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.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probably, or definite) should be reported via AdEERS.

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.

AdEERS REPORTING REQUIREMENTS (7/27/10)

AdEERS 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 AdEERS RT-only pathway.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting beginning October 1, 2010. All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site, http://ctep.cancer.gov.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Use the patient's case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS **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 AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **<u>Phase II & III Studies</u>: All unexpected potentially related SAEs;**
- **<u>Phase I Studies</u>: 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 the AdEERS System 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. The AdEERS System allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	3		**3**		**4 & 5**	**4 & 5**
	Unexpected		**Expected**			
	With Hospitalization	**Without Hospitalization**	**With Hospitalization**	**Without Hospitalization**	**Unexpected**	**Expected**
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		**3**		**4 & 5**	**4 & 5**
	Unexpected		**Expected**			
	With Hospitalization	**Without Hospitalization**	**With Hospitalization**	**Without Hospitalization**	**Unexpected**	**Expected**
Unrelated Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required
Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" – A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- **(7/27/10)** Any medical event equivalent to CTCAE, v. 4 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

6.10.2 <u>SPECIAL REPORTING FOR THIS STUDY</u>

Immediately upon identification of a serious adverse event (SAE) as defined in Section 13.1.1 and provided below), the site will telephone the 24-hour RTOG AE Report Line: 215-717-2762.

The site will provide details of the SAE to RTOG Headquarters and will be instructed to fax the completed lung adverse event form (AE), FAX: 215-940-8830 within 24 hours of discovery of the adverse event. The AE form is available on the RTOG web site, with all of the 0813 forms. The site also will report the adverse event via AdEERS (see Section 6.10).

All reported adverse events will be reviewed by 1 of 3 designated radiation/medical oncologists not associated with this study within 2 business days of receipt of all supporting documentation. The determination of those adverse events as a study DLT will be made by the designated independent reviewer.

Serious Adverse Events That Require Special Reporting (7/27/10)

- Grade 3-5 Cardiac Disorders
  - Pericardial effusion
  - Pericarditis
  - Restrictive cardiomyopathy
- Grade 4-5 Gastrointestinal Disorders
  - Dysphagia
  - Esophagitis
  - Esophageal fistula
  - Esophageal obstruction
  - Esophageal perforation
  - Esophageal stenosis
  - Esophageal ulcer
  - Esophageal hemorrhage
- Grade 3-5 Nervous System Disorders
  - Brachial plexopathy
  - Recurrent laryngeal nerve palsy
  - Myelitis
- Respiratory, Thoracic, and Mediastinal Disorders, Grade 3-5, except as noted below
  - Atelectasis (grade 4-5 only)
  - Bronchopulmonary hemorrhage
  - Mediastinal hemorrhage
  - Pleural hemorrhage
  - Tracheal hemorrhage
  - Bronchial fistula
  - Pulmonary fistula
  - Bronchopleural fistula
  - Tracheal fistula
  - Hypoxia (provided grade 3 is worse than baseline)
  - Bronchial obstruction
  - Tracheal obstruction
  - Pleural effusion
  - Pneumonitis
  - Pulmonary fibrosis
- Changes in Pulmonary Function Tests per the SBRT Pulmonary Toxicity Scale (see Section 6.9.5), Grade 3-5
  - FEV1 decline
  - Forced Vital Capacity decline
- Any Grade 5 adverse event attributed to treatment

RTOG REPORTING REQUIREMENTS (7/27/10)

AdEERS 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 AdEERS RT-only pathway.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting beginning October 1, 2010.

All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site, http://ctep.cancer.gov.

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 AdEERS. 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. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

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

6.10.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [2/9/11]

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

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 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 Non-permitted Supportive Therapy

No other therapy specifically intended as treatment for study cancer is permitted, except at disease progression.

10.0 TISSUE/SPECIMEN SUBMISSION

(2/16/10) Patients must be offered the opportunity to participate in the tissue/specimen component of the study. If the patient consents to participate in this component, the site is required to submit the patient's specimens (blood, urine, and tissue, if adequate tissue is available) as specified in this section. **Note**: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent form.

For patients who have consented to participate in the submission of tissue, urine, and blood for the study (See Appendix I)

(5/7/09) 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 translational research.

10.1 Tissue/Urine Submission for Banking (Optional and Highly Recommended) [8/20/10]

Note: Lack of tissue block, core, or slides should not exclude the collection and submission of urine.

10.1.1 Sites may submit the following specimens for banking:

10.1.1.1 Tissue submission is highly recommended but not required. For lung cancer trials, core biopsies are encouraged. If adequate tissue available, a paraffin-embedded tissue block of the tumor or a 1.5 mm diameter core of tissue, punched from the tissue block containing the tumor with a punch tool should be submitted in a plastic tube labeled with the surgical pathology number. If minimal tissue is available, 3-7 unstained slides can be substituted for the punch biopsy or the tissue block. **NOTE**: A kit with the punch tool, 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 At least 10 ml of clean-catch urine collected at the following time points:

- Within 3 days of delivering the first dose of SBRT;
- Ideally after the third and before the fourth doses of SBRT, but at least before the fifth dose of SBRT;
- At the 6 week follow-up visit.

10.1.2 If the patient consents to the submission of his/her tissue, the site must provide the following 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 or slides contain 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 A Specimen Transmittal Form documenting the date and time 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)** Submit materials for banking as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

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

10.2 Rationale/Hypotheses for Blood Collection for Biomarker Research

The most significant advantage of blood for biomarker research is its availability for early prediction, continuous monitoring, and the minimally invasive procedure associated with its sampling. Because it circulates in the body and carries molecules released or shed from tumors and normal tissues in response to tumor or external stimuli, blood has a potential to serve as a surrogate marker for the individual's intrinsic genomic responsiveness of tumor and normal tissue to radiation. Additionally, an individual's blood is relatively plentiful (about 5 liters) and stable in volume, and therefore, more reliable for quantitative analyses.

As discussed in Section 1.5, 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[57-58] 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.[57] These levels also may 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, post-treatment pulmonary toxicity, and post-treatment non-pulmonary toxicity.

10.3 Blood Collection for Translational Research (Optional and Highly recommended) [2/9/11]

Note: Lack of tissue block, core, or slides should not exclude the collection and submission of blood samples.

10.3.1 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 at rtog@ucsf.edu. Plasma, serum and whole blood (for DNA) will be collected at the following time points:

- Within 3 days before delivering the first dose of SBRT; Note: If a site misses collecting whole blood at this time point, the site may collect the sample at any of the time points listed below, but this information must be provided on the Specimen Transmittal Form.
- Ideally after the third and before the fourth doses of SBRT, but at least before the fifth dose of SBRT;
- At the 6 week follow-up visit.

10.3.2 The following materials must be provided in order or the case to be evaluable: A Specimen Transmittal Form documenting the date of collection of the plasma, serum, whole blood; the RTOG protocol number, the patient's case number, time point of study, and method of storage, (for example, stored at -80° C) must be included.

10.3.2.1 Storage Conditions

Store frozen specimens at –80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.3.3 **(5/7/09)** Submit blood samples for translational research to:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

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

For any study-specific questions regarding the blood sample handling protocol, 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 (2/9/11)

Specimens for Tissue Banking			
Specimens taken from patient:	**Specimens collected when:**	**Submitted as:**	**Shipped:**
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 1.5 mm diameter core of tissue, punched from the tissue block with a punch tool	From pre-treatment biopsy	Paraffin-embedded tissue block or punch biopsy; note: 3-7 unstained slides are acceptable if block cannot be provided or punched	Block or punch shipped ambient
A minimum of 10 mL clean-catch urine	Within 3 days before the first dose of SBRT; after the third and before the fourth doses of SBRT; at the 6 week follow-up visit.	A minimum of 10 mL unpreserved urine aliquotted into 2 sterile 15 ml polypropylene centrifuge tubes	Urine sent frozen on dry ice via overnight carrier

Specimens for Translational Research			
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Within 3 days before the first dose of SBRT; after the third and before the fourth doses of SBRT; at the 6 week follow-up visit.	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (5 to 10)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube # 1 (purple/lavender top) and centrifuge	Within 3 days before the first dose of SBRT; after the third and before the fourth doses of SBRT; at the 6 week follow-up visit.	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (5 to 10)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Within 3 days before the first dose of SBRT. If this time point is missed then this specimen can be collected at any time the patient comes in for treatment or follow up.	Frozen whole blood samples containing 1 ml per aliquot in 1 mL cryovials (3 to 5)	Whole blood sent frozen on dry ice via overnight

10.5 Reimbursement (8/20/10)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory 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 web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.6 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.)

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 for assessments and time frames.

11.2 Submission of Urine and Blood Specimens (2/9/11)

11.2.1 Urine for banking (optional) and blood for translational research (highly recommended) should be submitted at the following time points: (see Section 10 and Appendix VI for details)

- Within 3 days before delivering the first dose of SBRT (Note: If a site misses collecting whole blood at this time point, the site may collect the sample at any of the time points listed below, but this information must be provided on the Specimen Transmittal Form);
- Ideally after the third and before the fourth doses of SBRT, but at least before the fifth dose of SBRT;
- At the 6 week follow-up visit.

11.3 Criteria for Evaluation

11.3.1 *Response Determination* **(8/20/10)**

Response to SBRT will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 [*Eur J Cancer*. 2009;45:228-247.] See http://ctep.info.nih.gov/protocolDevelopment/docs/recist_guideline.pdf further detailsAdditional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define primary tumor control as described below.

11.3.2 *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

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.

11.3.3 *Response Criteria* **(8/20/10)**

Evaluation of Target and Involved Lobe Lesions	
Complete Response **(CR)**	Disappearance of the target lesion; ideally, this determination will be made based on CT image evaluation.
Partial Response **(PR)**	At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.
Stable Disease **(SD)**	Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started
Local Enlargement **(LE)**	At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; Ideally, this determination will be made based on CT image evaluation.
Primary Tumor Failure **(PTF)**	Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. For outcome analysis, Marginal Failures (MF; see below) will also be counted as PTF; however, they should be distinguished specifically as MF, not PTF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation.[46]
Marginal Failure **(MF)**	Refers to the appearance after protocol therapy of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV (see Section 6.4) and meeting the following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.
Primary Tumor Control **(PTC)**	The absence of Primary Tumor Failure.
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	
Regional Failure **(RF)**	Refers to the appearance after protocol therapy of measurable tumor within lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease only with dimension of at least 1.0 cm on imaging studies (preferably CT scans) within the lung, bronchial hilum, or the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma.
Metastatic Dissemination **(MD)**	Refers to the appearance after protocol therapy of cancer deposits characteristic of metastatic dissemination from non-small cell lung cancer. Appropriate

	evaluations for making this determination include physical examination and imaging studies. PET scan OR biopsy to confirm MD is encouraged but not required.

11.3.4 *Criteria for Discontinuation of Protocol Treatment*

- Progression of disease;
- A delay in protocol treatment, as specified in Section 6.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

11.4 Comorbidity Data and Rating (8/20/10)

11.4.1 Site CRAs will complete the Comorbidity Recording Sheet and The Charlson Comorbidity Index (CCI) following the instructions in Appendix V. The Recording Sheet and CCI must include the RTOG study number and case number; institution name and number; name of person completing the form; phone number of that person; and date of completion. The patient-specific label may be used; however, all pages must have a label affixed. **Comorbidity data will be submitted to RTOG Headquarters at the same time point as the initial assessment data (see Section 12.1).**

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

12.0 DATA COLLECTION

Data should be submitted to:

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

***If a data form is available for web entry, it must be submitted electronically.**

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 (2/16/10)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)** Charlson Comorbidity Index **(CN)** and Comorbidity Recording Sheet	Within 2 weeks of study entry
Lung Adverse Event Form **(AE)**	**Within 24 hours of identification of an adverse event, fax to 215-940-8830**; also at 12 months after start of SBRT.
Radiotherapy Form **(T1) Copy to HQ and ITC**	Within 1 week of RT end
Daily Treatment Record **(T5)**	**Fax to RTOG HQ: 215-940-8831, Attn: RT QA on the last day of the patient's treatment or by the end of the next business day, with a copy to ITC**

	NOTE: If for any reason the assigned course of treatment cannot be completed, RTOG RTQA must be notified at 215-574-3219 on the day the patient stops radiation.
Follow-up Form **(F1)**	Every 3 months in years 1-2; every 6 months in years 3-4, then annually

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [2/16/10]

Item	Due
Preliminary Dosimetry Information (DD) †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 • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrent 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".**	Within 1 week of start of RT
Final Dosimetry Information Radiotherapy Form **(T1) [copy to HQ and ITC]** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image Guided Therapy QA Center	Within 1 week of RT end

†Available on the ATC web site, http://atc.wustl.edu/

12.2.1 *Digital Data Submission to ITC* (2/16/10)

Digital data submission may be accomplished using media or the Internet.

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

itc@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 of Phase I Portion* **(7/27/10)**

The maximal tolerated dose (MDT) of SBRT radiation dose associated with a 0.20 probability of dose-limiting toxicity (DLT); DLT is defined as any grade 3 or worse toxicity (per CTCAE, v.4, MedDRA, v. 12.0), that occurs within 1 year from the start of SBRT, is possibly, probably, or definitely related to treatment, and is related to the following specific symptoms:

- Grade 3-5 Cardiac Disorders
  - Pericardial effusion
  - Pericarditis
  - Restrictive cardiomyopathy
- Grade 4-5 Gastrointestinal Disorders
  - Dysphagia
  - Esophagitis
  - Esophageal fistula
  - Esophageal obstruction
  - Esophageal perforation
  - Esophageal stenosis
  - Esophageal ulcer
  - Esophageal hemorrhage
- Grade 3-5 Nervous System Disorders
  - Brachial plexopathy
  - Recurrent laryngeal nerve palsy
  - Myelitis
- Respiratory, Thoracic, and Mediastinal Disorders, Grade 3-5, except as noted below
  - Atelectasis (grade 4-5 only)
  - Bronchopulmonary hemorrhage
  - Mediastinal hemorrhage
  - Pleural hemorrhage
  - Tracheal hemorrhage
  - Bronchial fistula
  - Pulmonary fistula
  - Bronchopleural fistula
  - Tracheal fistula
  - Hypoxia (provided grade 3 is worse than baseline)
  - Bronchial obstruction
  - Tracheal obstruction
  - Pleural effusion
  - Pneumonitis
  - Pulmonary fibrosis
- Changes in Pulmonary Function Tests per the SBRT Pulmonary Toxicity Scale (see Section 6.9.5), Grade 3-5
  - FEV1 decline
  - Forced Vital Capacity decline
- Any Grade 5 adverse event attributed to treatment

All reported serious adverse events (SAEs) listed above will be reviewed by 1 of 3 designated senior radiation/medical oncologists who have expertise in the treatment of lung cancer and who are not associated with this study within 2 business days of receipt of all supporting documentation. The determination of those SAEs as a study DLT will be made by the designated independent reviewer. All reported SAEs listed above will be considered DLTs until reviewed by the designated independent reviewer.

13.1.2 *Primary Endpoint of Phase II Portion* **(8/20/10)**

Two-year primary tumor control rate at the MTD of SBRT (See Section 11.3.3)

13.1.3 *Secondary Endpoints*

13.1.3.1 Progression-Free Survival (see Section 11.3.3);

13.1.3.2 Overall Survival (see Section 11.3.3);

13.1.3.3 Local Progression (see Section 11.3.3);

13.1.3.4 Regional nodal progression (see Section 11.3.3);

13.1.3.5 Distant metastases (see Section 11.3.3);

13.1.3.6 Any grade 3 toxicity other than a DLT occurring within the first year;

13.1.3.7 Late grade 3 toxicity.

13.1.4 *Tertiary Endpoints (Exploratory)* **[8/20/10]**

13.1.4.1 To study if molecular markers (proteomic or genomic) in the blood circulation will predict 2-year primary tumor control rate, or the occurrence of grade ≥ 2 pulmonary adverse events, or the occurrence of grade ≥ 2 non-pulmonary adverse events;

13.1.4.2 To study the prognostic significance of comorbidity status;

13.1.4.3 To describe the medical physics endpoints of tumor motion and inter-fraction (setup) errors.

13.2 Justification of Design (7/27/10)

Since this trial will provide an estimate of efficacy for the MTD dose, it can be thought of as a seamless phase I/II trial. Monte Carlo simulation is used to assess the operating characteristics of this trial with respect to each of these metrics in turn. Three simulations were performed for the true dose-conditional probability of toxicity, which are described in Table 13.1. Scenario 1 (DLT-td) is the initial trial design for true dose-conditional probability of toxicity. Scenario 2 (DLT+) is approximately twice as toxic as assumed by the trial design. Scenario 3 is more than twice as toxic as the trial design, with rapidly increasing toxicity at dose Levels 7 and higher (DLT++).

These scenarios are used to assess the robustness of the design to mis-specification of the probabilities of toxicity. The trial assumes that a patient has the same risk of developing a DLT at any point during the 1-year observation period (flat hazard rate). Because of this, the cumulative observation time across patients is acceptable. Within each scenario, this assumption is tested by assessing the operating characteristics of trials where: DLT is equally likely across 1 year (trial assumption); DLT is substantially more likely early in the trial; DLT is substantially more likely late in the trial (see insets, Figure 13.1 below). In 2 completed RTOG trials, 0236 and 0324, which used CTCAE, v. 3.0, the timing of the DLTs as defined in this study was examined during the first year. In both trials, there was no suggestion that the DLTs were more likely to occur later in the risk period. (see Appendix VII for further details). Two hundred and fifty trials were simulated for each of the nine sets of experimental conditions derived from the 3 scenarios and the 3 different hazard rates. The numbers of DLTs, estimated target doses, distribution of doses, and statistical power to identify at least 1 dose as possibly being superior to standard therapy are graphed in Figures 13.1 and 13.2 (below).

13.2.1 *Expected Number of Observed DLTs*

The distributions of the number of DLTs observed (out of 75 treated and evaluable patients) for the simulated trials are described in the box plots in Figure 13.1. The boxes indicate the 75th, 50th, and 25th percentiles (from top to bottom), and the stems extend to the 95th and 5th percentiles. The plus indicates the mean. The median number of DLTs ranges from 11 (14.7%) to 18 (24%). If the design assumptions about P(DLT) are correct (DLT-td), over 85% of the simulated trials have less than 15 DLTs (20%), and at least 99% have less than 18, irrespective of the hazard rate. If P(DLT) is under-estimated as in scenarios DLT+ and DLT++, the median number of toxicities for simulated trials in either scenario does not exceed 18, and the third quartile does not exceed 20 (26.7%). The number of toxicities observed is relatively insensitive to the mis-specification of the hazard rate.

13.2.2 *Accuracy of Selection of Target Dose*

The distributions of target doses that the trial selects are presented in the right column of Figure 13.1. If the design assumptions about P(DLT) are correct (DLT-td), the trials overwhelmingly pick the correct target dose, indicated by the asterisk (Level 9). If P(DLT) is underestimated as in scenario DLT+ , the target dose is picked within one level of the true target dose (i.e., with 0.15 ≤P(DLT) ≤0.30) in over 90% of the simulated trials. If the P(DLT) is more severely underestimated as in scenario DLT++ , that proportion is higher.

13.2.3 *Estimation of Primary Tumor Control* **(8/20/10)**

The average number of patients treated at each dose is displayed in the left column of Figure 13.2. Again, the target dose is denoted by an asterisk. In the DLT-td cases, 7-14 patients are treated at Levels 5-8 due to the starting dose (level 5, 10 Gy) and escalation restrictions. In the

DLT+ simulations, 8-14 patients on average are treated on either of the 2 dose levels (8 and 9) with P(DLT) > 0.3, which result, on average in 3-5 DLTs. In the DLT++ simulations, 8-15 patients on average are treated on 1 of 3 dose levels (7, 8, and 9) with P(DLT) > 0.3 which result on average in 4-8 DLTs.

Primary tumor control was modeled as a function of dose by logistic regression model. A one-sided test with a significance level of 0.05 was employed, which is appropriate for a Phase II proof-of-concept trial. The right column of Figure 13.2 (below) assesses the power of the test of the null hypothesis that P (primary tumor control) < 0.7 at the chosen target dose. For all the simulations, it was assumed that pl=P (primary tumor control | dose level) increased linearly in the regression model between 60% of p9 at the lowest level, and p9, where p9 is graphed on the lower axis (for instance, trials labeled 0.9 indicated P (primary tumor control) increased linearly from 0.54 at Level 1 to 0.9 at Level 9, and equaled p6=0.83 at the true target dose). It is seen that, for the (DLT-td) trials, where the most efficacious dose has acceptable toxicity, the power exceeds 80% when p9 is 0.89 or greater, but that estimated power is more modest for the DLT+ or DLT++ simulations, where the selected target dose, and hence the efficacy at that dose, is lower. For example, with the DLT+ simulations, level 6 was the most frequently selected target dose (~ 40%), while dose levels 8 and 9 were uncommon (~4.5% and ~1.0%) This is an appropriate outcome, because these would be trials where adequate efficacy can only be achieved at unacceptably toxic doses.

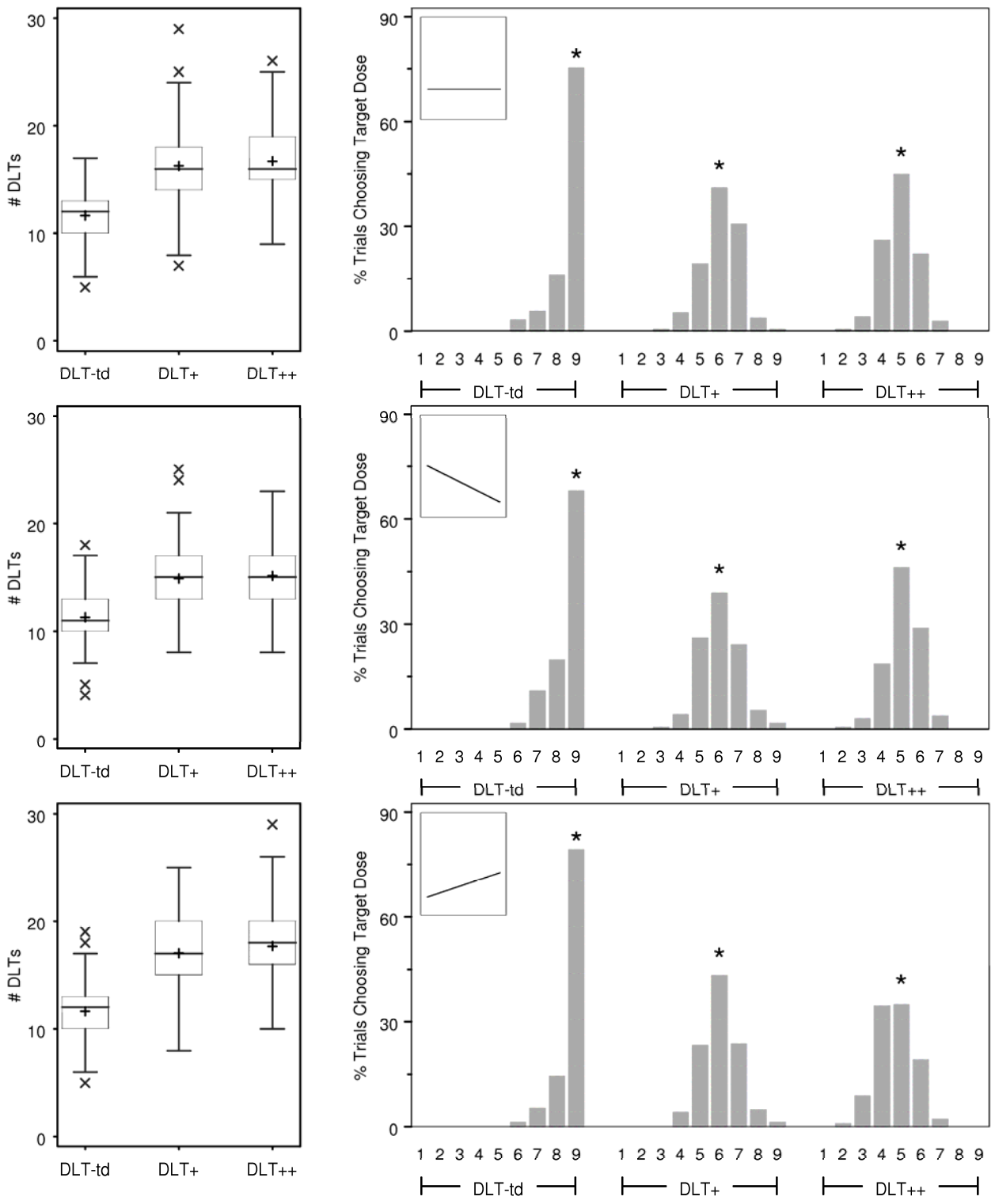
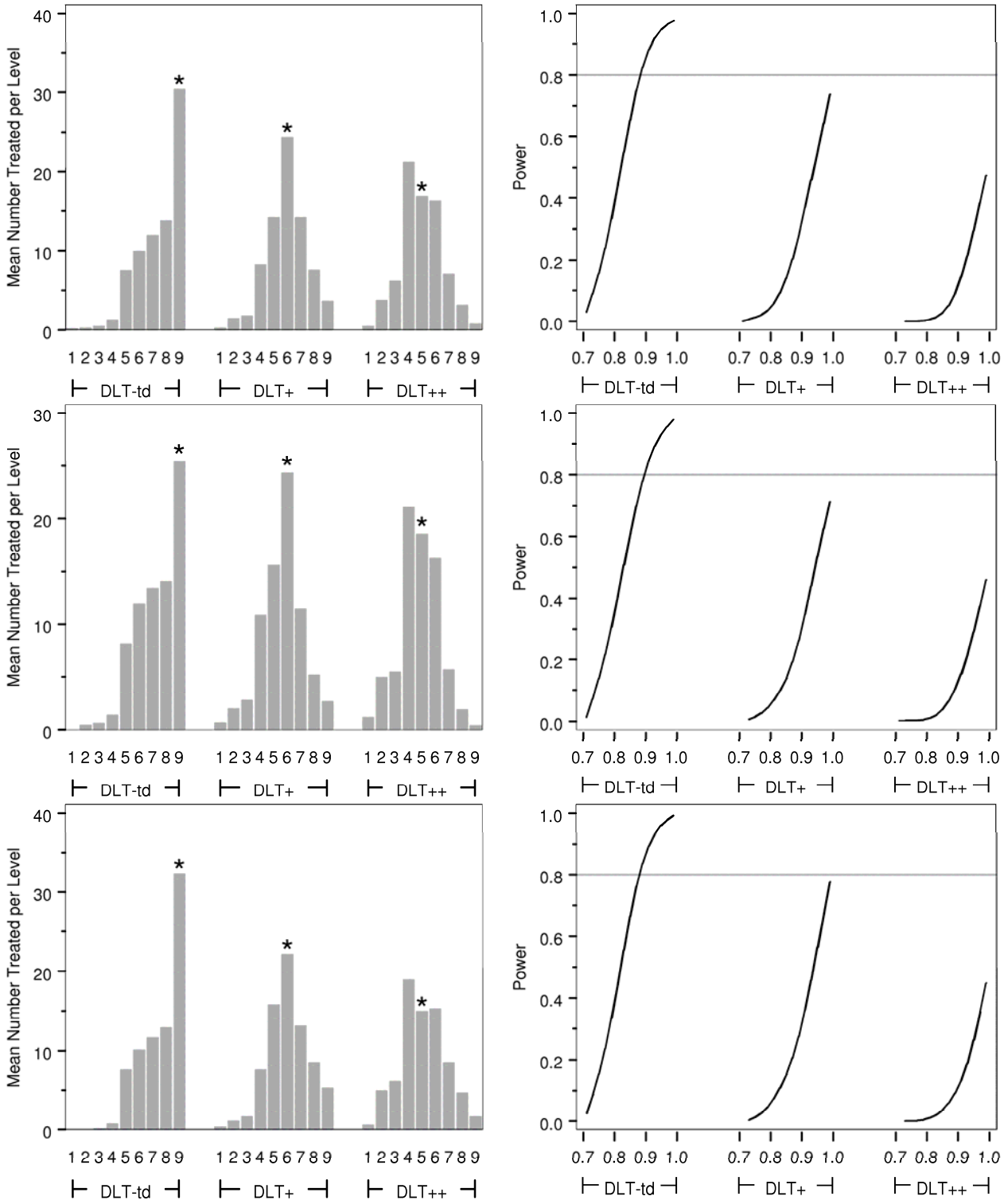


Figure 13.1: Operating characteristics for observed toxicity and selection of target dose from simulated trials. Inset describes hazard function. DLT-td, DLT+, and DLT++ are specified in Table 13.1. Asterisks indicate true target dose.



(8/20/10) Figure 13.2: Distribution of doses and power functions for simulated trials
Hazard function changes from top to bottom as in Figure 13.1. DLT-td, DLT+, and DLT++ are specified in Table 13.1 Left column indicates the expected number of patients treated at each dose, while the right-hand column indicates the power to test the null hypothesis that P(primary tumor control) < 0.7 at the target dose, as the P (primary tumor control) at Level 9 increases from 0.7 to 0.99 (see Section 13.6.3 for a more detailed description).

13.3 Sample Size (8/20/10)

This trial will accrue 75 patients fully evaluable for the DLT toxicity analysis.

Monte Carlo simulation was used to assess the operating characteristics of this design. Complete trials (2,250 for each trial scenario considered) were simulated using 3 different assumptions about the true probabilities of dose-limiting toxicity at each dose: 1) as assumed; 2) somewhat more toxic than assumed; 3) more toxic than assumed with significant increase in toxicity between doses 6 and 7. Among the operating characteristics considered in the sample size were the expected number of dose-limiting toxicities, the probability of selecting the correct dose (that associated with a 20% probability of DLT) as the target dose at the end of the trial, the time required to complete the trial, and the number of patients treated at or near the target dose. Sample sizes from 30 to 120 were evaluated, as were different rates of patient accrual. A sample size of 75 patients was determined to have acceptable probability of correctly selecting a dose with acceptable toxicity and enough patients treated about the target dose for characterization of the efficacy endpoints, while being feasible for completion of accrual within 4 years.

A patient is fully evaluable for toxicity analysis if:

1. The patient fails to complete treatment due to a DLT.
   OR
2. The patient receives all five RT fractions of the protocol treatment.
   AND
   A. Experiences a DLT within 1 year from the initiation of treatment
   OR
   B. Is observed per protocol for 1 year after the initiation of treatment and does not experience a DLT

Patients who complete protocol treatment but have progressive disease and no DLT within 1 year are still considered at risk for a DLT even if they receive chemotherapy. It is not likely that the addition of chemotherapy will greatly affect the occurrence of a SBRT-related DLT, and we did not want to exclude patients at risk of DLT.

A patient who does not complete protocol treatment because of non-protocol, treatment-related toxicity; non-protocol, treatment-related death; or refusal to complete protocol treatment will not be evaluable.

Patients who complete protocol treatment but cannot be observed for a DLT for 1 year (e.g., due to death from other than toxicity or patient refusal) will not count towards the accrual goal, but their data will be used to allocate doses to subsequent patients and in the final analyses for toxicity, primary tumor control and survival, they will be weighted, as appropriate, by the proportion of the observation period they have completed. Note: Patients, who have experienced a DLT, are fully weighted.

It is anticipated that average accrual will be 2 patients per month. Based upon RTOG 0236 (another RTOG trial utilizing SBRT), it is projected that 80% of patient entries will be evaluable for DLT analysis. So to accrue 75 evaluable patients, a total of **94 patients** will have to be entered, and this will take 4 years to complete.

13.4 Allocation of Participants to Doses

13.4.1

The Weighted Dose-Toxicity Model

Doses will be allocated to patients by means of the Time-to-Event Continual Reassessment Method (TITE-CRM) Phase I trial. A logistic dose-toxicity model was used for this trial with rescaled dose[1] $d = \log(p_o/(1-p_o))-3$.

$$p(d)=e^{3+\alpha d}/(1+e^{3+\alpha d}), \text{ (eq. 1)}$$

In the logistic dose-toxicity model, the prior distribution of the dose-toxicity parameter α is Gaussian with mean 1 and standard deviation of 0.3 which is based upon experience with other trials using this model. $\alpha=1.0$ represents our initial assumption about the toxicity of treatment, as displayed in the third column of Table 13.1

The weight function reflects the amount of information available from a patient. If a DLT is observed, the full information from this patient is available and the weight will be 1. Otherwise, the uniform weight function ranging from 0 to 12 months will be used. Each patient will be followed for DLT until the patient either reaches one year (12 months) from the start of SBRT without experiencing a DLT or experiences a DLT, whichever comes first. Let the time to a DLT of patient be U_i , then the weight function, w (u) = u/12.
This is translated into the following:

A) Patients who have enrolled in this trial but have not experienced a DLT have a weight equal to the proportion of the 12 months observation period they have completed.
B) Patients who have experienced a DLT before 12 months from the start of SBRT or complete protocol treatment without a DLT have a full weight, 1.

The goal of the trial is to determine the fraction size (dose) for SBRT most closely associated with a 0.20 probability of a DLT (specified as the *target rate*). As patients present for enrollment, they are assigned the highest dose associated with an estimated probability of a DLT less than or equal to the target rate of 0.2. The initial estimates of the probability of a DLT at each dose (column 3 of Table 13.1) are updated with the accumulated patient information using a Bayesian paradigm so that the estimation of the target dose, and, thereby, the assignment of the next dose, is based upon all the information available at the time of enrollment. To allow the trial to remain open to new patient entries without pause, while using the maximum available information, data from patients who have been enrolled but have not completed the 1 year observation period are weighted according to the proportion of the observation period the patient has completed (data from patients who have experienced a DLT are fully weighted).

Table 13.1: Toxicity probability estimates of trial design and simulation assumptions used to determine operating characteristics

		Probability of Toxicity			
			Scenario		
Dose Level	SBRT Fraction Dose (Gy)	Design (p_O)	DLT per trial design (DLT-td)	DLT+	DLT++
1	8.0	0.01	0.01	0.02	0.02
2	8.5	0.02	0.02	0.04	0.05
3	9.0	0.04	0.04	0.06	0.08
4	9.5	0.05	0.05	0.10	0.13
5	10.0	0.08	0.08	0.15	0.18
6	10.5	0.10	0.10	0.20	0.30
7	11.0	0.14	0.14	0.30	0.40
8	11.5	0.17	0.17	0.35	0.60
9	12.0	0.20	0.20	0.45	0.80

13.4.2 *Assignment of Dose*

The first patient will be treated at dose Level 5 (10 Gy). Whenever a subsequent patient presents for enrollment, the expected value of α, conditioned on the prior distribution and the data (weighted, where no DLTs have occurred, by the proportion of the 1 year observation period the patients have completed) will be calculated, from which the expected probability of a DLT at each dose level will be estimated. The patient will be assigned to the highest dose level with an expected probability of a DLT less than or equal to the target rate of 0.20, subject to the following escalation restrictions:

- Dose may only increase one level between consecutive patients;
- Dose may decrease any number of levels between consecutive patients;
- A patient may not be assigned to a next higher dose level unless there is at least 1 year of cumulative observation at the current dose level.

This cumulative observation may be distributed among several patients. Based on the data from RTOG 0236, most toxicity from SBRT occurs within 3 months of treatment. While it is possible that the 1-year cumulative observation may be distributed across many people, it is not expected that the actual distribution will include more than 4 patients, all of whom should have at least 3 months of observation time. The actual number of patients used to reach 1 year

of cumulative observation will be monitored, and appropriate action will be taken, such as not increasing to a new dose level, should the number of patients be deemed too excessive.

Under these rules, it is not possible to state in advance the number of patients who will be treated at each dose, but estimated distributions of dose allocations under several different assumptions about dose-toxicity models are presented in Figure 13.2.

Note: Due to technical reasons, a patient assigned to a dose level may actually have been treated at a lower dose level. As soon as this information becomes available, the patient will be analyzed at the lower dose level received prior to any calculations for the next patient's dose assignment in the next patient.

13.5 Analysis Plan

13.5.1 *Analysis of the Primary Endpoints* **(8/20/10)**

All patients evaluable per Section 13.3 will be used in the DLT analysis (the primary endpoint of the phase I portion), which will be performed after they have been potentially followed for the 1 year observation period. The patients treated at the MTD of SBRT will be used to estimate the 2-year primary tumor control rate (the primary endpoint of the phase II portion), which will be performed after they have been potentially followed for 2 years. Patients not evaluable will be reported separately. For each such patient, the reason for exclusion, protocol treatment received, and toxicities reported during the first year will be listed.

13.5.1.1 *Analysis of Dose-limiting Toxicities* **(7/27/10)**

The maximal tolerated dose (MTD) of SBRT radiation associated with a 0.20 probability of dose-limiting toxicity (DLT) will be determined as that dose having P(DLT) closest to the target rate of 0.20. DLT is defined as any grade 3 or worse toxicity (per CTCAE, v. 4, MedDRA, v. 12.0), that occurs within 1 year from the start of SBRT, is possibly, probably, or definitely related to treatment, and is related to the specific symptoms in Section 13.1.1). Markov Chain Monte Carlo will be used to estimate the probability of DLT at each dose, along with 95% posterior intervals, using the logistic dose-toxicity model (eg 1) described in Section 13.5.1. The observed proportion of patients experiencing a DLT will be calculated. The distribution of all toxicities will be tabulated by grade and category, as well as the following information:

I) Analysis by Assigned Dose Level
   a. Total number of patients assigned to that dose level
   b. Number of patients who received the assigned dose level
      i. Number of patients still in treatment
      ii. Number of patients not evaluable for DLT analysis
      iii. Number of patients evaluable for DLT analysis
         1. Number of patients who experienced a DLT
         2. Number of patients still at risk for a DLT
         3. Number of patients who completed the risk interval without a DLT
   c. Number of patients who did not receive the assigned dose level but who received a lower dose level
      i. Number of patients still in treatment
      ii. Number of patients not evaluable for DLT analysis
      iii. Number of patients evaluable for DLT analysis
         1. Number of patients who experienced a DLT
         2. Number of patients still at risk for a DLT
         3. Number of patients who completed the risk interval without a DLT

II) Analysis by Actual Dose Delivered
   a. Number of patients still in treatment
   b. Number of patients not evaluable for DLT analysis
   c. Number of patients evaluable for DLT analysis
      i. Number of patients who experienced a DLT
      ii. Number of patients still at risk for a DLT
      iii. Number of patients who completed the risk interval without a DLT

In addition, for those patients who did not receive the assigned dose level, the following information will be reported:

1. Dose level actually received
2. Assigned dose level

3. Reason for dose modification

13.5.1.2 *2-year Primary Tumor Control Rate at MTD* **(8/20/10)**

Primary tumor control is the absence of local progression (defined as local enlargement confirmed by PET or biopsy which occurs within 2 years from the start of treatment). Marginal failures, which are mentioned in Section 11.3.3, will be considered events for local progression. Distant metastases from the index lung cancer or a second primary tumor are not considered local progression. Patients who die with lung cancer but no documented local progression will be considered non-failures and will be censored on the day of their death. Patients who die without progressive lung disease and have no documented local progression will be considered non-failures and will be censored on the day of their death. Cumulative incidence method[59] will be used to estimate the 2-year primary tumor control rate at the MTD of SBRT. Using this confidence interval, the null hypothesis that the probability of 2-year primary tumor control at the selected target dose (MTD) is 0.7 or less will be tested. Ninety percent confidence interval for the probability of response will be constructed by bootstrapping.

13.5.2 Analysis of Secondary Survival Endpoints

13.5.2.1 *Progression-Free Survival and Overall Survival* **(8/20/10)**

The same patients used for DLT analysis will be used in these analyses, which will be performed after they have been potentially followed for 2 years. The failure event for progression-free survival (PFS) is defined as the first occurrence of local and/or regional disease progression, distant metastases, second primary tumor, or death due to any cause. Time to PFS is measured from the date of randomization to the date of the failure event for PFS. Overall survival (OS) time is measured from the date of randomization to the date of death due to any cause.

Kaplan-Meier estimation[60] will be used to calculate OS and PFS rate at each radiation dose level. Cox proportional hazards regression[61] will be used to characterize PFS and OS as a function of dose. As in the analysis of 2-year primary tumor control, possible confounding baseline demographic or clinical variables will be included in the regression model if there is evidence of significant imbalance between doses.

13.5.2.2 *Local Progression, Regional Failure, and Distant Metastases*

The same patients for DLT analysis will be used in these analyses, which will be performed after they have been potentially followed for 2 years.

The failure event for local progression (LP) is defined as local enlargement confirmed by PET or biopsy or a marginal failure per Section 11.3.3. The failure event for regional failure (RF) is defined as the first appearance of regional nodal disease. The failure event for distant metastases (DM) is defined as the first appearance of a distant metastases. The time to failure for these secondary endpoints (LP, RF, and DM) will be measured from the date of randomization to the date of the failure event.

The cumulative incidence method[59] will be used to estimate the rates of each endpoint. The treatment effect on these failures may impact the observable measures of outcomes, and other competing risks may dilute the sensitivity. Therefore, Fine and Gray's proportional hazards regression[62] will be used to characterize LP, RF, and DM as a function of dose. Possible confounding baseline demographic or clinical variables will be included in the regression model if there is evidence of significant imbalance between doses.

13.5.3 Analysis of Secondary Toxicity Endpoints

13.5.3.1 *Any Grade 3 or Worse Toxicity Other Than a DLT Occurring Within the First Year* **(7/27/10)**

This endpoint is defined as any grade 3 or worse toxicity (per CTCAE, v. 4) other than a DLT **occurring within the first year** that is possibly, probably, or definitely related to treatment and occurs within 1 year from the start of SBRT. The distribution of this toxicity will be tabulated by grade and category for each assigned dose level and actual dose received. If the number of applicable toxicities is adequate for analysis, logistic regression[63] will be used to model the distribution of acute adverse events with and without adjustment for demographic or clinical variables.

13.5.3.2 *Late Grade 3 or Worse Toxicity* **(7/27/10)**

This endpoint is defined as any grade 3 or worse toxicity (per CTCAE, v. 4) that is possibly, probably or definitely related to treatment and **occurs after 1 year** from start of SBRT. The distribution of this toxicity will be tabulated by grade and category for each assigned dose

level and actual dose received. If the number of applicable toxicities is adequate for analysis, logistic regression[63] will be used to model the distribution of acute adverse events with and without adjustment for demographic or clinical variables.

The time to late grade 3 or worse toxicity will be measured from the time protocol treatment starts to the time of the worst late grade 3 or worse toxicity after 1 year from start of SBRT. If no such late toxicity is observed until the time of the analysis, the patient will be censored at the time of the analysis. Death without late grade 3 toxicity will be considered as the competing risk for the events and the distribution of time to late grade 3 or worse toxicity will be estimated using the cumulative incidence method.

13.5.4 Analysis of Tertiary Endpoints (Correlative Studies)

The results from the analyses of tertiary endpoints (Section 13.1.4) will not provide definitive answers to any related research questions. In some instances, the questions concerning the medical physics endpoints of tumor motion and inter-fraction (setup) errors have not yet been clearly defined. Rather, these results will be considered exploratory to generate future hypotheses, for the following reasons: First, the study was not statistically powered for any tertiary endpoint, and secondly, patient participation in submission of specimens for study of the molecular marker is not mandatory in this trial.

The incidence rate of the local progression rate at 2 years will be analyzed with respect to molecular markers (proteomic or genomic) in the blood circulation. They are collected at baseline, during the course of treatment (between the third and fourth dose of SBRT), and at the first follow-up after SBRT. The time to first reported occurrence of grade ≥ 2 pulmonary adverse events and the first reported occurrence of grade ≥ 2 non-pulmonary adverse events will be separately analyzed with respect to molecular markers. The logistic and the proportional hazard regression models could be utilized to adjust for other possible confounding covariates.

13.5.5 *Interim Reporting*

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

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

To monitor the safety of this study, it will be officially reviewed by the RTOG Data Safety Monitoring Board for Phase I and II studies twice a year in conjunction with the RTOG semi-annual meeting and on an “as needed” basis between RTOG meetings.

13.5.6 *Clinical Data Update System (CDUS) Monitoring*

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5.7 *Reporting DLT analysis*

This analysis will occur after all evaluable patients have been potentially observed for 1 year. The report will include:

a. 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 Sections 13.1.1, 13.1.4, and 13.1.5.

13.5.8 *Reporting 2-year Primary Tumor Control Analysis* **(8/20/10)**

This analysis will occur after all evaluable patients have the necessary follow-up to estimate 2-year primary tumor control rate per dose level. The progression free survival and the overall survival will be also analyzed. The report will include:

a. 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 Sections 13.1.2, 13.1.3, and 13.1.5.

13.6 Inclusion of Women and Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and 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.[64] Furthermore, an analysis of race did not indicate an association with outcome.[65] The projected gender and minority accruals are provided in Table 13.2 below.

Table 13.2: Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	3	5
Not Hispanic or Latino	38	51	89
Ethnic Category: Total of all subjects	40	54	**94**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	3	4
Asian	1	3	4
Black or African American	3	2	5
Native Hawaiian or other Pacific Islander	0	0	0
White	35	46	81
Racial Category: Total of all subjects	40	54	**94**

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APPENDIX I

RTOG 0813

Informed Consent Template for Cancer Treatment Trials
(English Language)

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

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 early stage, centrally located non-small cell lung cancer that cannot be removed surgically due to medical problems.

Why is this study being done?

The usual treatment for early stage lung cancer is to remove the cancer with surgery. However, some patients may not be able to have standard surgery. Some patients cannot have surgery because of the location of their tumors. Some patients cannot have surgery because of other serious health problems like emphysema, diabetes, or heart disease.

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

Stereotactic body radiation therapy (SBRT) is a newer radiation treatment that gives fewer but higher doses of radiation than standard radiation. It uses special equipment to position the patient and guide focused beams toward the cancer and away from normal surrounding lung tissue. The higher dose technique may work better to kill cancer cells potentially with fewer side effects than standard radiation therapy. SBRT has not been used very often with patients who have centrally located early stage lung cancer.

The purpose of this study is to test the safety of SBRT at different dose levels with patients who have centrally located early stage lung cancer. We want to find out what effects (good and bad) SBRT has on you and your cancer.

In addition, this study also will gather information about your health and hospitalization history. This information will be used to find out if there are factors that can predict recovery or outcome of patients with lung cancer.

How many people will take part in the study?

At the beginning of the study, patients will be treated with a lower SBRT dose. If this dose does not cause bad side effects, the SBRT dose slowly will be made higher as new patients take part in the study. Your doctor will discuss the SBRT dose you will receive with you.

A total of 94 patients are the most that would be able to 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.

- A physical exam by several doctors
- Checking your weight
- Evaluation of your ability to carry out daily activities
- A chest x-ray (and CT scan: see "Before radiation treatment begins" below)
- A PET scan of your body: A small amount of radioactive material is injected into a vein, and a scanner makes a detailed picture of areas inside the body
- Blood tests, including a blood test to find out how much oxygen is delivered to the tissues beyond your lung
- Tests of your lung function
- For women who are able to have children, a test to see that they are not pregnant

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 these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

Before radiation treatment begins:

- You will be asked questions about your health and hospitalization history. Answering these questions will take approximately 10 minutes.
- You will have a treatment planning session. You will lie in a specific position, possibly within a frame device, and have a CT (Computed Tomography) scan of your lung with contrast injection. A CT scan is a study using x-rays to look at one part of your body. Contrast means that dye is injected into your vein to increase the differences between normal and abnormal tissue. Doctors will check your breathing and see how your organs move. The doctors will try to limit the effect of that movement on the position of your tumor by timing your breathing and possibly placing firm pressure on your stomach area to change the pattern of your breathing.

After the treatment planning session, you will receive a total of five radiation treatments, one treatment every other day for 1½ to 2 weeks. 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.

Before each of the 5 radiation treatments:

- You will have a physical examination to evaluate any side effects from treatment you may be having.
- Your ability to carry out daily activities will be evaluated.
- You may be given an anti-inflammatory medication (corticosteroid) before each treatment to decrease possible inflammation and/or swelling that the treatment may cause in the lung.
- Your doctor may give you pain medication before each treatment to decrease any discomfort you may have due to laying on a hard surface and/or due to laying with your arms held above your head for the one-hour duration of each treatment.

You will need these tests and procedures in follow-up visits:

At 6 weeks from the start of radiation treatment:

- You will have a physical examination to evaluate any side effects from treatment you may be having.
- A chest x-ray

Every 3 months in years 1-2, every 6 months in years 3-4 and then annually:

- Physical examination
- Checking your weight
- Evaluation of your ability to carry out daily activities
- Evaluation of any side effects from treatment you may be having

At 6 and 12 months

- Tests of your lung function
- A blood test to find out how much oxygen is delivered to the tissues beyond your lung

At 6, 12, 18, and 24 months:

- A CT scan with contrast

At 9, 15, and 21 months:

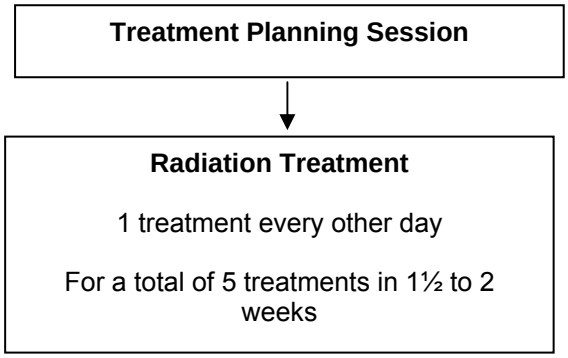
- A chest x-ray

If your study doctor recommends:

- A PET scan to check for recurrence of the cancer

Study Plan

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



How long will I be in the study?

You will receive SBRT for 1 ½ to 2 weeks. After SBRT is completed, the study doctor will ask you to visit the office for follow-up exams at 6 weeks from the start of radiation treatment, every 3 months in years 1-2 and every 6 months in years 3-4, then once a year 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?

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 SBRT is finished. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

Risks related to Stereotactic radiation therapy (SBRT) to the chest

Very Likely and Serious

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

Very Likely

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

Less Likely

- Cough
- Difficulty breathing
- Irritation of the esophagus, which may result in heartburn or pain on swallowing
- Fever
- Chest wall discomfort or pain
- Rib fracture, which may cause pain

Less Likely, But Serious

- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular or rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Damage or scarring of nerves in the chest, which may result in a hoarse voice or a tingling "pins and needles" sensation, or pain in the chest and rib area, depending on the nerve affected
- Damage or scarring of nerves at the top of the lungs, which may result in a tingling "pins and needles" sensation or pain or weakness of the muscles of the arm and hand, since these nerves provide sensation and muscle control for the arm and hand
- Narrowing of the esophagus (tube to the stomach), which can result in swallowing difficulty
- Thinning of the wall of the esophagus; rarely, this can cause a hole in the esophagus and/or communication between the esophagus and airway
- Irritation of the large blood vessels surrounding the heart; rarely, this can cause bleeding (coughing up blood) and/or death.

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as chest pain, shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. Treatment for this lung damage involves pain medicines, anti-inflammatory medicines (corticosteroids), and rarely, oxygen therapy, which may be permanent. You should tell your doctors immediately if you have any of these symptoms.

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

Reproductive Risks
You should not become pregnant or father a baby while on this study because the radiation therapy in this study can affect an unborn baby. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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 that SBRT will work better to kill cancer cells with fewer side effects compared to standard radiation therapy, 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:
- Getting standard radiation treatment without being in a study
- Taking part in another study
- Getting no treatment

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:
- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

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?

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 Monitoring Committee will be regularly meeting to monitor safety and other data related to phase I and phase 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 (2/9/11)

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 1-2 teaspoons of blood and about 2-5 teaspoons of urine at the following time points: Within 3 days before the first radiation treatment, between the third and fourth radiation treatment, and at six weeks from the start of radiation treatment. Some of the blood will be drawn at a time when you would not require any blood tests for your medical condition. You may experience some discomfort and pain related to the blood drawing, as a result of participation in this part of the study. The risk of any other side effects related to blood drawing, such as bleeding or infection, is extremely small.

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://www.rtog.org/tissue%20for%20research_patient.pdf

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 (tissue) or destroyed (urine or blood).

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 (2/16/10)

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?

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

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

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

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

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

Signature

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

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE (*See Sections 11.2 for details) [8/20/10]

Assessments	Pre-Treatment				During Treatment	Follow Up	
	Within 12 wks prior to registration	Within 8 wks prior to registration	Within 4 wks prior to registration	Within 2 wks prior to treatment	Before each SBRT	6 wks from start of SBRT	q3 mos. from the start of SBRT for years 1-2 then q6 mos. for years 3 & 4, then annually
History/physical			X		X	X	X
Weight			Within 4 wks prior to tx				X
Chest x-ray				X		X	At 9, 15, and 21 months
CT scan with contrast		X					At 6, 12, 18, and 24 months
PET with FDG		X					Recommended If suspicion of tumor recurrence
Performance status			X		X		X
Thoracic surgeon eval	X						
CBC w/ diff & ANC		Within 8 wks prior to tx					
Spirometry, lung volumes, diffusion capacity, arterial blood gases	Within 12 wks prior to tx						PFTs and blood gases at 6 and 12 months
Serum/urine pregnancy test (if applicable)				Within 72 hrs. prior to registration			
Tumor response eval							At 6, 12, 18, and 24 months
Charlson Index & hospitalization history	Within 12 wks prior to tx						
Tissue, urine, blood for banking & trans. research				X*	X*	X	
Adverse event eval**					X	X	X
T5 Form						Fax Daily Treatment Record (T5) to RTOG HQ on patient's last day of treatment	

*****See Sections 11.2 for details

****And as needed based on reporting requirements: See Sections 4.1.5, 6.10, and 12.1.**

APPENDIX III (2/16/10)

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 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 self-care. Totally confined to bed or**
5	**Death**

APPENDIX IV

AJCC Staging
Lung, 6th Edition, 2002

Primary Tumor (T)

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

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

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

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

STAGE GROUPING

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

APPENDIX V

Comorbidity Scoring

Instructions for completing the CHARLSON COMORBIDITY INDEX (CCI):

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.

Instructions for completing THE COMORBIDITY RECORDING SHEET:

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

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

The Recording Sheet and CCI must include the RTOG study number and case number; institution name and number; name of person completing the form; phone number of that person; and date of completion. The patient-specific label may be used; however, all pages must have a label affixed. **Comorbidity data will be submitted to RTOG Headquarters at the same time point as the initial assessment data (see Section 12.1).**

Rules for Completing the Charlson Comorbidity Index (CCI)

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

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

CHARLSON COMORBIDITY INDEX (CCI)

Scoring Sheet

RTOG 0813

RTOG Institution Name/Number:_____

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

Name of Person Completing Sheet:_____Phone Number:_____

Date Completed:__-___-_____

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

Total points: _____

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.

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

APPENDIX V (Continued)
COMORBIDITY RECORDING SHEET

RTOG 0813
RTOG Institution Name/Number:_____
Patient Initials (First Middle Last):_____RTOG Patient Case Number:_____
Name of Person Completing Sheet:_____Phone Number:_____
Date Completed:__-___-_____

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

Medications (PRN/scheduled)	

APPENDIX VI (2/9/11)

RTOG BIOSPECIMEN COLLECTION

RTOG FFPE Specimen Plug Kit Collection
RTOG Blood Collection Kit Instructions
RTOG Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

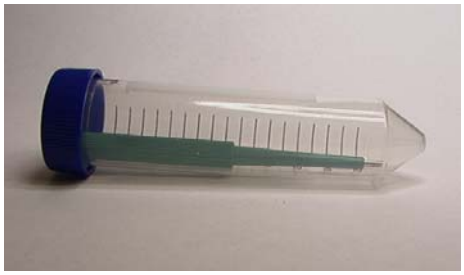
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label punch tool with proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID. ***NOTE**: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or call 415-476-RTOG(7864)/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE shipments
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Absorbent shipping material (3)
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal Form (STF)
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

Preparation and Processing of Serum, Plasma and Whole Blood: Blood samples for proteomic analysis should be handled gently and carefully to avoid platelet degradation or contamination. In addition, needles of large gauge (19-21 G) should be used to minimize platelet contamination from hemolysis. Keep tubes at 4°C until samples are processed.

A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (up to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 xG for 30 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.

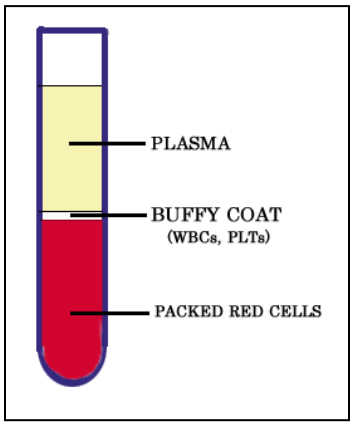
B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1 ml cryovials (5 to 10) as necessary for the plasma collected (5-10). Label them with the RTOG study and case number, collection date, time, time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) gently 1 to 2 times to ensure adequate mixing of EDTA. **Store the blood on ice or at 4°C within a few minutes.**
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 xG for 30 minutes at 4°C (preferred). If sites are unable to process samples at 4°C, then spinning at room temperature is acceptable if done immediately after draw but that must be noted on the STF.
3. If the interval between specimen collection and processing is anticipated to be greater than 10 minutes in room temperature, put specimen on ice as soon as possible until centrifuging is performed. Note the duration of room temperature on the STF.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.



C) Whole Blood For DNA (If requested): Purple Top EDTA tube #2

❑ Label as many 1 ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovial(s) "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with the RTOG study number, case number, collection date/time, time point collected, and clearly mark the specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection Timepoint on STF.

Storage and Shipping:

Freezing and Storage:

☐ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

❑ Store at –80°C (-70°C to -90°C) until ready to ship.

If a -80°C Freezer is not available,

- Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).

- OR:

- Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

- OR:

- Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).

❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.

❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.

❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***

❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice**. Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VI (Continued)

RTOG URINE COLLECTION KIT/INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipets
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

- A clean catch urine specimen will be collected. 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 container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as "urine".
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a-20°C or -80°C Freezer until ready to ship

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage

- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at –20°C or 80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).

OR:

  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.*
- Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223, San Francisco, CA 94115
Contact Phone: (415) 476-RTOG(7864

APPENDIX VII

Timing of Dose Limiting Toxicities (DLTs) During the First Year in Two Completed RTOG Lung Trials

RTOG 0236, "A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer"

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

Treatment: SBRT, 20 Gy per fraction for 3 fractions over 1½-2 weeks

Activated: 05/26/04 **Closed:** 10/13/06

Total accrual: 60, with 55 analyzable patients (Timmerman R, Paulus R, Galvin J., et al. Toxicity analysis of RTOG 0236 using stereotactic body radiation therapy to treat medically inoperable early stage lung cancer patients. In *Proc Amer Soc Thera Rad Onc (ASTRO)*, Paulus R, ed. 69: S86. *Int J Radiat Oncol Biol Phys*. Los Angeles, CA: Elsevier; 2007.

RTOG 0324, "A Phase II Study of Cetuximab (C225) in Combination with Chemoradiation in Patients with Stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)"

Study population: Histologically or cytologically documented NSCLC; Patients must be MO. Patients with T1-T2 with N2 or T3N1-2 are eligible, if inoperable. Patients withT4 with any N or any T with N2 or N3 disease are eligible if unresectable.

Treatment: Loading dose C225; Paclitaxel/Carboplatin/C225; RT: 63 Gy/7 weeks/35 daily fractions; Consolidation chemotherapy and C225

Activated: 03/08/04 **Closed:** 06/03/05

Total accrual: 93 with 87 analyzable patients (Blumenschein GR, Paulus R, Curran WJ, et al. A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small cell lung cancer (NSCLC): A report of the 2 year and median survival (MS) for the RTOG 0324 trial. *J Clin Oncol.* 26: Abstract 7516, 2008.

Timing of Dose Limiting Toxicities During the First Year in RTOG 0236 and 0324[66]

Interval (months)	# at Risk at Start of Interval	# of DLTs During Interval	Interval Probability	Cumulative Probability
RTOG 0236				
0 – 3	55	2	3.6%	3.6%
3 – 6	53	0	0%	3.6%
6 – 9	51	2	4.1%	7.6%
9 – 12	46	0	0%	7.6%
RTOG 0324				
0 – 3	87	6	7.2%	7.2%
3 – 6	74	3	4.3%	11.5%
6 – 9	63	1	1.7%	13.2%
9 – 12	52	0	0%	13.2%