

NRG ONCOLOGY

RTOG 0915
(NCCTG N0927)

A RANDOMIZED PHASE II STUDY COMPARING 2 STEREOTACTIC BODY RADIATION THERAPY (SBRT) SCHEDULES FOR MEDICALLY INOPERABLE PATIENTS WITH STAGE I PERIPHERAL NON-SMALL CELL LUNG CANCER

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NRG ONCOLOGY

**RTOG 0915
(NCCTG N0927)**

A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

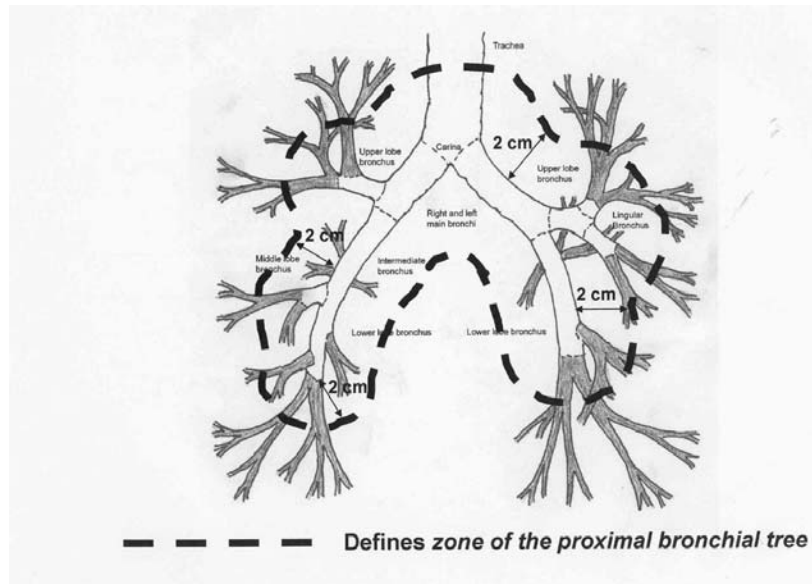
SCHEMA

S		R	Stereotactic Body Radiation Therapy (SBRT)
T	Zubrod Performance Status	A	
R	1. 0	N	Arm 1: 34 Gy in 1 fraction
A	2. 1	D	
T	3. 2	O	
I		M	Arm 2: 48 Gy in 4 once-daily consecutive fractions
F	T Stage	I	
Y	1. T1	Z	
	2. T2	E	

See Section 5.0 for site credentialing required prior to patient registration. See Section 6.0 for details of SBRT.

Patient Population: (See Section 3.0 for Eligibility)

Medically inoperable, biopsy proven early stage T1, T2 (< 5 cm) NSCLC patients; clinically node negative by PET, with peripherally located tumors (> 2 cm in all directions around the proximal bronchial tree; see figure below)



Required Sample Size: 88

- _____(Y) 1. Does the patient have a histologically confirmed (by biopsy or cytologically) diagnosis of non-small cell lung cancer (NSCLC)?
- _____(Y) 2. Is the patient's primary cancer one of the following types?
- Squamous cell carcinoma;
 - Adenocarcinoma;
 - Large cell carcinoma;
 - Large cell neuroendocrine;
 - Non-small cell carcinoma not otherwise specified.
- _____(Y) 3. Is the patient AJCC stage T1, N0, M0, or T2 (≤ 5 cm) based upon the minimum diagnostic workup specified in Section 3.1?
- _____(Y) 4. Was a history/physical examination including weight and assessment of Zubrod performance status performed within 4 weeks prior to registration?
- _____(Y) 5. Was the patient evaluated by an experienced thoracic cancer clinician within 8 weeks prior to registration?
- _____(Y) If yes, was the patient's resectable NSCLC considered medically inoperable by the thoracic cancer clinician?
- _____(Y) 6. Does the patient have measurable disease?
- _____(Y) 7. Was the pre-treatment imaging (CT scan with contrast; whole body or wide field FDG-PET) done within 8 weeks prior to registration?
- _____(Y) 8. Were the routine spirometry, lung volumes, and diffusion capacity performed within 8 weeks prior to registration?
- _____(Y) 9. Is the patient's Zubrod performance status 0-2?
- _____(Y) 10. Is the patient at least 18 years of age?
- _____(Y/NA) 11. If female, was there a negative serum or urine pregnancy test performed within 72 hours prior to treatment 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?
- _____(Y) 13. Did the patient provide study-specific informed consent prior to any protocol-specified procedure(s)?
- _____(N) 14. Is the primary tumor within or touching the zone of the proximal bronchial tree (as defined in Section 3.2.2)?

(Continued on the next page)

- _____ (N) 15. Is there direct evidence after appropriate staging studies of regional or distant metastases or synchronous primary malignancy or prior malignancy in the past 2 years (except for invasive malignancy that has been treated definitively and the patient remains disease free for > 3 years with a life expectancy of > 3 years or carcinoma *in situ* or early stage skin cancers that have been treated definitively]
- _____ (N) 16. Has the patient received prior radiotherapy to the lung or mediastinum?
- _____ (N) 17. Has the patient received chemotherapy for this lung or mediastinum tumor? [chemotherapy for another invasive malignancy is permitted if it has been treated definitively and the patient has remained disease free for > 3 years.
- _____ (N) 18. Has the patient received previous surgery for this lung or mediastinum tumor?
- _____ (N) 19. Does the patient plan to receive other concomitant antineoplastic therapy (including standard fractionated radiotherapy, chemotherapy, biological therapy, vaccine therapy, and/or surgery) while on this study, except at disease progression?
- _____ (N) 20. Does the patient have an active systemic, pulmonary, or pericardial infection?

The following questions will be asked at Study Registration:
SBRT CREDENTIALING IS 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 patient provided study-specific consent 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

(Continued on the next page)

RTOG Institution #
RTOG
Case #

ELIGIBILITY CHECKLIST (3/4/10)
(page 3 of 3)

- _____ 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.
- _____(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 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) 21. 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) 22. 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?
- _____ 23. Specify Zubrod Performance Status (0, 1 or 2)
- _____ 24. Specify T Stage (T1 or T2)
- _____(Y/N) 25. Specify use of IMRT

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

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Lung Cancer and the Medically Inoperable Patient

Lung Cancer is the most frequent cause of cancer death in the United States. Cancer statistics for 2008 estimated 215,020 new cases and 161,840 deaths due to lung cancer, making it the leading cause of cancer mortality in both men and women (Jemal 2008). Eighty percent of lung cancers are non-small cell (NSCLC) in histology. Approximately 15-20% of NSCLC patients present with early localized disease (Jemal 2008). Standard therapy for stage I NSCLC is surgical resection, consisting of either lobectomy or pneumonectomy, with 5-year overall survival (OS) ranging from 50% to 70%. A significant proportion of NSCLC patients present with impaired cardiopulmonary reserve, placing them at increased risk of perioperative complications and long-term disability with standard anatomic resections. Sublobar resections (wedge resections and segmentectomies) historically have been offered to compromised patients to mitigate the loss of lung parenchyma, but a randomized study has demonstrated that compared with lobectomy, limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function and is associated with a higher death rate and locoregional recurrence rate (Ginsberg 1995). In effect, early stage NSCLC patients with impaired lung function are generally deemed to be medically inoperable (Zierhut 2001).

Historically, medically inoperable early stage NSCLC patients have been offered external beam radiotherapy (RT) alone using conventional techniques as primary management (Zierhut 2001; Dosoretz 1993; Foote 1993; Sibley 1998; Qiao 2003; Dorosetz 1992) although treatment results have been consistently inferior to the results of surgery alone. Sibley, et al. (1998) reported on 141 patients with clinical stage I NSCLC treated with radiotherapy alone using modern techniques and staging. The median RT dose delivered was 64 Gy (range: 48 Gy to 80 Gy). The overall survival at 2 and 5 years were 39% and 13%, respectively (median 18 months), while the progression-free survival was 48% and 28% at 2 and 5 years, respectively. Forty-nine percent of patients had local failure as part of their relapse pattern. In a review of 18 studies published from 1988 to 2000 on conventional RT for stage I NSCLC, Qiao, et al. (2003) reported local recurrence to be the most common cause of failure with such treatment, with a wide range of failure rates reported, ranging from 6% to 70%. Many factors likely explain the discrepancy in outcomes for patients treated with RT compared to surgery. Clinically based staging alone in medically inoperable patients likely underestimates the disease extent (Zierhut 2001). Comorbidities significantly impact survivals; thus, cause specific survivals are 10-20% higher than overall survivals in medically inoperable patients due to mortality from competing causes (Sibley 1998; Dosoretz 1992; Slotman 1994; Hayakawa 1999). Additionally, local failures, up to 85% biopsy proven (Le Chevalier 1994), have continued to be a problem following curative radiation.

The high rates of local failure seen with conventional RT have prompted trials in dose escalation with conventional fractionation. Several have shown improved outcomes with higher doses (Sibley 1998; Zhang 1989; Kaskowitz 1993; Chen 2006; Cox 1990; Kong 2006). However, not all series have shown improved survival with higher doses (Slotman 1994; Sandler 1990). Use of alternate fractionation over conventional fractionation schemes also have been investigated as a means of improving radiation outcomes (Perez 1987; Saunders 1997). However, such alternate fractionation schemes employing conventional treatment margins have significantly increased toxicity, especially pulmonary toxicity (Saunders 1997). These efforts to increase the dose per fraction to the tumor while limiting the dose to surrounding normal tissues were among the motivating factors which prompted the development and introduction of stereotactic body radiation therapy (SBRT) as a novel modality in the management of medically inoperable early stage NSCLC.

1.2 SBRT in Medically Inoperable NSCLC

SBRT has been increasingly employed in the management of early stage medically inoperable NSCLC because it involves highly precise delivery of short courses (few fractions) of very high-dose (hyperfractionated) RT to accurately delineated, size-restricted malignant targets in which motion has been accounted for during the delivery process. For chest malignancies, tumor movement due to respiration is managed through a variety of approaches, including tumor tracking, gating delivery of treatment, and/or employing breath control techniques. SBRT administration achieves avoidance of normal tissue exposure to radiation during the planning process, by providing for sharp fall-off dose gradients outside the target (Song 2004; Nagata 2007).

An increasing number of reports in SBRT for lung cancer, and particularly those from prospective clinical trials, are establishing the feasibility, safety, and efficacy of this treatment modality in this patient population (Uematsu 2001; Nagata 2002; Wulf 2005; Baumann 2006; Timmerman 2003; McGarry 2005; Lee 2003; Wyte 2003; Onishi 2004; Fritz 2006; Le 2006; Timmerman 2006; Aoki 2007; Onishi 2007; Chang 2008; Dahele 2008; Nagata 2005; Wulf 2004; Hof 2007; Hara 2006). These reports suggest high rates of local control and improved overall survival with remarkably few high grade toxicities in what is otherwise a generally fragile patient population. To date, published data generally reflect single institution experiences and explains to some degree variations among institutions with respect to total dose, fractionation schedules, overall treatment time, and techniques of dose delivery. These differences have made it challenging to standardize dosimetric specifications in the administration of SBRT (Matsuo 2007). Nonetheless, reported rates from a range of series suggest at least 80% local control at a minimum of 3 years (Song 2004; Timmerman 2007).

In North America, final results from a recently completed RTOG phase II protocol in SBRT, RTOG 0236, should facilitate comparison across institutions by yielding results from a standardized treatment regimen (only preliminary toxicity data have been presented) [Timmerman 2007b]. In this study, 60 Gy was administered in 3 fractions over a period of 8 to 14 days. Currently in Japan, where experience with lung SBRT is extensive, a single arm phase II study is being run by the Japanese Clinical Oncology Group (JCOG 0403) as a dose exploration study consisting of 48 Gy in 4 fractions delivered over 4 to 8 days, with a planned accrual of 165 patients (Hiraoka 2008).

In view of these mutually confirmatory reports on feasibility, efficacy, and early safety, ongoing areas of interest in lung SBRT now include long term assessment of outcomes and further rationalization of treatment regimens, with a trend towards decreased number of fractions and increased dose per fraction.

1.2.1 Multiple Fraction SBRT (8/19/10)

The majority of SBRT published studies document the feasibility and safety of multiple fraction therapy for medically inoperable lung cancer. Selected U.S. and Japanese reports of interest are presented below.

The most comprehensive prospective U.S. SBRT series has come from investigators at Indiana University who conducted a foundational phase I study among 47 patients with Stage IA or IB NSCLC. The study began at a dose of 8Gy in 3 fractions and escalated to a dose of 24 Gy in 3 fractions. Significantly decreased rates of local recurrence (LR) [only 1 of 9] were noted among patients receiving >16 Gy per fraction. No significant toxicities were reported at 20 Gy per fraction. The maximum tolerated dose was realized at 72 Gy for tumors larger than 5 cm. Dose-limiting toxicity included bronchitis, pericardial effusion, hypoxia, and pneumonitis (Timmerman 2003; McGarry 2005). Subsequently, Timmerman, et al. (2006) carried out a prospective, phase II, 70 patient trial using stereotactic body radiation therapy (SBRT) to doses of 60 to 66 Gy in three fractions during 1 to 2 weeks. With a median follow up of 17.5 months, the 3-month major response rate was 60%. Kaplan-Meier local control at 2 years was 95%. Grade 3 to 5 toxicity occurred in a total of 14 patients. Six patients died as a consequence of treatment-related toxicity. Median overall survival was 32.6 months, and 2-year overall survival was 54.7%. Among patients experiencing toxicity, the median time to observation was 10.5 months. Tumors with GTV volume of more than 10 mL had an eight-fold risk of high grade toxicity compared with smaller tumors ($P = .017$). Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors.

Based on the early experience from Indiana University (Timmerman 2003), the Radiation Therapy Oncology Group (RTOG) initiated a prospective phase I/II (RTOG 0236) in medically inoperable NSCLC. This study went on to enroll 52 medically inoperable patients with peripherally located, node negative NSCLC measuring ≤ 5 cm. Patients received three 20 Gy fractions (without heterogeneity corrections) over 10-14 days. The trial was closed to accrual in October 2006. Early results in abstract form show 15% grade 3-4 toxicity. Specifically, with median follow up of 8.7 months, there was 1 (2%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment. Two of

the 7 patients demonstrated decreased pulmonary function, and there was 1 patient was reported as having cough/dyspnea, 1 with hypoxia, 1 with pneumonitis, 1 patient with cough/forced expiratory volume, and 1 reported pneumothorax. There was also a grade 3 dermatitis and a grade 3 syncope reported as related to protocol treatment. Unpublished review of RTOG 0236 indicates that primary tumor control has been maintained with longer follow up (estimated 93% actuarial at 2 years); however, grade 3 and 4 treatment-related toxicity is moderately high at 28% of analyzed patients. No treatment-related deaths have been reported (Timmerman 2009). As the median time to toxicity was previously reported in the previous Timmerman publication (2006) was 10.5 months, the observed toxicity reported in this RTOG abstract (with 8.7 months of follow up) can be expected to rise.

Also in the U.S., Chang, et al. (2008) at MD Anderson Cancer Center recently published their experience with a regimen of 50 Gy in 4 fractions. With a median follow up of 17 months (range, 6–40 months) for 27 patients, the crude local control at the treated site was 100% using 50 Gy. However, 3 of 7 patients had local recurrences when treated using 40 Gy. Of the patients with Stage I disease, 1 (7.7%) and 2 (15.4%) developed mediastinal lymph node metastasis and distant metastases, respectively. Of the patients with recurrent disease, 3 (21.4%) and 5 (35.7%) developed mediastinal lymph node metastasis and distant metastasis, respectively. Four patients (28.6%) with recurrent disease but none with Stage I disease developed Grade 2 pneumonitis. Three patients (11.1%) developed Grade 2-3 dermatitis and chest wall pain. One patient developed brachial plexus neuropathy. No esophagitis was noted in any patient.

In Japan, Uematsu, et al. (2001) have been pioneers in lung SBRT with some of the first publications of long term experience in stage I NSCLC. Their first report provided 5-year results for 50 patients with pathologically proven NSCLC treated in the early 1990s with SBRT. Of these, 21 patients were medically inoperable and the remainder were medically operable but refused surgery. In most patients, SBRT was given in 5-10 fractions for 1-2 weeks for a total of 50-60 Gy. With a median follow up period of 36 months (range 22-66), local progression had not been observed on follow-up CT scans in 47 (94%) of 50 patients, with a 3-year overall survival rate of 66% for 50 patients and 86% in the 29 medically operable patients. The 3-year cause-specific survival rate of all 50 patients was 88%. No definite adverse events related to SBRT were noted, except for 2 patients with a minor bone fracture and 6 patients with temporary pleural pain.

Nagata, et al. (2005) have reported on 45 early stage NSCLS patients treated with 4 fractions of 12 Gy over 5–13 (median = 12) days. At a median 30 months follow up, no grade 3 pulmonary toxicities were noted. For stage IA lung cancer, the disease-free survival and overall survival rates at 3 years were 72%, and 83%, respectively, and for stage IB lung cancer, 71% and 72%, respectively.

In one of the most mature retrospective series published in lung SBRT, Onishi, et al. (2007) reported outcomes among 257 patients treated with SBRT in 14 Japanese centers using a variety of dosing schemes (1-22 fractions at 3-12 Gy per fraction). Total dose ranged from 18 to 75 Gy. With 38 months median follow up, the local, regional nodal, and distant recurrence rates were 14.0%, 11.3%, and 19.8%, respectively. The overall 3- and 5-year survival rates for all patients were 56.8% (95% CI: 50.2%–63.5%) and 47.2% (95% CI: 38.7%–53.5%), respectively. Patients receiving a biologically equivalent dose (BED) of > 100 Gy experienced fewer local recurrences than those patients receiving < 100 Gy BED (42.9 vs. 8.1%, $p < 0.001$). Similarly, survival was significantly improved with higher BED doses (70.8 vs. 30.2% ($p < 0.05$)). Grade 3 or higher toxicity was observed in 5.4% of patients. Of note, the irradiation method and results for the 3 major institutions enrolled in this study were compared, and the local control and 3-year survival rates were almost identical.

As evident from the aforementioned reports, there are currently diverse practices and fractionation schedules used in the setting of SBRT for medically inoperable early stage NSCLC documenting the feasibility and safety of multiple fraction therapy; therefore, selecting a multiple-fraction schedule for further testing in a collaborative group setting is a pragmatic question. A recent practice survey from Japan (Nagata 2006) is informative in making such a

selection. This survey noted that the majority (52%) of practitioners were employing a 48 Gy/4fx schedule. This schedule appears to fit with anecdotal reports of U.S. non-trial based clinical practice. In that regard, this schedule has been chosen for further assessment in the RTOG.

1.2.2 Single Fraction SBRT

Data also has been published supporting the feasibility, safety, and efficacy for single fraction SBRT in the management of medically inoperable NSCLC.

Wulf, et al. (2004) described SBRT for primary lung cancer and pulmonary metastases using a variety of treatment regimens including single fraction therapy of 26 Gy. One of 20 NSCLC patients and 25 of 51 metastatic patients were treated with that fractionation. They reported no toxicity associated with the 26 Gy treatment and no local failure after median follow up of 11 months for the NSCLC patients.

Hof, et al. (2007) reported outcomes for 42 patients with stage I or II NSCLC treated with single dose SBRT (dose range 19-30 Gy.) With a median follow up of 15 months, overall survival and disease-free survival at 36 months were 37.4% and 49.1%, respectively. Local tumor control at 3 years was 67.9% at the same time points. Local tumor control was significantly improved in those patients receiving 26-30 Gy (n=32) versus lower doses (p=0.032). With respect to toxicity, no CTCAE grade 3 or 4 toxicities were noted. Follow-up CT scan of normal tissue changes (including pneumonitic changes and fibrosis) were noted in the treatment area in 64.3% of patients but were not clinically relevant. Minor cough and slightly increased dyspnea were the only clinical toxicities observed.

Fritz, et al. (2006) reported on outcomes for 33 patients with stage I NSCLC treated with a single dose of 30 Gy. With a median follow up of 18 months, local tumor control was 83% and overall survival was 39% at 4 years. There were no grade 3 or higher toxicities reported. In 8 NSCLC patients (24%), CT scans revealed radiographic changes consistent with pneumonitis but these were not associated with any clinical symptoms.

Whyte, et al. (2003) reported on the preliminary Stanford phase I experience of single-fraction SBRT in 23 patients (of which 15 had primary NSCLC) using a robotic, frameless radiosurgery system (CyberKnife®). Treatment consisted of 15 Gy in a single fraction. There were no grade 3 or higher toxicities noted for a median follow up of 7 months. These authors then reported on their subsequent dose escalation experience in single-fraction treatment (Le 2006). In this study, 33 three patients were reported on, of which 21 had NSCLC and 23 patients were from the phase I report. The authors found that at 25 Gy, pulmonary toxicity was noted in patients with a history of prior pulmonary irradiation and in those with treatment volumes greater than 50 cc; therefore, dose escalation to 30 Gy was applied only to unirradiated patients and treatment volume less than 50 cc. Treatment-related complications were noted for doses greater than 25 Gy and included four cases of grade 2-3 pneumonitis, 1 pleural effusion, and 3 possible treatment-related deaths. The 1-year freedom from local progression was 91% for doses greater than 20 Gy and 54% for doses less than 20 Gy in NSCLC (p = 0.03).

Hara, et al. (2006) reported outcomes for 59 patients with malignant lung tumors < 4cm in maximal dimension (11 primary lung tumors, 48 metastases) who were treated for primary or metastatic disease to the lung using doses ranging from 26 to 34 Gy in a single fraction. Median follow up was 12 months (range 2-42 months). The authors noted 1- and 2-year local progression-free rates of 93% and 78%. Improved local control was seen for patients receiving > 30 Gy versus 26-30 Gy (9 patients.) Local regrowth of the irradiated tumor was a direct cause of death in two patients. Only the minimal radiation dose to the reference target volume tended to have an influence on the local progression failure rate (LPFR) [P = 0.068]. Grade 3 respiratory symptoms were noted in 1 patient. Overall survival for the whole cohort at 2 years was 41%.

Since the results of Hara, et al. (2006) with a maximal dose of 34 Gy in one fraction stand as the most currently reported schedule demonstrating feasibility, safety, and efficacy, this fractionation scheme becomes worthy of further testing in a cooperative setting.

1.2.3 Radiobiological Considerations in SBRT Schedules

Conventionally fractionated RT involves daily delivery of small doses of radiation (e.g., 1.8 Gy-3 Gy per fraction) over many weeks and reflects radiobiological concepts favoring normal tissue protection; that is, dividing a total planned dose into a number of fractions permits normal tissues to repair sublethal damage from ionizing radiation more effectively than tumor tissues (Park 2008). In contrast, SBRT implies delivery of large ablative doses of radiation (e.g., 12-30 Gy in single fractions) and was derived from radiosurgery experience with similar schedules used for intracranial tumors (Park 2008). Ablative therapy usually is valid for small lesions for which normal tissue constraints are not a determining limitation. Given the differences in total dose, fractionation, and overall treatment time between conventionally fractionated treatments and SBRT, direct comparisons between schedules is not feasible (Song 2004). The linear quadratic (LQ) equation has been the generally accepted method for comparing different RT fractionation schemes. Use of this equation yields a biologically effective dose (BED) for a given schedule against which the potency another can be compared. Thus,

$BED = nd \left\{ 1 + \frac{d}{\alpha/\beta} \right\}$ where dose, d, represents individual fraction size in Gy, n the number of individual doses of radiation, and α and β are intrinsic properties of the tumor cells (Kavanagh 2006). For comparison purposes, an α/β ratio of 10 is assumed for tumor killing effects and was used for calculations by Kavanagh and Timmerman in the following table comparing BEDs for different radiation schedules (adapted from Kavanagh 2006).

Parameter	BED, Gy
Conventional radiation dose schedule	
60 Gy, 30 fractions	72
70 Gy, 35 fractions	84
SBRT dose schedule	
48 Gy, 3 fractions	125
60 Gy, 5 fractions	132
60 Gy, 3 fractions	180

There have been reports that relate the clinical efficacy of SBRT over different fractionations to a BED cutoff. Thus, Onishi, et al. (2007) reported that improved local control and survival are associated with SBRT regimens whose BED is >100 Gy.

Park, et al. (2008), however, have questioned the validity of the LQ model for describing the radiation effects of SBRT. They note that the biological model underpinning the LQ model deviates from measured data for high-dose-per-fraction regimens (>8 Gy per fraction). In its stead, they have developed an alternative method to analyze SBRT effects using a universal survival curve (USC) derived from the LQ model and another radiobiological model, the multitarget method. This has yielded two equivalence functions, the BED and the single fraction equivalent dose (SFED) allowing for more appropriate comparison of conventional and stereotactic radiation schedules. The following table adapted from that paper is illustrative of this.

Local Control Rate of Early-Stage Non-Small Cell Lung Cancer Treated with SBRT					
Investigator	Dose, Prescription	Approximate minimal total dose delivered to PTV (Gy)	SFED (Gy)	BED (Gy)	SED (Gy)
Timmerman, et al. (2006)	20-22 Gy x 3 (80% isodose)	60-66	56.4-62.4	132-147	107-119
Timmerman, et al. (2003)	18-20 Gy x 3 (80% isodose)	54-60	50.4-56.4	118-132	95-107
Nyman, et al. (2006)	15 Gy x 3 (PTV periphery)	45	41.4	96	78
Xia, et al (2006)	5 Gy x 10 (50% isodose)	50	34.3*	78	63
Zimmermann, et al. (2006)	12.5 Gy x 3 (60% isodose)	37.5	33.9	78	63
Wulf, et al. (2005)	12.5 Gy x 3 (65% isodose)	37.5	33.9	78	63
Hara, et al. (2006)	30-34 Gy x 1 (minimal dose to CTV or PTV)	30-34	30-34	68-78	55-63
Fritz, et al. (2006)	30 Gy x 1 (isocenter)	24	24	68	55
Hof, et al. (2003)	19-26 Gy x 1 (isocenter)	15.2-20.8	15.2-20.8	32-46	34-48
Nagata, et al. (2005)	12 Gy x 4 (isocenter)	48 Gy to isocenter	42.6 to isocenter	99 isocenter	80 to isocenter
Abbreviations: SBRT = stereotactic body radiotherapy; PTV = planning target volume; SFED = single fraction equivalent dose; BED = biologically effective dose; SED = standard effective dose; CTV = clinical target volume; CFRT = conventionally fractionated radiotherapy					
*Because dose per fraction is smaller than transition dose (D_t), this was calculated using $SFED_{cfrt}$					

This model also suggests that equivalent dose in SBRT is directly related to total dose delivered rather than on a number of fractions, reflecting the linear dependence of cell survival on dose for high dose fractions predicted by this model. It also may allow for predictions on differences between different schedules with respect to toxicity and tumor control. From this model and using single and multiple fraction data that have been published, one could predict, for example, that 34 Gy in 1 fraction may be a less toxic but a less ablative schedule than the RTOG 0236 reference regimen (Timmerman, 2009). As Park and colleagues (2008) note, the only way to appropriately assess different fractionation schemes is through prospective clinical trials.

1.2.4 Rationale for Current Study Design (8/19/10)

Results from the range of clinical studies in SBRT suggest that both single fraction and multiple fraction SBRT regimens are feasible and yield excellent primary tumor control, with minimal toxicity for the follow-up intervals reported. That said, most clinicians in the U.S. have employed SBRT regimens involving multiple (3-10) fractions. Given apparent equivalency in primary tumor control rates between single and multiple fractionated regimens over reported follow-up intervals, we propose that primary tumor control becomes a secondary measure of distinguishing efficacy between different SBRT regimens for a population of patients whose outcomes would then become predominantly affected by competing co-morbidities. Thus, in the present study, a comparison of 1 fraction versus multiple fractions is proposed within the setting of a clinical trial for medically inoperable patients to determine an optimized dose schedule for SBRT of the lung yielding the least chance of grade 3 or higher toxicity for equivalent cancer related control. Chang, et al. (2008) noted no grade 3 or higher toxicities at < 3 months, and Timmerman, et al (2006, 2009) noted that the median time to toxicity is > 6 months, Given that high-grade toxicities may not be recorded for many months, the individual arms will be assessed at 1 year after treatment delivery to compare toxicity rates.

Additional benefits from a prospective clinical trial will include correlating clinical outcomes against standardized and uniform delivery of SBRT. It should be noted that the SBRT prescription practice reported in Japanese studies involves dose prescribed to an isocenter. In comparison, in U.S. studies, dose is typically prescribed as a PTV coverage. In the current study, therefore, we are electing to adopt U.S. practice such that prescriptions will be to PTV coverage and also will employ heterogeneity correction.

The present study will further characterize the relationship, if any, between tumor size, outcomes, and dose. Nagata, et al. (2005) showed no relationship between T1 versus T2 and toxicity, primary tumor control, and survival. McCammon, et al. (2009) found no statistically significant relationship between GTV size and primary tumor control on multivariate analysis. The prospective nature of the trial and the uniformity in treatment administration also will facilitate assessment of toxicity, outcomes, cost, patient comfort, and radiobiologic and dosimetric comparisons.

This study also will provide a means for further prospective assessment of the role of FDG-PET imaging in the setting of SBRT for medically inoperable lung cancer. Hoopes, et al. (2007) investigated the utility of PET for 58 patients with medically inoperable stage I NSCLC who participated in prospective phase I and II trials of SBRT. They found that 1) pre-SBRT FDG-PET SUV did not predict 3-year overall survival or primary tumor control but more critically, 2) that moderate post-SBRT PET hypermetabolic activity may persist 2 years following treatment without definite evidence of recurrence. This latter observation has provided clinicians with a means of interpreting post-treatment imaging for the presence or absence of primary tumor failure when biopsying has proved to be not feasible. A further update on Hoopes, et al. (2007) suggests that since a substantial proportion of patients may have moderately elevated FDG-PET SUV(max) at 12 months without evidence of primary tumor failure on further follow up, likely those post-SBRT PET SUVs equal or above the pretreatment values should be further investigated (Henderson, et al. 2009). In a retrospective review of 74 patients, Burdick, et al. (2008) found that pre-treatment PET SUVs did not predict for primary tumor control, nodal failure, distant metastatic failure, or overall survival.

The current study design is, therefore, a randomized phase II comparison of 34 Gy in a single fraction selected as the most currently documented feasible single-fraction dose, versus a schedule based on the best reported and most actively utilized multi-fraction experience in Japan and the U.S., 48 Gy in 4 fractions. The goals for this randomized phase II study are to select the most favorable regimen on the basis of the least severe toxicity recorded at a defined interval of 1 year, with primary tumor control acting as a secondary endpoint and for that regimen then to be used as a comparison arm in a phase III trial against the current RTOG standard set by RTOG 0236. If both arms should prove equivalent with respect to adverse events, control, and survival, the presumption would be that the shortest schedule would be the most feasible for patients.

1.3 Translational Research

1.3.1 Proposed Primary Translational Study (8/19/10)

Probably one of the most important dose modification factors for radiation therapy is hypoxia, the condition of low oxygen level in the tumor (Hockel 2001; Brown 1998). Mechanistically, the presence of oxygen greatly enhances the efficiency of chromosomal radiation damage by chemically stabilizing radiation-induced free radical production in DNA. Thus, the radiation dose required to kill a given proportion of hypoxic cells is 2.5–3 times greater than that for an aerobic cell population, especially when radiation is delivered in a large single fraction as proposed for one of the arms in the current study (Hockel 2001). Fractionation can result in re-oxygenation; hence, mitigating the adverse effect of hypoxia on radiation sensitivity (Brown 1998). Hypoxia also has been shown to promote aggressive tumor phenotype, including a predisposition to metastasis via activation of several molecular pathways, the best known of which is the pathway regulated by the hypoxia inducible factor 1(HIF-1) [Yun 2003]. Several proteins and microRNA have been shown to be induced by hypoxia, and their levels can be readily measured in the blood. High levels of these markers also have been shown to correlate with poorer prognosis in patients with solid tumors treated with conventional therapy. These include osteopontin, VEGF (vascular endothelial growth factor), IL8 (interleukin 8), LDH5 (lactate

dehydrogenase 5) and microRNA 210 (MiR210) [Le 2003; Oc 2001; Dunst 2001; Yoshino 2003; Cairns 2007; Overgaard 2005; Pulkkinen 2008; Camps 2008]. As part of the correlative studies in this study, we propose to measure the levels of these putative circulating markers for hypoxia prior to SBRT and 6 weeks after SBRT. Our primary hypothesis is that the level of these markers should have a greater decline after treatment with fractionated SBRT than with single fraction SBRT and that their pretreatment levels also should be more prognostic for primary tumor control in the single arm as compared to the fractionated arm.

Primary Aim:

1. To determine whether radiation fractionation would influence the change in the pre- and post-SBRT circulating levels of several secreted hypoxia markers, including osteopontin, VEGF, IL8, LDH5, and MiR210. We will measure pre- and post-SBRT (6 weeks after completion of all RT) levels of osteopontin, VEGF, IL8, LDH5, and MiR210 and correlate the change in these levels to the 2 treatment arms.
2. To determine whether pretreatment levels of these circulating hypoxia markers are more predictive of primary tumor failure in the single-fraction arm as compared to the fractionated arm. We will correlate pretreatment levels of the above circulating hypoxia markers to the rate of primary tumor control for each treatment arm.

1.3.2 Exploratory Translational Studies (8/19/10)

Gene polymorphism in peripheral lymphocytes of core DNA repair proteins and the levels of circulating inflammatory cytokines before and after SBRT may reflect the individual's intrinsic radiation sensitivity and tumor response. We hypothesize that baseline DNA polymorphism of DNA repair genes and levels of the circulating cytokines before and after SBRT may be used as biomarkers to predict clinical outcome, including local regional recurrence, survival, and treatment-related toxicity, specifically pulmonary toxicity. In the future, these markers may help to classify patients for their probability to benefit from the therapeutic regimens, particularly dose escalated radiotherapy.

The current plan is to subject the pretreatment samples to DNA polymorphism analysis using restriction fragment length polymorphism-polymerase chain reaction. Pre- and post-SBRT circulating cytokine also will be measured using the cytokine microarray analysis (RayBio human cytokine array; RayBiotech) that measures levels of 174 cytokines and growth factors implicated in human diseases. Although the assays yield relative quantification, it is adequate for the initial exploratory analysis because two groups of patients and samples from the same individuals before and after treatment will be compared. It is quite possible that any or all of these assays could be outdated by the time accrual to the study is complete and the data are analyzable with respect to clinical outcome. Therefore, if other methods are 'state of the art' at that time, these methods will be substituted.

The following is the list of potential biomarkers that will be studied for this exploratory analysis. It can, however, be subject to change based on information that is unknown at this time.

1. DNA repairing gene polymorphism such as p53, XRCC1, ERCC1, XPA, XPC, XPD, XPF, XPG; we will perform SNP analyses for these genes and correlate them to both the rate of grade 2 or higher radiation pneumonitis and primary tumor control.
2. Radiation-induced symptom related cytokines such as TGF-Beta, IL-1 and IL-6; we will measure pre- and post-treatment of these cytokines and correlate them to the radiation of grade 2 or higher radiation pneumonitis.

2.0 OBJECTIVES

2.1 Primary Objective

The rate of 1-year grade 3 or higher adverse events definitely, probably, or possibly related to treatment (see Section 13.1 for specific adverse events)

2.2 Secondary Objectives (8/19/10)

2.2.1 1-year primary tumor control rate;

2.2.2 1-year overall survival and disease-free survival rate;

2.2.3 Assessment of FDG PET SUV changes as a measure of treatment response and outcomes;

2.2.4 Pulmonary function changes by treatment arm and response;

- 2.2.5 Association between biomarkers and primary tumor control and/or grade 2 or higher radiation pneumonitis.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility (8/19/10)

- 3.1.1 Histological confirmation (by biopsy or cytology) of non-small cell lung cancer (NSCLC) prior to treatment; the following primary cancer types are eligible: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, large cell neuroendocrine, or non-small cell carcinoma not otherwise specified; **Note:** although bronchioloalveolar cell carcinoma is a subtype of NSCLC, patients with the pure type of this malignancy are excluded from this study because the spread of this cancer between adjacent airways is difficult to target on CT.
- 3.1.2 Stage T1, N0, M0 or T2 (≤ 5 cm), N0, M0, (AJCC Staging, 6th Ed.), based upon the following minimum diagnostic workup:
- 3.1.3.1 History/physical examination, including weight and assessment of Zubrod performance status, within 4 weeks prior to registration;
- 3.1.3.2 Evaluation by an experienced thoracic cancer clinician (a thoracic surgeon, medical oncologist, radiation oncologist, or pulmonologist) within 8 weeks prior to registration;
- 3.1.3.3 CT scan with intravenous contrast (unless medically contraindicated) within 8 weeks prior to registration of the entirety of both lungs and the mediastinum, liver, and adrenal glands; the primary tumor dimension will be measured on the CT. PET evaluation of the liver and adrenal glands also is permitted. In addition, if the enrolling institution has a combined PET/CT scanner and both aspects are of diagnostic quality and read by a trained radiologist, the PET/CT will meet the staging requirements for both CT and PET.
- 3.1.3.4 Whole body or wide field FDG-PET within 8 weeks prior to registration with adequate visualization of the primary tumor and draining lymph node basins in the hilar and mediastinal regions and adrenal glands; in the event of lung consolidation, atelectasis, inflammation or other confounding features, PET-based imaging correlated with CT imaging will establish the maximal tumor dimensions. **Note:** PET data will be used for the analysis of a secondary endpoint (see Section 2.2.2). SUV must be measured on PET. To be included in this analysis, the patient's PET studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner. PET scanners with sodium iodide (NaI) detectors are not acceptable. If the baseline PET study is performed at the treating institution (or its affiliated PET facility), it is recommended that the reassessment PET scans (see Section 11.1.4) be performed at the same site.
- 3.1.3.5 Pulmonary function tests (PFTs): Routine spirometry, lung volumes, and diffusion capacity, within 8 weeks prior to registration; arterial blood gases are optional. **Note:** All patients enrolled in this study must have these pulmonary assessments whether or not the reason for their medical inoperability is pulmonary based, since the objective assessment of pulmonary factors is a component of the outcomes assessment for this study.
- 3.1.4 Patients with hilar or mediastinal lymph nodes ≤ 1 cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Patients with > 1 cm hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but non-diagnostic uptake) may still be eligible if directed tissue biopsy of all abnormally identified areas are negative for cancer.
- 3.1.5 The patient's resectable NSCLC must be considered medically inoperable by an experienced thoracic cancer clinician (a thoracic surgeon, medical oncologist, radiation oncologist, or pulmonologist) or a standard lobectomy and mediastinal lymph node dissection/sampling procedure. The patient may have underlying physiological medical problems that would prohibit a surgery due to a low probability of tolerating general anesthesia, the operation, the postoperative recovery period, or the removal of adjacent functioning lung. These types of patients with severe underlying health problems are deemed "medically inoperable." Standard justification for deeming a patient medically inoperable based on pulmonary function for surgical resection of NSCLC may include any of the following:
- Baseline FEV1 $< 40\%$ predicted;
 - Postoperative 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;
- Severe chronic heart disease.

If the patient has resectable disease but declines surgery after consulting with a thoracic surgeon, he/she will be considered eligible.

3.1.6 The patient must have measurable disease.

3.1.7 Zubrod Performance Status 0-2;

3.1.8 Age \geq 18;

3.1.9 Negative serum or urine pregnancy test within 72 hours prior to registration for women of childbearing potential;

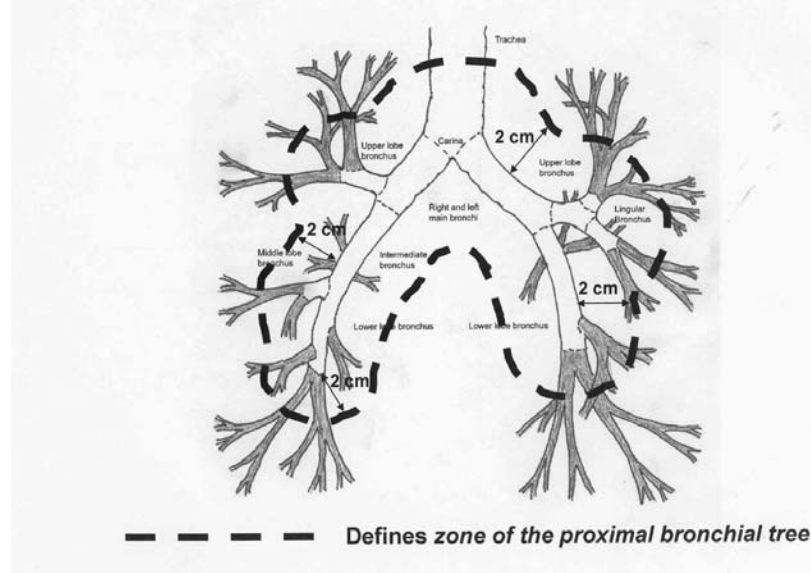
3.1.10 Women of childbearing potential and male participants must agree to use a medically effective means of birth control, such as condom/diaphragm and spermicidal foam, intrauterine device (IUD), or prescription birth control pills, throughout their participation in the treatment phase of the study

3.1.11 The patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with T2 primary tumors $>$ 5 cm or involving the central plural and/or structures of the mediastinum;

3.2.2 The primary tumor of any T-stage within or touching the *zone of the proximal bronchial tree* (see figure below), 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);



3.2.3 Direct evidence of regional or distant metastases after appropriate staging studies, or synchronous primary malignancy or prior malignancy in the past 2 years except for invasive malignancy that has been treated definitively and the patient remains disease free for $>$ 3 years with life expectancy of $>$ 3 years or carcinoma *in situ* or early stage skin cancers that have been treated definitively;

3.2.4 Previous radiotherapy to the lung or mediastinum;

3.2.5 Previous chemotherapy for this lung or mediastinum tumor; chemotherapy for another invasive malignancy is permitted if it has been treated definitively and the patient has remained disease free for $>$ 3 years.

3.2.6 Previous surgery for this lung or mediastinum tumor;

3.2.7 Plans for the patient to receive other concomitant antineoplastic therapy (including standard fractionated radiotherapy, chemotherapy, biological therapy, vaccine therapy, and surgery) while on this protocol except at disease progression;

3.2.8 Patients with active systemic, pulmonary, or pericardial infection;

3.2.9 Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Required Evaluations/Management

- 4.1.1** CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
- 4.1.1.1** Absolute neutrophil count (ANC) $\geq 1,800$ cells/mm³;
 - 4.1.1.2** Platelets $\geq 100,000$ cells/mm³;
 - 4.1.1.3** Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);
- 4.1.2** Documentation of measurable disease (tumor size in cm) on the I1 case report form (see Section 12.1).

5.0 REGISTRATION PROCEDURES

5.1 Regulatory Pre-Registration Requirements (11/1/12)

- 5.1.1 U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/readfile.aspx?fname=public/CTSUS-IRBcertif_Final.PDF, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
*Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.1.2 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.1.2.1 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

5.1.2.2 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.

5.2 Pre-Registration Requirements for SBRT Treatment Approach

All participating institutions must use the superposition/convolution or Monte Carlo based dose calculation algorithms. Credentialing for stereotactic body radiation therapy and heterogeneity corrections by the Advanced Technology Consortium (ATC) is necessary 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. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit <http://rpc.mdanderson.org/rpc> and select "Credentialing" and "Credentialing Status Inquiry".

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 the RTOG Quality Assurance Center.

Credentialing includes the 5 steps outlined in Sections 5.2.2.1 to 5.2.2.5. Centers previously credentialed for some of the technologies/procedures involved may not have to be re-credentialed. However, institutions (not using superposition/convolution algorithms) 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 have changed 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. Institutions that have changed from standard IMRT to Tomotherapy, CyberKnife® or volume arc IMRT delivery will be required to re-credential.

5.2.2 SBRT Credentialing Process

- 5.2.2.1 Facility Questionnaire:** Each participating institution must complete a Facility Questionnaire available on the ATC web site, <http://atc.wustl.edu>. Information in a previous Facility Questionnaire can be extended to meet this requirement by simply adding data that is

specific to this SBRT protocol. Each institution must submit the completed Facility Questionnaire by e-mail, fax, or mail to RTOG Headquarters.

All questions in the Facility Questionnaire pertaining to IMRT (if this treatment modality is to be used), heterogeneity corrections, respiratory movement control, and IGRT must be answered.

5.2.2.2 IGRT Verification Study: 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 verification procedure 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 ATC web site, <http://itc.wustl.edu>) will be reviewed by the Medical Physics Co-Chair, William Parker, MSc. Upon approval of the images and spreadsheet by Mr. Parker, RTOG Headquarters will notify the institution that it is credentialed. Similar information must be sent for the first patient treated on this protocol before a second patient is treated. This process also must be followed for the second patient entered on the protocol. If either of these patients is treated with a single fraction, the IGRT information before and after repositioning must be sent.

5.2.2.3 (3/4/10) Electronic Submission: Each participating institution must contact the ITC (itc@wustl.edu) and request an SFTP account for digital data submission. (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.)

5.2.2.4 Phantom Irradiation: 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 treatment plan for irradiation of the phantom must be submitted electronically to the ITC (see Section 5.2.2.3).

This trial allows IMRT techniques (including CyberKnife® and Tomotherapy), and the phantom irradiation requirements vary according to the combination of delivery technique and respiratory control methodology. In general, institutions using conformal techniques and abdominal compression for respiratory motion control together with the recommended margins (see Section 6.4.1) will irradiate the stationary version of the phantom. The exception is for institutions intending to use either tracking or gating techniques when lesions do not remain within the stated margins. These institutions will be required to irradiate the moving phantom for credentialing. Additionally, institutions using CyberKnife® or Tomotherapy delivery will be required to irradiate the moving phantom for all methods of respiratory control.

5.2.2.5 Dry Run Submission and Rapid Review Process: Each participating institution must successfully complete and submit a protocol-specific Dry-Run Test to demonstrate its ability to digitally transfer data to the ITC. If the institution has credentialed previously for another SBRT protocol and its treatment planning has not changed, this step can be skipped. However, independent of any previous credentialing, the treatment plan for the first patient on each arm to be treated at the institution on this protocol must be submitted to the ITC for review PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The plan will be reviewed centrally by the PIs, 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.

5.3 Registration

5.3.1 Online Registration

Patients can be registered only after eligibility criteria are met.

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

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://phrp.nihtraining.com/users/login.php>).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

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

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

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrrs.org.

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

6.0 RADIATION THERAPY

NOTE: 3-D conformal and intensity modulated radiation therapy (IMRT) are allowed with proper credentialing (see Section 5.0)

Protocol treatment must begin within 4 weeks after registration/randomization.

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 (Potters 2004). 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 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 a 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

Arm 1 patients will receive 34 Gy in 1 fraction to the prescription line at the edge of the PTV (see Section 6.4.2.1 for more prescription details).

Arm 2 patients will receive 4 fractions, 12 Gy per fraction, to a total dose of 48 Gy to the prescription line at the edge of the PTV. Treatments should be given on 4 consecutive days. The time between fractions is at the discretion of the investigator, but a minimum of 18 hours is required.

6.1.3 Premedications

Although not mandatory, it is recommended that patients receive corticosteroid premedication (e.g., Dexamethasone, 4 mg, p.o. in a single dose, or equivalent) 15-60 minutes before each SBRT treatment for the intended purpose of modulating immediate pulmonary inflammatory effects. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

6.2 Technical Factors

6.2.1 Physical Factors

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

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 for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements listed in Section 6.4 for small lesions (< 2.5 cm axial 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 IMRT with a standard multileaf collimator or Tomotherapy or for the CyberKnife® unit where by design the entire PTV is not encompassed for each beam.

6.2.3 Dose Verification at Treatment

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

6.2.4 Treatment Platforms

The trial allows most commercially available photon producing treatment units except the exclusion of units described in Section 6.2.1 (e.g., cobalt units and charge particle accelerators). As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used with conformal dose delivery or IMRT. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol and are used in a fashion that passes the accreditation tests required by the protocol.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patient Positioning

Patients will be positioned in a stable position. For Arm 2 patients, this position should be capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system (see Section 6.1). All positioning systems must be validated and accredited by the Study Committee

(Principal Investigator and Co-Investigators) before enrolling or treating patients on this trial. Patient immobilization must be reliable enough to insure that in combination with the techniques used to inhibit target motion (described in Section 6.2.3), 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.

6.3.2 Inhibition of Effects of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques. All systems used to account for internal organ motion must be validated and accredited by the Study Committee (Principal Investigator and Co-Investigators) 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 should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices, an in-room helical CT device, tomotherapy helical CT, cone-beam CT equipment, or standard EPID imaging. In all cases, the RTOG Image Guidance Guidelines must be followed. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained. For institutions using equipment that does not allow this double-check capability, agreement between the treatment unit isocenter or reference point in space must be carefully checked for agreement with the imaging isocenter.

For Arm 2 of this study, after treatment verification CT scans or verification planar images may be taken at the discretion of the participating institution but are not required for protocol participation. For Arm 1, where a single fraction is used, after treatment verification imaging must be used. The localization images will be submitted for quality assurance (QA) purposes to the ITC. When possible, these images must be sent using the DICOM format. When this is not possible, JPEG images must be sent.

6.4 Treatment Planning/Target Volumes

6.4.1 Image Acquisition (3/4/10)

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. Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels within 8 weeks of registration on the trial. If not, i.v. contrast should be given during the planning CT; i.v. contrast at simulation may be omitted even in this case if contraindicated (e.g. allergy or 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 \leq 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. 4-dimensional CT image guided GTV delineation to take tumor motion into consideration will be allowed. **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).**

There are 2 acceptable methods to define the PTV depending on the method of CT simulation:

- a. Conventional (helical) CT-simulation (non-4DCT): The PTV will include the GTV plus an additional 0.5 cm margin in the axial plane and 1.0 cm margin in the longitudinal plane (craniocaudal).

- b. 4D CT-simulation: An internal target volume (ITV) around the GTV, accounting for tumor motion may be defined from the 4D CT dataset. The PTV will include the ITV plus an additional 0.5 cm margin uniformly applied to the ITV.

These margins will be used at all institutions, even if a particular institution uses equipment or techniques felt to be more accurate.

6.4.2 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. In order to obtain acceptable coverage, 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 should 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 (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pre-treatment depending on the results from localization imaging studies) and translated to the treatment record.

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity corrections. The particular algorithm used for such correction must be approved by the RTOG Physics Committee in advance.

6.4.2.1 Prescription Dose Constraints for Treatment Planning (3/6/14)

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

1. **Maximum dose:** The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
2. **Prescription isodose:** The prescription isodose surface must be $\geq 60\%$ and $< 90\%$ of the maximum dose.
3. **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 ($PTV_{V_{100RX}} = 95\%$) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose ($PTV_{V_{90\%RX}} > 99\%$).
4. **High Dose Spillage:**
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.

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. The "None" and "Minor" entries in this table define the Per Protocol, Variation Acceptable and Deviation Unacceptable Compliance Criteria (see Section 6.7).

5. Intermediate Dose Spillage (11/1/12)

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 D_{2CM} where D_{2CM} 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 in the table below. This table is used for all prescription requirements in Section 6.4.2 irrespective of calculation algorithm and total treatment dose.

(11/1/12) 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} (%)		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 (3/4/10)

The following table lists maximum dose limits to a point or volume within several critical organs. Except for the rib, these are absolute limits, and treatment delivery that exceeds these limits will constitute a protocol violation (See Section 6.7). The dose is listed as total delivered. These limits were formulated with the approval of the study committee (Principal Investigators and Co-Chairs) using tolerance data, historical data as listed in section 1 with special weighting to the RTOG experience (in reference to the 34 Gy dose) and that of Chang, et al. from MD Anderson (in reference to the 12 Gy times 4 fractions arm).

Arm 1: One Fraction (34 Gy)

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.35 cc <1.2 cc	10 Gy 7 Gy	14 Gy	myelitis
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	14 Gy	17.5 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	10.5 Gy	20.2 Gy	stenosis/fistula
Rib**	<1 cc	22 Gy	30 Gy	Pain or fracture
Skin	<10 cc	23 Gy	26 Gy	ulceration
Stomach	<10 cc	11.2 Gy	12.4 Gy	ulceration/fistula
Parallel Tissue	Critical Volume (cc)	Critical Volume Dose Max (Gy)		Endpoint (≥Grade 3)
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.4 Gy		Pneumonitis

(11/1/12) Arm 2: Four Fractions (4 x 12 Gy)

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.35 cc <1.2 cc	20.8 Gy (5.2 Gy/fx) 13.6 Gy (3.4 Gy/fx)	26 Gy (6.5 Gy/fx)	myelitis
Esophagus*	<5 cc	18.8 Gy (4.7 Gy/fx)	30 Gy (7.5 Gy/fx)	stenosis/fistula
Brachial Plexus	<3 cc	23.6 Gy (5.9 Gy/fx)	27.2 Gy (6.8 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	28 Gy (7 Gy/fx)	34 Gy (8.5 Gy/fx)	pericarditis
Great vessels	<10 cc	43 Gy (10.75 Gy/fx)	49 Gy (12.25 Gy/fx)	aneurysm
Trachea and Large Bronchus*	<4 cc	15.6 Gy (3.9 Gy/fx)	34.8 Gy (8.7 Gy/fx)	stenosis/fistula
Rib**	<1 cc	32 Gy (8 Gy/fx)	40 Gy (10 Gy/fx)	Pain or fracture
Skin	<10 cc	33.2 Gy (8.3 Gy/fx)	36 Gy (9 Gy/fx)	ulceration
Stomach	<10 cc	17.6 Gy (4.4 Gy/fx)	27.2 Gy (6.8 Gy/fx)	ulceration/fistula
Parallel Tissue	Critical Volume (cc)	Critical Volume Dose Max (Gy)		Endpoint (≥Grade 3)
Lung (Right & Left)	1500 cc	11.6 Gy (2.9 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	12.4 Gy (3.1 Gy/fx)		Pneumonitis

*Avoid circumferential irradiation

**Rib limit may be exceeded if rib structure lies within PTV; see Section 6.5.1.1 below.

6.5.1.1 The Rib/Chest Wall As Critical Structures

As follow-up intervals following SBRT become longer with increased patient survival, delayed morbidity from therapy is becoming increasingly recognized. In particular, recent reports have highlighted that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication. Factors associated with increasing chest wall toxicity are currently active areas of investigation. It also is evident that tumor location, especially peripheral lesions as in this protocol, will enhance the potential for any such risk. Therefore, in this protocol, it is the intent of the investigators to prospectively document dose

to ribs. The goal of any plan will be to optimize target treatment parameters per this protocol, be mindful of rib dosing (as low as reasonably achievable [ALARA]), but in no way compromise target coverage or restrict potential delivery parameters for the sake of rib dosing. Rib “limits’ provided in the table above may in that respect be exceeded for an otherwise excellent plan. This will not be considered a violation.

Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instructions for the contouring of these organs are as follows in Section 6.5.2.

6.5.2 Contouring of Normal Tissue Structures

All structures listed in Sections 6.5.2.1 through 6.5.2.9 should be contoured in every patient irrespective of the location of the PTV. The structures listed in Sections 6.5.2.10 through 6.5.2.11 are only required if the named structure lies within 5 cm of the PTV.

6.5.2.1 Spinal Cord

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

6.5.2.2 Esophagus

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

6.5.2.3 Brachial Plexus

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

6.5.2.4 Heart

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

6.5.2.5 Trachea and Proximal Bronchial Tree

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

6.5.2.5.1 Proximal Trachea

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

6.5.2.5.2 Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in Section 3.2.2. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedium bronchus, the right middle lobe bronchus, the lingular bronchus,

and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

6.5.2.6 Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

6.5.2.7 PTV Plus 2 cm

As part of the QA requirements for “low dose spillage” listed in Section 6.4, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning.

6.5.2.8 Proximal Bronchial Tree Plus 2 cm

As part of adhering to the ineligibility requirements for not enrolling patients with tumors in the zone of the proximal bronchial tree listed in 3.2.2 above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not be treated with the protocol therapy. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment planning software to ensure protocol compliance.

6.5.2.9 Skin

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

6.5.2.10 Rib

Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

6.5.2.11 Great Vessels (8/19/10)

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.

6.5.2.12 Other Structures

The constraints tables above contain other structures. These are required if the treated lesion is within 5 cm of the PTV.

6.6 Documentation Requirements

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 Compliance Criteria

6.7.1 Dosimetry Compliance

Section 6.4.2.1, Table 1 describes appropriate conduct for treatment planning dosimetry for target coverage and the dose falloff. The Principal Investigators will evaluate plans as described in Section 6.8. Criteria for both Per Protocol (listed in the table as “None”) and Variations Acceptable (listed under the heading of “Minor”) are given in this table. Deviations Unacceptable occur when the stated Minor limits are exceeded. The table in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these dose limits by more than 2.5% constitutes a Variation Acceptable. However, exceeding these dose limits by more than 5% constitutes a Deviation Unacceptable.

6.7.2 Treatment Delivery Compliance

Setup films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.5 cm in the transverse plane and 1.0 cm in the craniocaudal plane will be considered compliant. Deviations from 0.5-1.0 cm in the transverse plane and 1.0-1.25 cm in the craniocaudal plane will be considered as Variation Acceptable. Deviations greater than those listed as minor will be considered as Deviations Unacceptable.

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. Videtic and his Co-Investigators, Drs. Singh and Chang, will perform an RT Quality Assurance Remote Review after complete data for the first 20 cases enrolled have been received at ITC. Drs. Videtic, Singh, and Chang will perform the next review after complete data for the next 20 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 Radiation Therapy Adverse Events

6.9.1 Central Airway/Bronchial Injury (7/26/10)

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 often will 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 11.0 to avoid such mis-characterization.

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.

6.9.2 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.

6.9.3 Changes in Pulmonary Function Tests (7/26/10)

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%

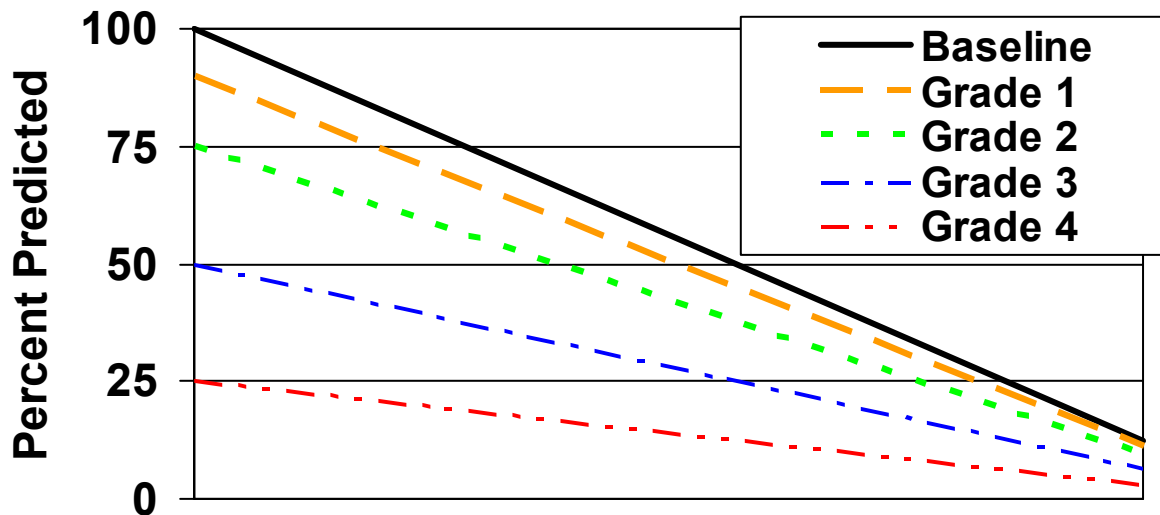
conveys that the patient is able to perform the PFT test to a result that is 90% of what would be expected for the normal general population of the same height, age, and sex. The CTCAE version 4 specified grading criteria for PFTs assumes that all patients have normal baseline pulmonary function. This 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, v. 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					
Adverse Event	Grade				
	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

PFT (FEV-1, FVC, DLCO) Decline



6.9.4 Other Significant Toxicity

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

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

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

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

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines:

Adverse Event Reporting Requirements. February 29, 2012;
[http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

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, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study, including a male patient's impregnation of his partner, must be reported via CTEP-AERS as a medically significant event.

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, probable, or definite) should be reported via CTEP-AERS.

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

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

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

As of October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA version 12.0 for grading of all adverse events. A copy of the CTCAE v. 4 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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 CTEP-AERS . CTEP-AERS can be accessed via the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>). Use the patient's case number without any leading zeros as the patient ID when reporting via CTEP-AERS. In order to ensure consistent data capture, AEs and SAEs reported using CTEP-AERS **must also be reported to RTOG on the AE case report form (see Section 12.1)**. In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

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

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

Any event that meets the above outlined criteria for an SAE but is assessed by CTEP-AERS as "expedited reporting NOT required" must still be reported for safety reasons. Sites must bypass the "NOT Required" assessment and complete and submit the report.

CTEP-AERS allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under within 30 Days of the Last Administration of the Intervention^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)				
<p>NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	
<p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> o “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. o “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. 				

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

RTOG REPORTING REQUIREMENTS (3/6/14)

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

As of October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, MedDRA, version 12.0, for grading of all adverse events. A copy of the CTCAE v. 4 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (<http://ctep.info.nih.gov>) or the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>).

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

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

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

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

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis. If 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

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.

Additional adjuvant treatment is not recommended but is permitted at the discretion of the treating physician.

9.2 Non-permitted Supportive Therapy

Concurrent antineoplastic therapy while on study is not permitted.

10.0 TISSUE/SPECIMEN SUBMISSION

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

NOTE: Patients must be offered the opportunity to participate in the tissue/specimen submission component of the study. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

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. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking and serum, lymphocytes, and plasma will be collected for translational research.

10.2 Specimen Collection for Tissue Banking (Highly recommended but not required)

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

10.2.1 One H&E stained slide

10.2.2 **(8/19/10)** A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

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

10.2.4 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.

10.3 Serum, Plasma, and Lymphocyte Collection for Translational Research (Highly recommended but not required)

See Appendix V for blood kit contents and detailed collection instructions.

Baseline levels of the RNA, proteins, and/or changes of the levels after SBRT may be used as biomarkers to predict clinical outcome including survival, local regional recurrence, distant metastasis, and treatment related toxicity. These markers may help us in the future to classify patients for their probability to benefit from the therapeutic regimens, particularly dose escalated radiotherapy.

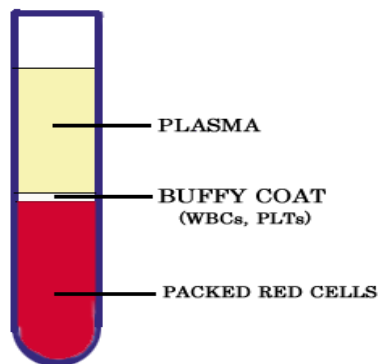
One of the critical issues in studying biomarkers is the availability of biological materials. For patients with non-small cell lung cancer (NSCLC), repeated biopsies from tumors are difficult and cannot be performed routinely. Serum circulating in the body and carrying proteins or peptides from tumors and their surrounding environment may be a candidate surrogate tissue that provides important information about the individual's intrinsic genetic background and its response to the disease in the lungs. It may be informative in assessing response and toxicity following treatment. Furthermore, an individual's serum is relatively stable in volume, and therefore more reliable for quantitative analyses. A major advantage of using serum is its accessibility as it can be obtained easily without invasive procedures, particularly if only a small volume is required. In fact, associations between levels of certain serum proteins and responses to chemotherapeutic regimens have been reported. Blood lymphocytes are cellular components easily accessible from patients. Although they are not cancer cells, their response to treatment may reflect their genomic background. Information obtained from these cells might provide additional information about treatment response and toxicity if the genomic background indeed plays a role.

10.3.1 Blood Sample Preparation

20 ml peripheral blood (one 10 ml EDTA tube and one 10ml Red-top tube) will be taken from each individual before treatment and 6 weeks after completion of SBRT. Use sterile techniques to avoid contamination.

10.3.2 Buffy Coat Cell and Plasma:

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



10.3.3 Frozen Plasma Samples for Biomarker Analysis

- a. Collect one 10 ml tube of blood using one EDTA (purple top) tube.
- b. Invert six to seven times to ensure adequate mixing with anticoagulant.
- c. Centrifuge within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
- d. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- e. Carefully pipette and transfer ~1ml aliquots of plasma into 4-5 cryovials taking care to avoid collecting any blood cells (red/white blood cells).
- f. Place tops on cryovials and make sure tops of cryovials are on securely.
- g. Tube should be clearly labeled (see Section 10.5).
- h. Place tubes in a Styrofoam holder and then place into a zip lock bag.
- i. Store plasma cryovials at -80°C until packed and shipped.

10.3.4 Blood Sample for Isolation of Lymphocytes

- a. Collect one 10 ml tubes of blood using one EDTA (purple top) tube. You may use the same tube that the plasma was collected from.
- b. Carefully remove plasma close to the buffy coat.
- c. Remove the buffy coat cells carefully and place into three (3) 1ml cryovials labeled "buffy coat" (it is okay if a few packed red cells are inadvertently collected in the process).
- d. Tubes should be clearly labeled (see Section 10.5).
- e. Place all three cryovials in a Styrofoam holder and then place into a zip lock bag.
- f. Store buffy coat cryovials at -80°C until packed and shipped (shipped on dry ice).

10.3.5 Frozen Serum Samples for Biomarker Analysis

- a. Collect one 10 ml tube of blood without coagulants (Red top).

- b. Sit at room temperature for 30 min to allow clot formation.
- c. Centrifuge in a standard clinical centrifuge at 3000g at 4°C for 30 minutes.
- d. Transfer ~1ml aliquots of separated serum into 4-5 cryovials.
- e. Place tops on cryovials and make sure tops of cryovials are on securely.
- f. Tube should be clearly labeled (see Section 10.5).
- g. Place tubes in a Styrofoam holder and then place into a zip lock bag.
- h. Store serum cryovials at -80°C until packed and shipped.

10.3.6 Storage Conditions (8/19/10)

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: Monday-Tuesday).

OR:

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

OR:

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

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

10.3.7 Documentation for Submission of Serum, Plasma, and Lymphocytes

Submit materials for Tissue Banking, Central Review, Translational Research as follows:

The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, and lymphocytes; the RTOG protocol number; the patient's case number; and method of storage (e.g., stored at -80° C), must be included.

10.4 Submit materials for Tissue Banking and Translational Research as follows: (11/1/12)

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

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

U.S. Postal Service Address: For all non-urgent, ambient specimens-FFPEs, slides, blocks

**RTOG Biospecimen Resource
University of California San Francisco
UCSF Box 1800
(2340 Sutter St., Room S341)
San Francisco, CA 94143-1800**

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

10.5 Reimbursement (11/1/12)

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/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323>). 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 (11/1/12)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx> 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 the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

- 11.1 Study Parameters:** See Appendix II for a summary of assessments. See details and exceptions in Sections 11.1.1-11.1.4 below:

- 11.1.1** Pulmonary function tests (PFTs) include spirometry, lung volumes, and diffusion capacity. Arterial blood gases are optional. Subsequent to the follow-up visit 12 weeks post-SBRT, PFTs should be done every 6 months for 5 years.
- 11.1.2** Alternate chest x-ray and CT scan with contrast in follow-up visits, with initial chest x-ray at 6 weeks post-SBRT and the initial CT scan with contrast at 12 weeks post-SBRT. Continue alternating the studies in follow-up visits.
- 11.1.3** With the chest x-ray at 6 weeks post-SBRT, monitor for signs of radiation pneumonitis (see Section 6.9).
- 11.1.4** FDG-PET is recommended but not required at 12 weeks post-SBRT and at 1 year post-SBRT as a measure of response.

Note: FDG PET data will be used for the analysis of a secondary endpoint (see Section 2.2.2). To be included in this analysis, the patient's PET studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner. PET scanners with sodium iodide (NaI) detectors are not acceptable. If the baseline PET study is performed at the treating institution (or its affiliated PET facility), it is recommended that the reassessment PET scans be performed at the same site. FDG PET studies should be conducted according to the institutional policies and quality assurance measures of each treating institution and should reflect the standards of practice as delineated in reports such as Shankar, et al. (2006).

11.2 Measurement of Response

- 11.2.1 Response Determination (8/19/10)**
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 for further details.

Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define primary tumor control as described below.

- 11.2.2 Baseline Documentation of "Target" and "Non-Target" Lesions**
Patients enrolled to this protocol should have clinical stage I (T1 or T2, N0, M0) [T < 5 cm] NSCLC. At time of treatment, they should have only one site of gross disease in the lung, with no metastases. The primary lung tumor should be identified as the **target lesion** and recorded and measured at baseline and with each follow-up imaging evaluation.

The longest diameter (LD) for *the target lesion* will be calculated **from the treatment planning CT scan** using pulmonary windowing and reported as the baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor. For follow-up assessment, diagnostic CT scans performed using a 5 mm contiguous reconstruction algorithm using pulmonary windowing taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response. When CT scans are not available, chest x-ray determination will be allowed as long as the target lesion is clearly visible. Changes in serum tumor markers will not be allowed for assessment of either local tumor progression or metastatic progression.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy

consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor. In order to make the assessment more objective, a central radiology review for CT response evaluation will be required for this protocol.

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

11.2.3 Response Criteria (8/19/10)

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 Criteria for Discontinuation of Protocol Treatment

- Disease progression at any time during treatment or in the follow-up period; the patient should be restaged and sites of recurrence and/or progression should be documented. Rebiopsy is strongly encouraged.
- Development of intercurrent, noncancer related illnesses that prevent the continuation of treatment or protocol-specified follow up.
- Unacceptable toxicity;
- The patient may elect to withdraw from study treatment at any time for any reason.

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

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

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Slides/Blocks (P2)	Within 2 weeks of registration
Radiotherapy Form (T1) Daily Treatment Record (T5) Copy to HQ and ITC	Within 1 week of RT end
Follow-up Form (F1)	Every 3 months for 2 years; every 6 months for next 2 years; then annually

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [3/4/10]

<u>Item</u>	<u>Due</u>
Preliminary Dosimetry Information (DD) †Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: <ul style="list-style-type: none">• CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3)• Digital beam geometry for initial and boost beam sets• Doses for initial and boost sets of concurrently treated beams• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)	Within 1 week of start of RT

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”.

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

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

12.2.1 *Digital Data Submission to ITC (3/4/10)*

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

For network submission: The SFTP 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 Primary Endpoint (7/26/10)

The rate of 1-year grade 3 or higher adverse events definitely, probably, or possibly related to treatment for the following adverse events:

- 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 Injury, Poisoning, and Procedural Complications
 - Fracture (to be limited to rib fractures only)
- 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
- Grade 3-5 Skin and Subcutaneous Disorders
 - Skin ulceration (thorax only)
- 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

13.2 Secondary Endpoints (8/19/10)

13.2.1 Primary tumor control;

13.2.2 Overall survival and disease-free survival;

13.2.3 Distribution of FDG PET SUV changes as a potential measure of treatment response and outcomes;

13.2.4 Distribution of pulmonary function changes by treatment arm and response;

13.2.5 Biomarkers for primary tumor control rate at 1 year and grade 2 or higher radiation pneumonitis.

13.3 Randomization and Stratification

Patients will be randomized to one of two treatment arms in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution. Additionally, patients will be stratified by Zubrod Performance Status (0 vs. 1. vs. 2) and T Stage (T1 vs. T2).

13.4 Sample Size

The goals for this randomized phase II study are to select the most favorable treatment regimen on the basis of the grade 3 or higher adverse events at 1 year and for that regimen to be used then as a comparison (experimental) arm in a phase III trial against the current RTOG standard SBRT treatment set by RTOG 0236.

Based on the results of previous studies (Hara 2006, Onishi 2007, Timmerman 2007), we expect that at most 5% of patients will experience a grade 3 or higher adverse event. We will not investigate further any regimen in this study that yields > 17% grade 3 or higher adverse events by 1 year. We consider any regimen in this study that yields $\leq 5\%$ grade 3 or higher adverse events by 1 year to be a treatment regimen to investigate further. For each arm, the null hypothesis (H_0) is that the regimen is not safe versus the alternative hypothesis (H_A) that the regimen is safe. Let p denote the proportion of patients who have not experienced a grade 3 or higher adverse event by the end of year 1 among all analyzable patients (eligible patients who received any protocol treatment) in each arm. The hypotheses for each arm are:

$$H_0: p < 0.83 \text{ vs. } H_A: p \geq 0.95$$

Based on the hypotheses above, the sample size was calculated with Fleming's Multiple Testing Procedure (1982), specifically two-stage testing, at a significance level of 0.1 and 90% statistical power. At these type I and II error rates, 41 patients will be needed for each arm. This sample size will yield an actual significance level of 0.06 and an actual statistical power of 83%. Adjusting the number of cases for ineligible or unanalyzable cases by 7%, 44 patients are needed for each arm; **a maximum of 88 patients is required for this study.**

13.5 Patient Accrual

Based on patient accrual in previous RTOG studies, the initial 6 months accrual will be negligible while institutions are obtaining IRB approval. Based upon patient accrual in previous RTOG NSCLC studies, the patient accrual is projected to be 2 patients per month. Assuming a similar accrual rate of 2 per month for this study, we expect to complete accrual for this study in 4.5 (> 4.3) years.

If the accrual rate is higher than the projected date, we will amend the protocol to reflect the actual accrual rate. If the accrual rate is too low, the feasibility of completing the study will be discussed with the Study Chairs, the RTOG Lung Cancer Committee Chair, and the RTOG Executive Committee.

13.6 Analysis Plans

The analysis for reporting the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 1 year from the end of protocol specified treatment. Only patients that meet the eligibility requirements of this protocol and start protocol treatment will be included. Analyzable patients are defined as eligible patients who received any protocol treatment.

13.6.1 Analysis of the Primary Endpoint (8/19/10)

The NCI Common Terminology Criteria for Adverse Events (CTCAE, v. 4) for scoring the treatment-related adverse events will be used.

The adverse events of interest in this study are listed in Section 13.1.

The rates of grade 3 or higher adverse events at 1 year will be calculated as the proportion of patients who have any adverse event of interest by the end of year 1 among the total analyzable patients in each arm. These rates will be reported by T stage (T1 versus T2).

The stopping and continuation rules in Table 1 will be applied for the interim analyses for each arm separately. At any stage, we will report the results when the results from both arms are available. If at any stage, we stop and reject the null hypothesis (H_0), we would conclude that this regimen is safe, stop the accrual to this arm, and continue to accrue patients to the other arm (if applicable). If we stop and reject the alternative hypothesis (H_A) at any stage, we would conclude that the regimen is not safe, stop the accrual to this arm, and continue to accrue patients to the other arm (if applicable). If we continue until the last stage, we will conclude that the regimen is safe or not safe.

Based on a number of studies of SBRT, we assume similar high rates of primary tumor control rate for single and multiple fraction doses. However, we will monitor the primary tumor control rate for both arms.

1. If the primary tumor control rate at 1 year of both arms are higher than 90% and the adverse event rate for both arms is $\leq 17\%$, then both arms will be strongly considered as a potential arm in a subsequent phase III study, assuming treatment delivery is acceptable. If both arms meet these criteria, then the treatment arm that has lower adverse event rate at 1 year will be chosen.
2. If the primary tumor control rate at 1 year of both arms is less than 90% and the adverse event rate for both arms is $\leq 17\%$, then the Study Chairs will reassess the validity of either fractionation as a potential comparator arm for a phase III comparison with the RTOG 0236 standard treatment.
3. If any of the arms have more than 17% grade 3 or higher adverse events by 1 year, then we will conclude that the experimental regimen is not promising for further investigation regardless of primary tumor control rates at 1 year.
4. If only 1 of the arms has a higher than 90% primary tumor control rate at 1 year, with the adverse event rate for both arms being $\leq 17\%$, then the treatment arm that has a primary tumor control rate higher than 90% will be chosen.

Table 1: Number of Patients Having Grade 3 or Higher Adverse Events at 1 Year for Stopping and Continuation Rules

Number of analyzable patients*	Stop and conclude that this regimen is safe	Continue Accrual	Stop and conclude that this regimen is not safer
21	0	1-3	≥ 4
41	≤ 4	N/A	≥ 5

*Analyzable patients are defined as eligible patients who received any protocol treatment with at least 1 year of follow-up beginning from the start of SBRT.

If a grade 5 adverse event definitely, probably, or possibly related to treatment is reported at any time, it will be reviewed by the Study Chairs, the Study Statistician, the RTOG Lung Cancer Committee chair, and the RTOG Executive Committee. Case report forms (CRFs), source documentation, and a statistical report summarizing the study data will be reviewed as soon as possible. During this review, accrual will be suspended (if applicable). Following this review, the Study Chairs, the Study Statistician, the RTOG Lung Cancer Committee chair, and the RTOG Executive Committee will discuss the findings and make a decision about amending and/or continuing the study.

In each arm, logistic regression (Agresti 1996) will be used to model the distribution of grade ≥ 3 adverse events. Both unadjusted and adjusted odd ratios and the respective 90% confidence interval will be computed.

The following will be reported at the time of primary endpoint analysis:

- Tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important prognostic baseline and other pretreatment variables;
- Frequency and severity of adverse events;
- Compliance rates of treatment delivery with respect to the protocol prescription.

13.6.2 Analysis of Secondary Endpoints

13.6.2.1 Survival Outcomes (8/19/10)

The survival endpoints for this trial are primary tumor control, overall survival, and disease-free survival at 1 year.

The failure event for overall survival is a death due to any cause. Survival time is measured from the date of randomization to the date of death or last follow up. The failure event for disease-free survival is defined as death due to any cause, local failure, marginal failure, involved node failure, regional failure, distant metastasis, or second primary. Time to disease-free survival is measured from the date of randomization to the earliest event or to the date of most recent follow-up if no event occurred. Primary tumor control is defined as the absence of local progression as defined in Section 11.2.3. Marginal failures will be considered events for primary tumor failure. The primary tumor control rate at 1 year will be calculated as the number of patients who do not have a local progression event by the total number of analyzable patients in each arm at 1 year.

The Kaplan-Meier method (1958) will be used to estimate overall survival and disease-free survival at 1 year. Time to overall survival and disease-free survival will be modeled by Cox (1972) proportional hazards regression. Unadjusted and adjusted hazard ratios and the respective 90% confidence intervals will be computed. Logistic regression (Agresti 1996) will be used to model the distribution of the primary tumor control rate. Both unadjusted and adjusted odd ratios and the respective 90% confidence interval will be computed. At the least, Zubrod performance status, and T-stage (and other factors as appropriate) will be adjusted in these models.

No statistical comparison will be made between the 2 arms. Further subgroup analyses will be undertaken if the sample sizes involved in each subgroup are adequate to support such analyses.

13.6.2.2 Assessment of FDG PET SUV Changes as a Measure of Treatment Response and Outcomes

Whole body FDG-PET scan will be done within 8 weeks prior to registration (required), and 12 weeks and 12 months post-SBRT (recommended but not required). The peak standard uptake value (SUV), normalized SUV (peak SUV of regions of interest/mean SUV of the aortic arch), and the change of SUV and normalized SUV (subtracting SUV and normalized SUV at reassessment from baseline data respectively) will be used as PET scan data. The grade 3 or higher adverse event, overall survival, and disease-free survival will be the outcomes. The distribution of the peak SUV and normalized SUV will be reported for each time point, respectively. The distribution of change of SUV and normalized SUV will be reported.

13.6.2.3 Descriptive Pulmonary Function by Treatment Arm and Response

The descriptive statistics of changes of FEV1 and diffusion capacity before and after treatment will be reported in each arm (at least mean, standard deviation, median, and range). These data will be reported by 4 local response categories (complete response; partial response; stable disease; local enlargement) in each arm.

13.6.2.4 Translational Research: Biomarkers for Primary Tumor Control and Grade 2 or Higher Radiation Pneumonitis (8/19/10)

At the time of data maturity of this study, we will propose specific details of the markers to be investigated. However, we propose the following list of potential biomarkers, subject to change based on information that is unknown at this time: Radiation treatment-related hypoxia markers (osteopontin, VEGF, IL8, LDH5, and MiR210), DNA repairing gene polymorphism (such as p53, XRCC1, ERCC1, XPA, XPC, XPD, XPF, XPG), and radiation-induced symptom related cytokines (such as TGF-Beta, IL-1 and IL).

We will address the assays that will be used and a list of specific correlative aims with appropriate statistical considerations. The following is a general guideline of the statistical consideration for this analysis. This analysis will be done in each arm separately to test the prognostic value of each biomarker. The patients with biomarkers will be compared with the patients without a value for that biomarker to determine if there are any differences with respect to distribution of baseline. A k-fold cross validation method with $k \geq 2$ (which will be

decided at the time of analysis) will be used to validate the results of the following analyses. It is entirely possible that factors and biomarkers shown to be statistically significant in other published series may not be found here.

13.6.2.4.1 Primary Endpoint of Translational Research (8/19/10)

We hypothesize that the changes of hypoxia circulating markers (Osteopontin, VEGF, IL8, LDH5, and microRAN 210) have a greater decline after treatment with fractionated SBRT (Arm 2) than with single fraction SBRT (Arm 1). The change of each putative hypoxia circulating marker from baseline to 6 weeks after SBRT is calculated in each arm. Two-sided t-test statistics (if normal distribution assumption is met) or Wilcoxon rank sum test statistics (if normal distribution assumption is not met) are calculated and tested at the significance level $\alpha=0.05$ for each marker.

We will test to see if the baseline level of each hypoxia circulating marker is a statistically significant factor for primary tumor control rate at 1 year for each arm using logistic regression (Agresti 1996) in each arm. The 95% confidence interval of odds ratio (OR) of each marker in each arm and OR will be calculated. No testing will be done between the two arms.

13.6.2.4.2 Secondary Endpoints of Translational Research (8/19/10)

Exploratory analysis for the correlation of DNA repairing gene polymorphism (such as p53, XRCC1, ERCC1, XPA, XPC, XPD, XPF, XPG) and both the rate of grade 2 or higher radiation pneumonitis and primary tumor control will be performed. Single Nuclear Polymorphism (SNP) data from these DNA repairing genes will be correlated to the rate of grade 2 or higher radiation pneumonitis and primary tumor control at 1 year using logistic regressions. The Hardy Weinberg Equilibrium (HWE) assumption will be checked for each SNP by Fisher's Exact test to test the null hypothesis that HWE law holds. The multiple testing problem will be addressed using such as the adjust p-value controlling false discovery rate (Benjamini 1995) or false positive rate (Story 2004). All two-sided testing using an adjusted p-value is done at a significance level of 0.05. Multiple logistic regression models are utilized to see the genotype effects of each SNP adjusted for other covariates.

The 3 possible factors, 1) the change between pre-and post-SBRT; 2) pre-SBRT level; and 3) post-SBRT level of cytokines (such as TGF-Beta, IL-1 and IL-6), will be correlated to the rate of grade 2 or higher radiation pneumonitis separately. The logistic regression will be used in each arm for each factor.

13.6.3 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.

13.7 Gender 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 {ref 9}. Furthermore, an analysis of race did not indicate an association with outcome {ref 10}. The projected gender and minority accruals are provided in the table below.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	3	5
Not Hispanic or Latino	36	47	83
Ethnic Category: Total of all subjects	38	50	88
	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	33	42	75
Racial Category: Total of all subjects	38	50	88

REFERENCES

- Agresti A. *An Introduction to Categorical Data Analysis*. New York: John Wiley & Sons, Inc., 1996.
- Aoki M, Abe Y, Kondo H, et al. Clinical outcome of stereotactic body radiotherapy of 54 Gy in nine fractions for patients with localized lung tumor using a custom-made immobilization system. *Radiat Med*. 25:289-294, 07.
- Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. *Acta Oncol*. 45:787-795, 2006.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. Roy Stat Soc, Series B*. 57: 289-300, 1995.
- Brown JM, et al. The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. *Cancer Res*. (58): 1408-16, 1998.
- Burdick MJ, Stephans KL, Reddy CA, Djemil T, Videtic GMM. SUVs from staging FDG-PET do not predict treatment outcomes for early stage NSCLC treated with SBRT. *Int J Radiat Oncol Biol Phys*. 72 (1): supplement S451, 2008.
- Cairns RA. Metabolic targeting of hypoxia and HIF1 in solid tumors can enhance cytotoxic chemotherapy. *PNAS*. 104(22): 9445-9450, 2007.
- Camps C, Buffa FM, Colella S, et al. hsa-miR-210 is induced by hypoxia and is an independent prognostic factor in breast cancer. *Clin Cancer Res*. 14: 1340-1348, 2008
- Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 72:967-971, 2008.
- Chen M, Hayman JA, Ten Haken RK, et al. Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non-small-cell lung cancer: is low incidence of regional failure due to incidental nodal irradiation? *Int J Radiat Oncol Biol Phys*. 64:120-126, 2006.
- Cox JD, Azarnia N, Byhardt RW, et al. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *J Clin Oncol*. 8:1543-1555, 1990.
- Cox DR. Regression models and life tables. *J Royal Stat Soc (Series B)* 34:187-229, 1972.
- Dahele M, Pearson S, Purdie T, et al. Practical considerations arising from the implementation of lung stereotactic body radiation therapy (SBRT) at a comprehensive cancer center. *J Thorac Oncol*. 3:1332-1341, 2008.
- Dosoretz DE, Katin MJ, Blitzer PH, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. *Int J Radiat Oncol Biol Phys*. 24:3-9, 1992.
- Dosoretz DE, Galmarini D, Rubenstein JH, et al. Local control in medically inoperable lung cancer: an analysis of its importance in outcome and factors determining the probability of tumor eradication. *Int J Radiat Oncol Biol Phys*. 27:507-516, 1993.
- Dunst J, Stadler P, Becker A, et al. Tumor hypoxia and systemic levels of vascular endothelial growth factor (VEGF) in head and neck cancers. *Strahlenther Onkol*. 177: 469-473, 2001.
- Fleming T. One-sample multiple testing procedure for phase II clinical trials. *Biometrics*. 38:143-151, 1982.

References (Continued)

- Foote RL, Robinow JS, Shaw EG, et al. Low-versus high-energy photon beams in radiotherapy for lung cancer. *Med Dosim*. 18: 65-72, 1993.
- Fritz P, Kraus HJ, Mühlnickel W, et al. Stereotactic, single-dose irradiation of stage I non-small cell lung cancer and lung metastases. *Radiat Oncol*. 1:30-38, 2006.
- Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg*. 60:615-622, 1995.
- Graham M, et al. Comparison of prognostic factors and survival among black patients and white patients treated with irradiation for non-small cell lung cancer. *J Nat'l Canc Instit*. 84: 1731-1735, 1992.
- Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. *Cancer*. 106:1347-1352, 2006.
- Hayakawa K, Mitsuhashi N, Saito Y, et al. Limited field irradiation for medically inoperable patients with peripheral stage I non-small cell lung cancer. *Lung Cancer*. 26:137-142, 1999.
- Henderson MA, Hoopes DJ, Fletcher JW, et al. A pilot trial of serial 18f-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009 May 25. [Epub ahead of print].
- Hiraoka M. A phase II study of stereotactic body radiation therapy in patients with T1N0M0 non-small cell lung cancer (JCOG 0403). JCOG Radiation Therapy Study Group (RTSG). Slide set: http://atc.wustl.edu/protocols/jcog/0403/JCOG0403_summary.pdf
- Hockel M, V.P., Tumor hypoxia: Definitions and current clinical, biologic, and molecular aspects. *J Natl Cancer Inst*. 93: 266-276, 2001.
- Hof H, Herfarth KK, Münter M, Hoess A, Motsch J, Wannemacher M, Debus JJ. Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys*. 56: 335-341, 2003.
- Hof H, Muentner M, Oetzel D, et al. Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer (NSCLC). *Cancer*. 110:148-155, 2007.
- Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. *Lung Cancer*. 56(2): 229-34, 2007.
- Jemal A, Siegel R, Ward E, et al. Cancer statistics 2008. *CA Cancer J Clin*. 58:71-96, 2008.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 53:457-481, 1958.
- Kaskowitz L, Graham MV, Emami B, et al. Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 27:517-523, 1993.
- Kavanagh BD, Timmerman RD. Stereotactic radiosurgery and stereotactic body radiation therapy: an overview of technical considerations and clinical applications. *Hematol Oncol Clin North Am*. 20:87-95, 2006.
- Kim K, Tsiatis AA. Study duration for clinical trials with survival response and early stopping rule. *Biometrics*. 46:81-92, 1990.
- Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. *Int J Radiat Oncol Biol Phys*. 65:1075-1086, 2006.

References (Continued)

- Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. *Lung Cancer*. 10 Suppl 1:S239-244, 1994.
- Le QT, Sutphin PD, Raychaudhuri S, et al. Identification of osteopontin as a prognostic plasma marker for head and neck squamous cell carcinomas. *Clin Cancer Res*. 9:59-67, 2003.
- Le QT, Loo BW, Ho A, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol*. 1:802-809, 2006.
- Lee SW, Choi EK, Park HJ, et al. Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung. *Lung Cancer*. 40:309-315, 2003.
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep*. 50:163-170, 1966.
- Matsuo Y, Takayama K, Nagata Y, et al. Interinstitutional variations in planning for stereotactic body radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 68:416-425, 2007.
- McCammon R, Schefter TE, Gaspar LE, et al. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 73:112-118, 2009.
- McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys*. 63:1010-1015, 2005.
- Nagata Y, Negoro Y, Aoki T, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys*. 52:1041-1046, 2002.
- Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys*. 63:1427-1431, 2005.
- Nagata Y, Matsuo Y, Takayama K, et al. Survey of stereotactic body radiotherapy in Japan. *Int J Radiat Oncol Biol Phys*. 66(suppl):s150-s151, 2006.
- Nagata Y, Matsuo Y, Takayama K, et al. Current status of stereotactic body radiotherapy for lung cancer. *Int J Clin Oncol*. 12:3-7, 2007.
- Nyman J, Johansson KA, Hultén U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer--mature results for medically inoperable patients. *Lung Cancer*. 51:97-103, 2006.
- Oc P, Rhys-Evans P, Eccles SA. Expression of vascular endothelial growth factor family members in head and neck squamous cell carcinoma correlates with lymph node metastasis. *Cancer*. 92:556-568, 2001.
- Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer*. 101:1623-1631, 2004.
- Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol*. 2(7 Suppl 3):S94-100, 2007.
- Overgaard J, et al. Plasma osteopontin, hypoxia, and response to the hypoxia sensitizer nimorazole in radiotherapy of head and neck cancer: Results from the DAHANCA 5 randomized doubleblind placebo-controlled trial. *Lancet Oncol*. 6(10): 757-764, 2005.

References (Continued)

- Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys.* 70:847-852, 2008.
- Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer.* 59:1874-1881, 1987.
- Potters L, Steinberg M, Rose C, et al. American Society for Therapeutic Radiology and Oncology; American College of Radiology. American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 60:1026-1032, 2004.
- Pulkkinen K, Malm T, Turunen M, Koistinaho J, Ylä-Herttuala, S. Hypoxia induces microRNA miR-210 *in vitro* and *in vivo*: Ephrin-A3 and neuronal pentraxin 1 are potentially regulated by miR-210. *FEBS Letters.* 582, 2397-2401. 2008.
- Qiao X, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. *Lung Cancer*41:1-11, 2003.
- Sandler HM, Curran WJ, Jr., Turrisi AT, 3rd. The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys;* 19: 9-13, 1990.
- Saunders M, Dische S, Barrett A, et al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomised multicentre trial. CHART Steering Committee. *Lancet.* 350:161-165, 1997.
- Scott C, et al., Recursive partitioning analysis of 1592 patients on four RTOG studies in inoperable non-small cell lung cancer. *Lung Cancer.* 17(suppl 1): S59-S74, 1997.
- Shankar LK, Hoffman JM, Bacharach S, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med.* 47:1059-1066, 2006.
- Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. *Int J Radiat Oncol Biol Phys.* 40:149-154, 1998.
- Slotman BJ, Njo KH, Karim AB. Curative radiotherapy for technically operable stage I nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys.* 29:33-37, 1994.
- Song DY, Kavanagh BD, Benedict SH, et al. Stereotactic body radiation therapy. Rationale, techniques, applications, and optimization. *Oncology.* (Williston Park). 18:1419-1430, 2004.
- Storey JD, Taylor JE, Siegmund D. Strong control, conservative point estimation, and simultaneous conservative consistency of false discovery rates: A unified approach. *J Roy Stat Soc, Series B.* 66: 187-205, 2004.
- Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest.* 124:1946-1955, 2003.
- Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol.* 24: 4833-4839, 2006.
- Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. *J Thorac Oncol.* 2(7 Suppl 3): S101-12, 2007.

References (Continued)

(b) Timmerman RD, 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. *Int J Radiat Oncol Biol Phys.* 69 (3 Suppl):S86, 2007.

Timmerman, Robert. Personal Communication. 2009.

Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys.* 51:666-670, 2001.

Whyte RI, Crownover R, Murphy MJ, et al. Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial. *Ann Thorac Surg.* 75:1097-1101, 2003.

Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. *Int J Radiat Oncol Biol Phys.* 60:186-196, 2004.

Wulf J, Baier K, Mueller G, et al. Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol.* 77:83-87, 2005.

Xia T, Li H, Sun Q, Wang Y, Fan N, Yu Y, Li P, Chang JY. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 66:117-125, 2006.

Yoshino O, Osuga Y, Koga K, et al. Upregulation of interleukin-8 by hypoxia in human ovaries. *Am J Reprod Immunol.* 50:286-290, 2003.

Yun Z, et al. Tumor deprivation of oxygen and tumor suppressor gene function. *Methods Mol Biol.* 223: 485-504, 2003.

Zhang HX, Yin WB, Zhang LJ, et al. Curative radiotherapy of early operable non-small cell lung cancer. *Radiother Oncol.* 14:89-94, 1989.

Zierhut D, Bettscheider C, Schubert K, et al. Radiation therapy of stage I and II non-small cell lung cancer (NSCLC). *Lung Cancer.* 34 Suppl 3: S39-43, 2001.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis.* 27:365-375, 1974.

Zimmermann FB, Geinitz H, Schill S, Thamm R, Nieder C, Schratzenstaller U, Molls M. Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small-cell lung cancer (NSCLC). *Acta Oncol.* 45:796-801, 2006.

APPENDIX I

Informed Consent Template for Cancer Treatment Trials **(English Language)**

RTOG 0915 (9/3/09)
(NCCTG N0927)

A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

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

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

Why is this study being done?

Early stage lung cancer is cancer that is limited to the lung and has not spread to the chest lymph nodes or other parts of the body. Standard treatment for early stage lung cancer is surgery to remove the cancer-bearing lung. Patients like you cannot have surgery because of other serious health problems such as emphysema, diabetes, or heart disease. These patients often receive radiation therapy.

Standard radiation therapy can involve daily treatment for several weeks and may not be as effective as surgery at getting rid of the cancer. Standard radiation also may lead to a large amount of scarring of the normal lung surrounding the tumor, which may make other serious health problems worse.

A new radiation therapy called stereotactic body radiation therapy (SBRT) is now being offered to patients with early stage lung cancer who cannot have surgery. The goal of SBRT is to get rid of the lung tumor and spare the lung. SBRT gives fewer but higher doses of radiation than standard radiation. It uses special equipment to position the patient and guide focused x-ray beams toward the cancer and away from normal lung tissue. Research so far suggests that SBRT can reduce the size or eventually eliminate lung tumors effectively and is relatively safe for lungs.

There are a number of different approaches and timeframes used in giving SBRT for early stage lung cancers. The purpose of this study is to compare two previously studied methods of delivering high dose radiation to the lung to see if one treatment is better. In this study, you will receive a single SBRT treatment OR 4 SBRT treatments over 4 days.

How many people will take part in the study?

About 88 people will take part in this study

What will happen if I take part in this research study?

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

If you are in Group 1 (often called "Arm 1"), you will receive one SBRT treatment of 34 Gy (Gy is a measure of radiation dosage).

If you are in Group 2 (often called “Arm 2”), you will receive 4 SBRT treatments, 1 each day for 4 consecutive days, for 48 Gy.

Before you begin the study (8/19/10)

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

- Physical examinations by several doctors
- Checking your weight
- Evaluation of your ability to carry out daily activities
- A CT (Computed Tomography) scan of your lungs and abdomen with contrast: 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.
- A PET (Positron Emission Tomography) scan of your body: A small amount of radioactive material is injected into your vein, and a scanner makes a detailed picture of areas inside your body
- Blood tests, including a blood test to find out how much oxygen is delivered to the tissues beyond your lung, if recommended by your doctor (about 1-2 teaspoons of your blood will be taken)
- Tests of your breathing and 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.

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

Before SBRT begins, you will have a treatment planning session. You will lie in a specific position, possibly within a frame device or on a large plastic bag filled with tiny foam balls similar to a bean bag. The purpose of the frame or bag is to hold your body as still as possible for planning and treatment. After you are positioned, 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. They may use a device to control the depth of your breathing or one to monitor the rate and pattern of your breathing so that they will be able to deliver the radiation to the tumor while accounting for the effect of breathing.

Radiation Treatment: Usually 7-10 days after the radiation planning session, you will return to the radiation medicine department for your radiation treatment. For your treatment, you will lie in the device that was used for your planning session. You will lie as still as possible and breathe normally while your radiation is delivered. It will take approximately one to two hours to deliver the radiation. During the process of radiation, participants can become claustrophobic. Medications can be given to make you feel more comfortable should this happen. Also, 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 during the treatment.

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

At 6 weeks after the SBRT:

- A physical examination
- Checking your weight
- Evaluation of your ability to carry out daily activities
- Blood tests
- A chest x-ray
- Evaluation of any side effects from treatment you may be having

At 12 weeks after the SBRT:

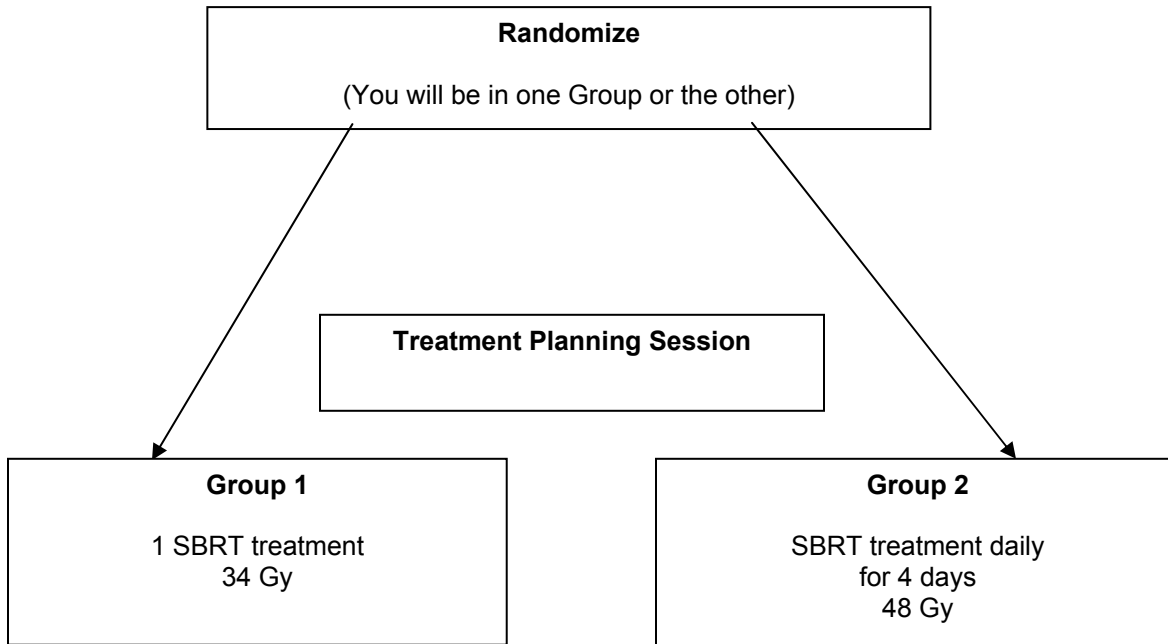
- A physical examination
- Checking your weight
- Evaluation of your ability to carry out daily activities
- Tests of your breathing and lung function
- A CT scan with contrast
- Blood tests
- Evaluation of any side effects from treatment you may be having
- If recommended by your doctor, a PET scan to find out the effect of SBRT on your tumor

Every 3 months in years 1-2, every 6 months in years 3-4 and then once a year: (8/19/10)

- A physical examination
- Checking your weight
- Evaluation of your ability to carry out daily activities
- Tests of your breathing and lung function every 6 months for 5 years
- Beginning at 6 months in year 1, a chest x-ray; in the next follow-up visit (at 12 months), a CT scan with contrast: Your doctor will continue to alternate these studies in follow-up visits.
- If recommended by your doctor, a PET scan at 1 year from SBRT to find out the effect of SBRT on your tumor
- Blood tests
- Evaluation of any side effects from treatment you may be having

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 either 1 SBRT treatment or 4 SBRT treatments in 4 days. After your treatment is completed, you will be seen in follow-up visits with your doctor at 6 and 12 weeks after SBRT, every 3 months in years 1-2, every 6 months in years 3-4 and 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 you stop taking the SBRT. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

Risks and side effects related to the SBRT

Likely

- Damage to surrounding normal lung and/or collapse of a portion of treated lung
- Changes in the lungs as the tumor shrinks; these changes will be recognized by your radiation doctor on your x-rays or scans as expected "scarring" that is developing. In most patients, no noticeable symptoms will result from this lung damage.
- Fatigue
- Redness or irritation of the skin in the treatment
- Hair loss in the treatment area (chest hair)
- Some soreness of the ribs with an increased risk of rib fracture. Treatment for such symptoms usually consists of rest, heat, and pain medication.

Less Likely

- Cough
- Increased phlegm production
- Difficulty breathing
- Fever

Rare but Serious.

- Some patients can have the following symptoms associated with lung scarring: shortness of breath, cough, fever, and/or pain in the chest wall. These patients may require oxygen for a short time or permanently. Lung damage can be life threatening.
- Damage to the lining of the heart, which can cause fluid accumulation around the heart and chest pain, shortness of breath, and/or irregular or rapid heart beat
- Damage to the heart muscle, which can cause heart attack, heart failure, or death
- Damage to the spinal cord, which can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs
- Damage to the esophagus, which can cause problems with swallowing

- Damage to the large blood vessels surrounding the heart, which could cause coughing up of blood and possibly death
- Severe pain or skin damage leading to an open wound

During the process of treatment planning and radiation, you will lie in a specific position, possibly within a frame device, and some patients can become claustrophobic. Medications can be given to make you feel more comfortable should this happen. Also, 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 during the treatment.

Reproductive risks

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

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

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

Are there benefits to taking part in the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Different approaches and timeframes of delivering SBRT may work better at killing cancer cells with fewer side effects, but this benefit is not guaranteed. We hope the information learned from this study will benefit other patients with early stage lung cancer in the future.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Standard radiation therapy
- Taking part in another study
- Getting no treatment except for medicine to make you feel better

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

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

Who can answer my questions about the study?

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

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

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

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

You can say “yes” or “no” to [each of] the following study[ies]. Below, please mark your choice [for each study].

Consent Form for Use of Tissue for Research

About Using Tissue and Blood for Research (11/1/12)

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

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

In addition to the tumor tissue, we would like to collect some blood for research. You will be asked to provide about 4 teaspoons of blood at each of the following time points: before SBRT and at 6 weeks after SBRT, at the same time you are having other tests required in the main part of this study.

Your tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue 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 and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

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

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

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 and blood is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records. Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new treatments for cancer in the future.

Benefits

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

Risks

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

Making Your Choice

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

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

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
 - Tissue 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
 - 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? (11/1/12)

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

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

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

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

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

Signature

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

Participant _____

Date _____

APPENDIX II

STUDY PARAMETER TABLE (8/19/10)
***See Section 11.1 for details and exceptions**

Assessments	Pretreatment Timeframes are in weeks prior to registration	During SBRT	6 wks post- SBRT	12 wks post- SBRT	Every 3 mos. for 2 years; every 6 mos. for 2 years; then annually
Histologic confirmation (biopsy or cytology)	X				
History/physical	Within 4 weeks	X	X	X	X
Performance status and weight	Within 4 weeks	X	X	X	X
Thoracic clinician eval	Within 8 weeks	X			
Chest x-ray			X*		X*
CT scan with contrast	Within 8 weeks			X*	X*
FDG PET	Within 8 weeks			X*	At 1 year*
PFTs*	Within 8 weeks			X	Every 6 mos. for 5 yrs.
CBC w/ diff & ANC	Within 2 weeks		X	X	X
Serum pregnancy test (if applicable)	Within 72 hours				
Tumor response eval				X	X
Adverse event eval		X	X	X	X
Tissue for banking and blood for translational research (if patient consents)	X		X		

APPENDIX III

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

Staging System

TUMOR (T)

The primary tumor (T) is classified according to the following categories:

- TX: Tumor cannot be evaluated or tumor is proven by the presence of cancer cells in the sputum or bronchial washings, but it cannot be seen during imaging or bronchoscopy ("occult" tumor)
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 3 centimeters (< 3 cm) or less in greatest dimension, surrounded by lung or pleura, and not located in the main stem bronchus
- T2: Tumor more than 3 centimeters (> 3 cm) in greatest dimension, or tumor involving the main stem bronchus, 2 cm or more from the carina, or tumor invading the visceral pleura, or tumor with incomplete lung expansion or obstructive lung infection that does not involve the entire lung
- T3: Tumor of any size that directly invades the chest wall, diaphragm, pleura, or pericardium, or tumor that involves the main stem bronchus less than 2 centimeters (< 2 cm) from the carina (ridge between the right and left main stem bronchi), or tumor that is associated with complete lung collapse or obstructive lung infection involving the entire lung.
- T4: Tumor of any size that invades the heart, great vessels (aorta, superior or inferior vena cava, pulmonary artery, or pulmonary vein), trachea, esophagus, vertebral body, or carina, or separate tumor nodules in the same lung lobe, or tumor associated with a malignant pleural effusion.

NODES (N)

The regional lymph nodes (N) are clinically divided into the following categories:

- NX:** Regional lymph nodes cannot be assessed
- NO:** Regional lymph nodes contain no metastases
- N1:** Metastasis to same-side peribronchial (around the bronchi) and/or hilar (pit in the lungs where vessels enter and exit) lymph nodes and nodes within the lungs that are involved by direct spread of the primary tumor
- N2:** Metastasis to same-side mediastinal and/or subcarinal (under the carina, or tracheal ridge) lymph nodes.
- N3:** Metastasis to opposite-side mediastinal or hilar nodes or to same- or opposite-side scalene (neck/upper rib) or supraclavicular (above collarbone) lymph nodes.

METASTASIS (M)

The state of metastasis (M) is defined as follows:

- MX:** Distant metastases cannot be assessed
- M0:** No distant metastases are found
- M1:** Distant metastases are present (this also includes separate tumor nodules in a different lobe of lung on either side).

Staging

Stage Ia: T1, N0, M0

Stage Ib: T2, N0, M0

Stage IIa: N1, M0

Stage IIb: T2, N1, M0 or T3, N0, M0

Stage IIIa: T1-2, N2, M0 or T3, N1-2, M0

Stage IIIb: T(any), N3, M0 or T4, N(any), M0

Stage IV: T(any), N(any), M1

APPENDIX V

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Ten (10) 1ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

Serum (if requested):

- ❑ Using four (4) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, 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 3000g at 4° Celsius for 30 minutes.
3. Aliquot a minimum of 0.5 ml serum (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and store serum at –80° Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested):

- ❑ Using three (3) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

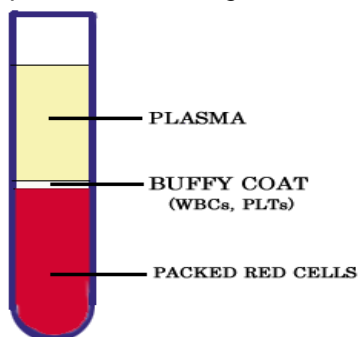
Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
4. Carefully pipette and aliquot a minimum of 0.5ml plasma (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and store plasma –80° Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat (if requested):

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



- ❑ Using one (1) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

APPENDIX V (Continued)

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 30 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into cryovials labeled “buffy coat” (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and time point collected.
5. Place cryovials into biohazard bag and store buffy coat samples frozen (-80° Celsius) until ready to ship. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:

- Include all RTOG paperwork in pocket of biohazard bag.
- Ship specimens overnight Monday-Wednesday. Avoid shipping on a weekend or around a holiday.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*

Ship: Specimens and all paper work as follows: (11/1/12)

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

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

U.S. Postal Service Address: For all non-urgent, ambient specimens-FFPEs, slides, blocks

**RTOG Biospecimen Resource
University of California San Francisco
UCSF Box 1800
(2340 Sutter St., Room S341)
San Francisco, CA 94143-1800**

For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu

APPENDIX VI (9/3/09)

INSTRUCTIONS FOR NCCTG INSTITUTIONS

Section 5.0 - RANDOMIZATION PROCEDURES

5.2 Pre-Registration Requirements for SBRT Treatment Approach: See page 11, Section 5.2

5.3 Registration Requirements

IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to CTSU is necessary until RTOG terminates the study (RTOG will include NCCTG Headquarters on the termination broadcast.)

NCCTG institutions must fax (507-284-0885) a completed eligibility checklist to the NCCTG Registration Office between 8 a.m. and 3:30 p.m. Central Standard Time, Monday through Friday to register a patient.

At the time of registration/randomization, Registration Office personnel will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)

Upon confirmation of eligibility, the NCCTG Registration Office will contact the RTOG Headquarters to register the patient. The NCCTG Registration Office will then contact the registering institution with the treatment assignment.

All investigators must be registered with CTEP, DCTD by the annual submission of the FDA Form 1572 and a current CV. To obtain an NCI/CTEP investigator number, investigators should complete and submit (by US Mail or Express Courier...faxes are not acceptable) an FDA Form 1572, with an original signature, and a current curriculum vitae to the PMB at:

Pharmaceutical Management Branch, CTEP, DCTD, NCI
6130 Executive Boulevard, Room 7149
Rockville, MD 20852
Phone: 301-496-5725

A copy of this submission should be sent to the NCCTG Operations Office.

The FDA Form 1572, with instructions, is available on the NCI home page (<http://ctep.info.nih.gov>) or by calling the PMB at 301-496-5725.

Section 6.10 ADVERSE EVENT REPORTING REQUIREMENTS

Follow the guidelines as stated in the protocol.

(Continued on next page)

APPENDIX VI (Continued)

INSTRUCTIONS FOR NCCTG INSTITUTIONS

Section 10.0 TISSUE/SPECIMEN SUBMISSION

Follow the guidelines as stated in the protocol. RTOG will reimburse NCCTG institutions for submission of specimens as specified in the protocol.

Section 12.0 DATA COLLECTION

NCCTG institutions will access the case report forms for the study on the RTOG web site, www.rtog.org (no password required; access "0915 Forms" next to the protocol). Institutions must **mail** the completed paper forms at the timeframes required in Section 12.1 of the protocol to:

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

All forms must have a label attached to each page. NCCTG institutions can access a label template on the RTOG web site, www.rtog.org (no password required; access "Member Info", then "RA Corner". Item #8 is the label template.)

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.

Data queries:

RTOG will send requests for additional information or clarification of data to NCCTG Headquarters for distribution to the individual institution. NCCTG institutions will **mail** responses to RTOG queries directly to:

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

Periodically (generally 3 times per year), RTOG prepares computer generated lists identifying delinquent material. These reminders requesting response to queries will be sent to NCCTG Headquarters for distribution to individual institutions.

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

Follow the guidelines as stated in the protocol.