Title: Feasibility study of the utility of pulmonary dynamic contrast enhanced MRI for assessment of tumor response and lung injury and for treatment planning for stereotactic body radiation therapy for early stage Non-small Cell Lung Cancer

NCT Number: NCT01799135

IRB Approval Date: 03/28/2021

Title: A Feasibility Study of the Utility of Pulmonary Dynamic Contrast Enhanced MRI for Assessment of Tumor Response and Lung Injury and for Treatment Planning for Stereotactic Body Radiation Therapy for Early Stage Non-small Cell Lung Cancer

NCI Protocol #: N/A

Local Protocol #: 12-004

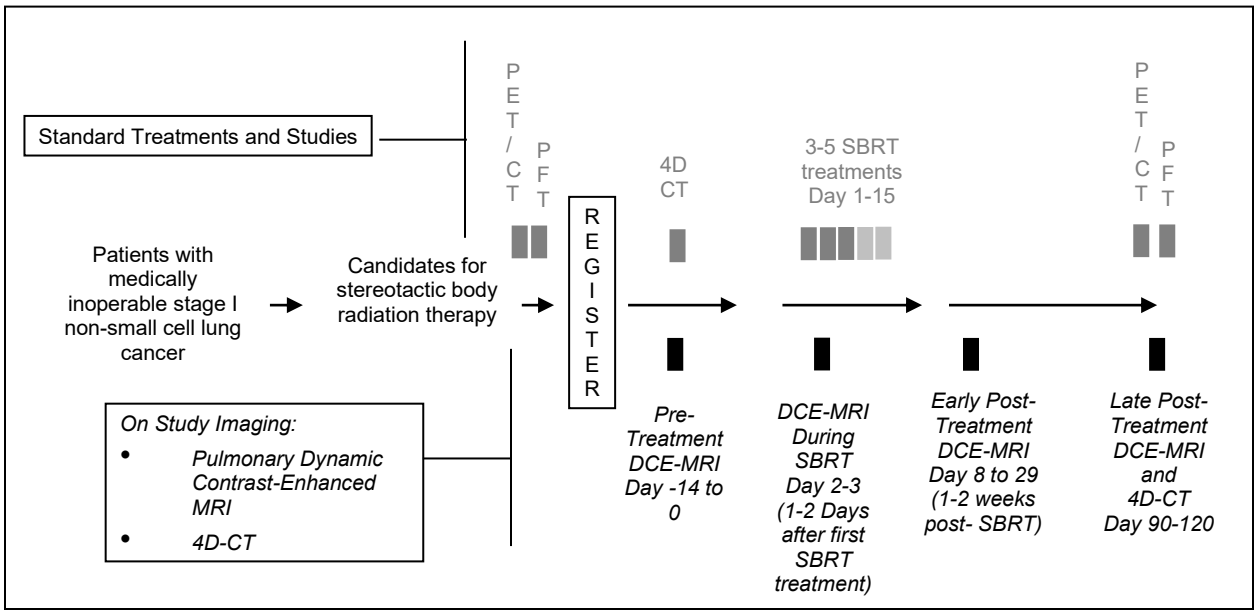
Principal Investigator: Raymond H. Mak, M.D.

Study Statistician: [redacted]

Version Date: 1/6/2015

Index

SCHEMA



DCE-MRI: Pulmonary dynamic contrast-enhanced magnetic resonance imaging
PET-CT: Positron emission tomography
PFT: Pulmonary function test
4D-CT: 4-dimensional computed tomography

1. INTRODUCTION

1.1 Study Disease

The standard of care for treatment of early-stage non-small cell lung cancer is surgical resection. However, many patients with this disease have other medical co-morbidities, which may preclude them from undergoing a surgical procedure. Historically, patients with medically inoperable stage I non-small cell lung cancer (*i.e.,* patients who are not surgical candidates due to medical co-morbidities) have been treated with conventionally fractionated radiation therapy, which typically entails treatment with 30 to 35 small doses of radiation given in 2- to 2.5-Gray (Gy) fractions daily over 6 to 8 weeks. Outcomes with this approach have been poor, with local control rates of less than 50% and overall survival of less than 10 to 15% (Dosoretz et al. 1993; Sibley et al. 1998).

Recent advances in image-guided radiation therapy have allowed the safe delivery of hypofractionated radiation therapy (fewer fractions of treatment with a higher dose per fraction). In theory, the use of high doses per fraction may overcome radioresistance and reduce the influence of tumor repopulation (Hall and Giaccia 2006). This technique of using high doses of highly precise, image-guided radiotherapy in only a few fractions of radiotherapy is called stereotactic body radiotherapy (SBRT). SBRT provides patients with medically inoperable lung tumors a promising new treatment, and surgical candidates with a less invasive alternative. Several single-institution series (Onishi, Araki et al. 2004; Grills, Mangona et al. 2011) and phase II studies (Timmerman et al. 2006; Baumann et al. 2009; Fakiris et al. 2009; Timmerman et al. 2010), including a multi-institutional Radiation Therapy Oncology Group (RTOG) study, have demonstrated high local control rates of greater than 80-90% with this approach, and a low risk of severe toxicity (<10%) when patients are appropriately selected.

1.2 Rationale

Perfusion-Based Imaging to Assess Tumor Response
Since SBRT is a novel treatment for early stage lung cancer, predictors of response to treatment and tumor control have not been clearly identified. Radiological evaluation of changes in lung tumor perfusion after the high-dose radiation therapy delivered by SBRT may provide a novel, early predictor of response to treatment. Magnetic resonance imaging (MRI) provides high resolution imaging, and dynamic contrast-enhanced MRI (DCE-MRI) utilizes intravenous gadolinium contrast to evaluate differential enhancement of tumors compared with normal tissue (Tofts et al. 1999; Brasch et al. 2000). Because tumors have increased angiogenesis and vascular permeability, DCE-MRI can be used to distinguish between tumor and normal tissue by assessment of the pharmacokinetic properties of contrast agent uptake in tissues as changes of signal intensity over time, referred to as time–intensity curves. Pharmacokinetic parameters, including the volume transfer constant (K_{trans}; permeability surface area product per unit volume of tissue), the fractional volume of extravascular extracellular space per volume of tissue (v_e), and the rate constant (k_{ep};

efflux rate from extravascular extracellular space back to plasma), can be estimated by fitting a pharmacokinetic model to the actual time–intensity curves obtained from the DCE-MRI.

DCE-MRI has been utilized to provide high resolution spatial imaging of the extent of soft-tissue tumors such as prostate adenocarcinomas (Cheikh, Girouin et al. 2009), and to monitor changes in tumor perfusion in response to therapy (Low, Fuller et al. 2011). Work conducted at Brigham and Women's Hospital has demonstrated that DCE-MRI can be utilized to assess perfusion in pulmonary nodules, with the addition of motion correction to pharmacokinetic measurements (Tokuda et al. 2011).

DCE-MRI is currently under active study as a potential imaging tool for response assessment after SBRT. A preliminary study using DCE-MRI to assess changes in tumor perfusion after SBRT has been conducted for prostate cancer, and demonstrated decreases in prostate tumor perfusion as early as 2 months after treatment (Low, Fuller et al. 2011). This study demonstrated a 40% decrease in average tumor perfusion (measured by K_{tran}) at 2 months, 75% decrease at 6 months, 82% decrease at 12 months and 87% decrease at 24 months after SBRT. A small series from Cai et al demonstrated that lung tumor perfusion changes after SBRT can be assessed by pulmonary DCE-MRI (Cai, Sheng et al. 2007). Thus, further exploration of this imaging technology in conjunction with SBRT is of great interest.

SBRT Toxicity

Since SBRT is a new technology and novel method of radiation therapy delivery, the long-term toxicity of its use for lung cancers remains to be seen, and the pathophysiology of radiation-induced injury at such high doses is not fully characterized. Of particular concern is the potential development of long-term pulmonary toxicity, which may manifest as radiation pneumonitis or more subacute gradual worsening of dyspnea, hypoxia, and/or decline in pulmonary function test metrics. This spectrum of potentially radiation-related lung injury was observed at a moderate to severe grade (Grade 3-4) in 16% of patients in the phase II RTOG 0236 study (Timmerman, Paulus et al. 2010).

Since the majority of patients receiving SBRT for early stage lung cancer in the United States have significant co-morbidities and/or compromised pulmonary function from underlying lung disease such as chronic obstructive pulmonary disease (COPD), minimizing radiation-induced lung injury is of paramount importance. Prior studies have established the importance of maintaining tight constraints on the volume of lung receiving low to moderate doses of radiation (5 Gy to 20 Gy) to minimize the risk of radiation pneumonitis with both conventionally fractionated radiation therapy (Kwa, Lebesque et al. 1998; Graham, Purdy et al. 1999; Hernando, Marks et al. 2001; Wang, Liao et al. 2006) and SBRT (Barriger et al. 2010; Ong et al. 2010). However, theses studies did not distinguish whether the volumes of lung receiving these doses of radiation were functional or not.

Incorporating Functional Lung Imaging into SBRT Treatment Planning

It would be of great interest to utilize functional imaging to guide SBRT treatment planning and to assess treatment response and potential toxicity. Prior studies have attempted to incorporate functional imaging into conventional radiation therapy planning. For instance, studies have demonstrated that functional information from perfusion single positron emission computed tomography (SPECT) can be used to plan radiation therapy (Christian, Partridge et al. 2005; Lavrenkov, Christian et al. 2007; Lavrenkov, Singh et al. 2009) and used to quantify radiation-induced lung injury (Marks, Spencer et al. 1993; Abratt and Willcox 1995; Boersma, Damen et al. 1995; Seppenwoolde, De Jaeger et al. 2004). Furthermore, ventilation/perfusion (V/Q) SPECT has been shown in one study to provide additional useful information for treatment planning beyond perfusion-SPECT (Yuan, Frey et al. 2011). While these nuclear medicine approaches are of interest, they require radioactive tracers that may expose patients to additional radiation, and have inherent limitations in image resolution.

Other groups have studied the role of hyperpolarized helium (He) magnetic resonance imaging (MRI) as a means of incorporating functional imaging into radiation therapy planning. Ireland et al demonstrated in 6 patients that fusion of He-MRI images with planning CT is feasible (Ireland, Bragg et al. 2007; Ireland, Woodhouse et al. 2008), and subsequently demonstrated that incorporating He-MRI images into radiation planning allowed for sparing of functional lung (Bates, Bragg et al. 2009). Cai et al applied this functional imaging technology for SBRT planning using tomotherapy, and demonstrated potential modest sparing of functional lung (Cai, McLawhorn et al. 2011).

In our department, Allen et al studied the role of He-MRI both before and after RT in individuals with locally advanced non-small cell lung cancer, and demonstrated that CT and PET target volumes correlated well, but had poor correlation with He-MRI target volumes defined based on ventilation defects (Allen, Albert et al. 2011). These findings may be related to the decreased spatial resolution seen with He-MRI, and may be one of the key limitations in adapting this modality for radiation treatment planning and assessment of response.

Recently, studies have been published on the potential use of 4D-CT to define regions of functional lung base on voxelized ventilation maps (Guerrero, Sanders et al. 2006; Castillo, Castillo et al. 2010; Nyeng, Kallehauge et al. 2011; Yamamoto, Kabus et al. 2011; Yamamoto, Kabus et al. 2011). These techniques perform deformable image registration between phases of 4D-CT images, and use the density or volume changes as a surrogate for ventilation. Such a technique would be appealing for SBRT because 4D-CT scans are routinely acquired for treatment planning, and no additional imaging studies would be required. However, the physiological accuracy of these novel methods has not yet been thoroughly validated in patient data (Yamamoto, Kabus et al. 2011; Yamamoto, Kabus et al. 2011). Also, the method can only be used to determine lung ventilation, and does not include critical information about perfusion.

Functional Lung Imaging and Radiation-Induced Lung Injury

Another potential application of functional lung imaging includes assessment of radiation-induced lung injury. Preliminary studies by Ireland et al demonstrated that

He-MRI findings can be correlated with CT-based emphysematous changes and also with areas of potential radiation pneumonitis seen on CT (Ireland, Din et al. 2010). Ward et al demonstrated in rat models that after high dose radiation (5 x 8 Gy), He-MRI correlated well with radiation-induced fibrosis (Ward et al. 2004).

Advantages of Perfusion-Based Functional Lung Imaging
Perfusion-based MRI scans have the potential advantages of assessing early tumor response to radiation therapy via changes in tumor perfusion after treatment, higher spatial resolution, improved registration, and patient convenience (routine scan that does not require gas inhalation). Furthermore, these studies may allow assessment of tumor motion while still allowing identification of areas of functional lung, which may allow improved SBRT planning.

Study Rationale
To our knowledge, pulmonary DCE-MRI has not been systematically studied as both an early predictor of tumor response and lung injury and as a SBRT treatment planning tool.

Thus, in this pilot study, we propose to explore the feasibility of pulmonary DCE-MRI in 1) assessing tumor response during and after SBRT treatment; 2) characterizing regions of radiation-induced lung injury after SBRT treatment, and correlating these regions of injury with ventilation changes found on 4D-CT; and 3) identifying regions of functional lung for SBRT treatment planning.

2. OBJECTIVES

2.1 Primary Objective

To determine the feasibility of utilizing pulmonary DCE-MRI to assess for changes in tumor perfusion during SBRT (1-2 days after the first treatment) and post-treatment (at 1-2 weeks and at 3-4 months after SBRT treatment) for stage I NSCLC

2.2 Secondary Objective(s)

2.2.1 To evaluate the feasibility of pulmonary DCE-MRI in characterizing acute and subacute (3 months) radiation-induced lung injury after SBRT, and correlate these findings with clinical outcomes

2.2.2 To evaluate the feasibility of integrating 4D-CT ventilation imaging with DCE-MRI perfusion imaging in characterizing subacute (3 months) radiation-induced lung injury after SBRT

2.2.3 To determine the feasibility of using pulmonary DCE-MRI to identify regions of functional lung for SBRT treatment planning

3. PARTICIPANT SELECTION

3.1 Conditions for Participant Eligibility

3.1.1 Participants should preferably have histologically confirmed non-small cell lung cancer, but patients with a clinical and radiographic diagnosis of non-small cell lung cancer who are candidates for stereotactic body radiation therapy may also be eligible.

3.1.2 The tumor must be $\geq$ 1 cm and $\leq$ 6 cm

3.1.3 Participants must have no evidence of nodal involvement (N0) or distant metastases (M0) on staging studies, which may include positron emission tomography (PET), computed tomography (CT), and/or mediastinoscopy.

3.1.4 Participants must be age 18 years or older

3.1.5 ECOG performance status $\leq$2 (see Appendix A)

3.1.6 Participants must be evaluated by radiation oncology and deemed to be a candidate for stereotactic body radiation therapy for NSCLC.

3.1.7 Ability to lie still during DCE-MRI which may last for up to 60 minutes

3.1.8 Adequate renal function to tolerate intravenous gadolinium contrast injection (estimated glomerular filtration rate $\geq$ 45 mL/min/1.73 m^2 prior to initial DCE-MRI and estimated glomerular filtration rate $\geq$ 30 mL/min/1.73 m^2 for subsequent DCE-MRI scans).

3.1.9 Ability to understand and the willingness to sign a written informed consent document

3.2 Conditions for Participant Ineligibility

3.2.1 Primary tumor size > 6 cm

3.2.2 Prior thoracic radiotherapy directed to the ipsilateral lung or prior surgical wedge resection in the involved lobe

3.2.3 An implanted pacemaker or cardiac defibrillator

3.2.4 Contraindications to receiving intravenous gadolinium contrast injection including prior allergic reaction and/or chronic renal insufficiency (estimated glomerular filtration rate < 45 mL/min/1.73 m^2 prior to initial DCE-MRI and estimated glomerular filtration rate < 30 mL/min/1.73 m^2 for subsequent DCE-MRI scans).

3.2.5 Any contraindication to undergoing MRI (e.g., pacemakers, cochlear implants, shrapnel injuries, or other types of metal or electric devices in the body, severe claustrophobia, cataract surgery with certain ocular implants—see below)

3.2.5.1 The following ocular implant models from Bausch & Lomb are considered unsafe for MRI: Intraocular Lens, Models 12A, 12P, 12S, 24P, 31P, 42P, 61P, 71, 71B, 71M, 71P, 71PC, 71R, 75M, 75P, EXP D

3.2.6 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.7 Pregnant women are excluded from this study because radiotherapy has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with radiotherapy, breastfeeding should be discontinued if the mother is treated with radiotherapy. These potential risks may also apply to other agents used in this study.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Women, minorities and other underrepresented populations are all at risk to develop non-small cell lung cancer, with smoking as the critical risk factor for the disease. Socioeconomically-deprived populations tend to have higher rates of smoking, and therefore it is possible this study will be more likely to enroll these individuals. However, the proposed MRI studies and the standard SBRT treatment will not have a differential effect on these populations. The eligibility criteria should not substantially differentially affect their enrollment in the trial, although some minority populations are more likely to have renal failure, which may preclude them from the trial.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Screening and Non-Study Pretreatment Evaluations

This visit will be performed within 4 weeks prior to the initiation of the stereotactic body radiation therapy. Potential participants will be evaluated for their performance status, and interviewed for their medical history and concomitant medications, followed by a physical examination. Vital signs (oral body temperature, heart rate and blood pressure) will be measured. Baseline blood tests will be performed. In addition, a blood pregnancy test will be performed for females of child-bearing potential.

Eligibility in the context of the study inclusion and exclusion criteria will be evaluated by the investigator. Potential participants will be asked to sign the informed consent and will be assigned a participant study number in a sequential order. If participants do not have a FDG PET/CT scan within 10 weeks and a pulmonary function test within 6

months prior to the scheduled date of initiation of SBRT, they will undergo a repeat FDG PET/CT and/or pulmonary function test at the study site, as part of standard of care procedures.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

6. STUDY DESIGN

6.1 Design/Study Type

This study is a non-randomized single-arm prospective study evaluating the feasibility of utilizing pulmonary DCE-MRI to assess for treatment response during and after SBRT and to guide SBRT treatment planning. The primary objective of this study is to test the feasibility of using pulmonary DCE-MRI scans to assess for changes in tumor perfusion during treatment (1-2 days after the first SBRT fraction) and after SBRT treatment (at 1-2 weeks and 3 months after SBRT) for early stage NSCLC. The study will have a two-stage design with a preliminary assessment of feasibility after enrollment of 7 eligible participants (see Section 15.1, Statistical Considerations). If the feasibility criteria are met, a total of 20 eligible participants will be enrolled.

Secondary objectives include determining the feasibility of 1) using pulmonary DCE-MRI to assess for lung injury 3 months after SBRT; 2) correlating ventilation changes

as measured by 4D-CT with the perfusion changes measured with DCE-MRI at 3 months after SBRT; and 3) incorporating pulmonary DCE-MRI into SBRT treatment planning.

The radiation therapy itself, which will be delivered using SBRT techniques, is not investigational and will be delivered per the standard of care. While one of the secondary study objectives is to determine the feasibility of incorporating pulmonary DCE-MRI into SBRT treatment planning, participants on this pilot study will **NOT** have their SBRT treatment planning influenced or guided by the results of the pretreatment pulmonary DCE-MRI, and will be treated per the standard of care, which includes utilizing free-breath contrast-enhanced CT, 4D-CT and PET/CT for treatment planning.

The research specific pulmonary DCE-MRI and post-treatment 4D-CT scans will be paid for by the study. The patient and/or insurance company will be responsible for the visits, work-up (e.g. PET-CT and PFTs), SBRT treatment planning (including planning 4D-CT), treatment delivery, and post-treatment surveillance studies (e.g. PET-CT and PFTs) performed as part of the patient's standard clinical care, and not for research purposes.

7. STUDY IMAGING PROCEDURES

7.1 Sequence of Imaging and Standard SBRT Work-up and Treatment

	Pre-Registration	Day -14 to 0	Day 1-15	Day 8-29 (1-2 wks post SBRT)	Day 90-120
Study DCE-MRI		x	x	x	x
MRI Screening	x		x	x	x
Study 4D-CT					x
Timing of Standard Treatments and Work-up					
SBRT Treatments			x		
PET-CT	x				x
PFT	x				x
Blood Tests	x		x	x	x
History	x			x	x
Physical Exam	x			x	x

7.2 Description of Pulmonary DCE-MRI Imaging

Participants will undergo pulmonary DCE-MRI at baseline before the stereotactic body radiation therapy, during treatment (1-2 days after the first SBRT fraction) and post-treatment (1-2 weeks and then 3-4 months). Pulmonary DCE-MRI scans will be performed per the standard protocol of the Brigham and Women's Hospital's Department of Radiology. MR images will be obtained following the intravenous bolus injection of 0.1 mM/kg of body weight of gadolinium at the rate of 3 milliliters (mL)/second, followed by 20 mL of saline at the rate of 3 mL/second. Each scan is approximately 60 minutes.

The devices and software that will be used for DCE-MRI have FDA (510K) approval and are commercially available.

Time to peak perfusion signal and enhancement ratio (defined as post- to pre-contrast perfusion signal) at the time of maximal parenchymal enhancement (TMPE) will be measured on each DCE-MRI scan. Pharmacokinetic parameters, including the volume transfer constant (K_{trans}), the fractional volume of extravascular extracellular space of the target tissue (v_e), and the rate constant (k_{ep}), will be estimated by fitting a pharmacokinetic model to the actual time–intensity curves obtained from the DCE-MRI.

We will adopt the generalized kinetic model (Tofts, Brix et al. 1999), which is described as follows

$$dC_t / dt = K^{trans} (C_p – C_t / v_e) = K^{trans}C_p – k_{ep} C_t$$

where C_t : tracer concentration in tissue, C_p : tracer concentration in arterial blood plasma, K^{trans} : transfer constant, v_e: extravascular extracellular space fraction volume, k_{ep}: rate constant.

The solution to the above mentioned equation with the initial condition that $C_p = C_t = 0$ at t=0, is

$$C_t (t) = K^{trans} \int C_p (\tau) \exp(–k_{ep}(t- \tau)) d\tau$$

The tissue response to a short arterial pulse of concentration = 1/ (pulse duration), i.e., a delta function, is

$$h(t) = K^{trans}\exp(-k_{ep} t)$$

Thus K^{trans} determines the amplitude of the initial response (the amount of tracer entering the extravascular extracellular space), and k_{ep} determines the washout rate from the extravascular extracellular space back into the blood plasma.

The mean residence time is then:

$$\tau = = \int_0 t\, h(t)dt \;/\; \int_0 h(t)dt$$

The response to a step change in arterial plasma concentration, from 0 to C_p, at time t=0, is

$$C_t(t) = K^{trans} C_{p0} / k_{ep} (1- \exp(-k_{ep} t)) = v_e C_{p0} (1- \exp(-k_{ep} t))$$

The response to a step change from C_{p0} to zero is

$$C_t(t) = K^{trans} C_{p0} / k_{ep} \exp(-k_{ep} t) = v_e C_{p0} \exp(-k_{ep} t)$$

During the analysis, intra-tumor heterogeneity will be corrected for using the recently published method of pixel-wise pharmacokinetic analysis for DCE-MRI of the lung, utilizing pixel-by pixel fitting (Tokuda, Mamata et al. 2011).

Pulmonary DCE MRI scans will be performed at the following time points:

7.2.1 Pre-treatment: The first pulmonary DCE-MRI will be performed within 2 weeks prior to the start of SBRT. Protocol DCE-MRI must begin within 4 weeks of registration.

7.2.2 During SBRT MRI: 1-2 days after the first SBRT treatment (Day 2-3)

7.2.3 Early post-SBRT MRI: 1-2 weeks after completion of SBRT

7.2.4 Late post-SBRT MRI: 3-4 months after completion of SBRT

7.3 DCE-MRI Adverse Events

As this study involves pulmonary DCE-MRI with gadolinium contrast, which is a FDA approved procedure, severe adverse reactions related to the study imaging would not be expected to occur. Any adverse events that do occur will be reported to the IRB and the patient's primary radiation oncologist. See Appendix C for Adverse Event Reporting Guidelines.

7.3.1 DCE-MRI Anticipated reactions

As a consequence of participation in the study, participants may experience frustration or anxiety related to time spent obtaining the additional study MRI scans. Participants would also be at risk of the typical reactions from MRI with gadolinium contrast administration:

Occasional (occurring in 2 or 3 out of 100 patients):

- Mild nausea (with or without vomiting), tingling sensation, headache, dizziness, coldness at the injection site, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching

Rare (occurring in 1 patient or less out of 100):

- Severe anaphylactic reaction

- Severe Nephrogenic Systemic Fibrosis (NSF) in patients with chronic renal insufficiency

7.4 Description of Study 4D-CT

4D-CT scanning will be performed per standard protocol in the Brigham and Women's Hospital's Department of Radiation Oncology. 4D-CT is an FDA-approved imaging technique in which a longer-duration CT scan is acquired that accounts for the breathing motion of the patient. In anatomic regions where motion is present (e.g., the lung), 4D-CT is better for determining the tumor volume (Keall, Starkschall et al. 2004) than conventional CT which is insensitive to periodic motion. Each scan is approximately 15 minutes in duration.

The devices and software that will be used for 4D-CT have FDA (510K) approval and are commercially available.

Participants receive an additional radiation dose of 30 mSv-50 mSv (Murphy et al. 2007) when subjected to a 4D-CT scan. This dose is equivalent to 5-8 times the annual radiation dose to the general public (National Council on Radiation Protection and Measurements., National Council on Radiation Protection and Measurements. Scientific Committee 6-2 on Radiation Exposure of the U.S. Population. et al. 2009) and is not associated with deterministic effects of radiation.

7.5 4D-CT Adverse Events and Anticipated Reactions

As a consequence of participation in the study, participants may experience frustration or anxiety related to time spent obtaining the additional study 4D-CT scan. Additional adverse events due to 4D-CT are extremely rare but potentially severe:

Extremely Rare (occurring in 1 patient or less out of 1000)

- Radiation-induced tumors

8. RADIATION THERAPY

8.1 Radiotherapy: Stereotactic Body Radiation Therapy (SBRT)

All SBRT treatment planning, plan evaluation and treatment delivery will be conducted per the standard of care, and there is no investigational aspect to the radiotherapy delivered to participants on this study. The following description is for guidance but the treating radiation oncologist may alter the plan if circumstances warrant after discussion with the Principal Investigator.

8.2 Dose Specifications: Stereotactic Body Radiation Therapy (SBRT)

8.2.1 Dose will be normalized such that 95% of the PTV receives the prescription dose as per normal treatment protocol. The minimum allowable dose within the PTV is >95% of the prescribed dose.

8.2.2 Patients shall receive prescription doses to the PTV (with the above constraints). All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below in Table 1. See Section 8.6 below for specifics regarding when to implement a dose reduction. The final prescription dose will be recorded on a patient-by-patient basis.

8.2.3 The treating radiation oncologist will use our standard risk-adapted SBRT treatment approach to select the prescription dose. If critical-structure dose constraints are met (see Table 1), then the standard dose prescription would be 54 Gray in 3 fractions. However, if dose constraints to critical organs such as the bronchial tree and chest wall cannot be met at this dose prescription, than the treating radiation oncologist may chose to deliver the treatment over 5 fractions with a dose of 10 to 12 Gray.

Table 1. Critical-Structure Dose Constraints

Constraints for 3 Fractions

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**
Spinal cord and medulla	<0.35 cc <1.2 cc	18 Gy (6 Gy/fx) 12.3 Gy (4.1 Gy/fx)	21.9 Gy (7.3 Gy/fx)
Spinal cord subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	18 Gy (6 Gy/fx)	21.9 Gy (7.3 Gy/fx)
Esophagus*	<5 cc	17.7 Gy (5.9 Gy/fx)	25.2 Gy (8.4 Gy/fx)
Brachial plexus	<3 cc	20.4 Gy (6.8 Gy/fx)	24 Gy (8 Gy/fx)
Heart/pericardium	<15 cc	24 Gy (8 Gy/fx)	30 Gy (10 Gy/fx)
Great vessels	<10 cc	39 Gy (13 Gy/fx)	45 Gy (15 Gy/fx)
Trachea and large bronchus*	<4 cc	15 Gy (5 Gy/fx)	30 Gy (10 Gy/fx)
Bronchus-smaller airways	<0.5 cc	18.9 Gy (6.3 Gy/fx)	23.1 Gy (7.7 Gy/fx)
Rib	<1 cc	28.8 Gy (9.6 Gy/fx)	36.9 Gy (12.3 Gy/fx)
Skin	<10 cc	30 Gy (10 Gy/fx)	33 Gy (11 Gy/fx)
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500 cc	10.5 Gy (3.5 Gy/fx)	
Lung (Right & Left)	1000 cc	11.4 Gy (3.8 Gy/fx)	
Liver	700 cc	17.1 Gy (5.7 Gy/fx)	

*Avoid circumferential irradiation

Constraints for 5 Fractions

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**
Spinal cord and medulla	<0.35 cc <1.2 cc	23 Gy (4.6 Gy/fx) 14.5 Gy (2.9 Gy/fx)	30 Gy (6 Gy/fx)
Spinal cord subvolume (5-	<10% of	23 Gy (4.6 Gy/fx)	30 Gy (6 Gy/fx)

6 mm above and below level treated per Ryu)	subvolume		
Esophagus*	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)
Brachial plexus	<3 cc	27 Gy (5.4 Gy/fx)	30.5 Gy (6.1 Gy/fx)
Heart/pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/fx)
Great vessels	<10 cc	47 Gy (9.4 Gy/fx)	53 Gy (10.6 Gy/fx)
Trachea and large bronchus*	<4 cc	16.5 Gy (3.3 Gy/fx)	40 Gy (8 Gy/fx)
Bronchus-smaller airways	<0.5 cc	21 Gy (4.2 Gy/fx)	33 Gy (6.6 Gy/fx)
Rib	<1 cc	35 Gy (7 Gy/fx)	43 Gy (8.6 Gy/fx)
Skin	<10 cc	36.5 Gy (7.3 Gy/fx)	39.5 Gy (7.9 Gy/fx)
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)	
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)	
Liver	700 cc	21 Gy (4.2 Gy/fx)	

*Avoid circumferential irradiation

Constraints for 3 or 5 Fractions

Serial Tissue	Dose-Volume Histogram Parameter	Constraint
Lung (Right & Left)	V20	<10%
Lung (Right & Left)	V10	<12%
Lung (Right & Left)	Mean lung dose	4 Gray
Chest wall	V30	< 30 cc

8.3 Technical Factors: Stereotactic Body Radiation Therapy (SBRT)

8.3.1 SBRT will be delivered with linear accelerators at energies ≥6 MV.

8.3.2 SBRT immobilization, simulation, planning, localization, and image-guidance will be utilized in all participants per standard clinical care as described below.

8.3.3 SBRT may be delivered using 3D-conformal or volumetric modulated arc therapy (VMAT) techniques per standard clinical care as described below.

8.4 SBRT Localization, Simulation, and Immobilization

Participants will be simulated using four-dimensional computed tomography (4DCT), which incorporates tumor motion into planning. The free-breathing scan will be performed with 2.5 mm slice thickness, and the use of contrast at the time of simulation is preferred if feasible, which is our departmental standard protocol for lung simulations. Patients will be simulated in the Elekta Stereotactic frame or similar stereotactic custom immobilization device for stabilization and setup reproducibility. Abdominal compression will be used if the tumor moves more than 1 cm with respiratory motion. Target volumes and normal critical structures will be defined in the

slices in which they are visualized. The 3D conformal cases must utilize "beam's eye view" representations to define final beam aperture.

8.5 Treatment Planning/Target Volumes

8.5.1 The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

8.5.1.1 The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT. The internal target volume (ITV) will include the GTV and the movement of the GTV as measured by 4D-CT.

8.5.1.2 The Planning Target Volume (PTV) will provide a margin around the ITV to compensate for the variability of treatment set up and internal organ motion. A margin of 5 mm around the ITV is required to define each respective PTV. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan.

8.5.1.3 The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

8.5.1.4 Normal Critical Structures to be defined on the treatment planning CT scan will include the following: All structures will be contoured in their entirety as solid organs. See the ITC web site (**http://atc.wustl.edu**) to view examples of target and normal tissue contours.

8.5.1.5 The PTV forms the entire target as described. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

8.6 Critical Structures

Critical-structure dose constraints shall remain consistent with Table 1 above. While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this. A dose reduction should be considered at the discretion of the treating radiation oncologist (for instance, in the case of an increase in critical-structure volume greater than 5% receiving more than the specified dose).

8.7 Treatment Verification

8.7.1 Per standard clinical treatment protocols, prior to each SBRT treatment, localization will include initial alignment to infrared markers attached to the stereotactic board. On-line target localization will then be performed first by using kV imaging with the ExacTrac system, and then by cone beam CT. The use of image guidance or daily target localization including the specific type implemented must be documented by the treating physician per normal clinical practice.

8.7.2 Management of Radiation Dose to the Patient from Daily Localization

According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy for BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from kV cone beam CT on Elekta Synergy machine are estimated to range from 1 to 3 cGy. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.006 to 0.6% to a daily dose of 18 Gy. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivers greater than 3 cGy/dy to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

8.8 Quality Assurance

8.8.1 Documentation Requirements

The institution will archive treatment prescription and verification images for later review as per standard practice.

8.9 Radiation Quality Assurance Reviews

Since there are no experimental components to radiation therapy on this study, SBRT treatment plans will be subject to standard peer-review and departmental quality assurance reviews per departmental standards. RT quality assurance reviews will be facilitated by the study chair.

8.10 Radiation Adverse Events

8.10.1 All participants will be seen at each SBRT treatment and 1 week after treatment by their treating radiation oncologist. Any observations with respect to the following symptoms/side effects will be recorded:

Immediate Reactions	Long Term Reactions
Common:	**Common:**
• Moderate tiredness • Moderate skin reddening & irritation • Mild to moderate cough • Mild to moderate trouble swallowing/sore throat • Mild decreased blood cell count • Mild temporary loss of hair in the treated area	• Mild scarring of the lung, not requiring treatment • Mild shortness of breath • Mild dryness of the skin in the area of treatment
Uncommon	**Uncommon**
• Moderate inflammation of the lung	• Moderate scarring or inflammation of the lung requiring treatment • Mild to moderate inflammation of the heart • Mild permanent darkening of the skin • Mild to moderate cough • Rib fracture causing moderate pain • Mild to moderate inflammation of the muscle of the chest wall
Rare:	**Rare:**
• Mild to moderate nausea	• Severe brachial plexus injury
Extremely Rare:	**Extremely Rare:**
	• Severe swallowing difficulties requiring surgery • Heart attack (severe) • Severe nerve damage • Severe spinal cord injury • Fatal inflammation or scarring of the lungs • Tumors caused by radiation

8.10.2 Clinical discretion may be used in managing radiotherapy-related side effects.

8.11 Radiation Adverse Event Reporting

See Appendix B for Adverse Event Reporting Guidelines.

9. DRUG THERAPY

N/A

10. SURGERY

N/A

11. OTHER THERAPIES

As per standard clinical care, participants that require pre-medication for anxiety or claustrophobia prior to MRI may be given lorazepam 0.5-1 mg by mouth (or equivalent medications) prior to the MRI at the discretion of the treating physician. As per standard clinical care, participants will be pre-medicated with a single dose of dexamethasone 4 milligrams by mouth the morning prior to each SBRT treatment. Participants may receive medications for management of potential expected adverse effects secondary to SBRT per standard clinical care.

12. TISSUE/SPECIMEN SUBMISSION

N/A

13. PATIENT ASSESSMENTS

13.1 Schedule of Patient Assessments

See Table of patient assessments in Section 7.1.

13.2 Study Pulmonary DCE-MRI

The participants will undergo a pulmonary DCE-MRI prior to SBRT, during SBRT (1-2 days after the first SBRT treatment) and then two post-treatment DCE-MRI scans, the first within 1-2 weeks after the final treatment and then 3-4 months after SBRT.

13.3 PET-CT and PFT

As part of the standard pre-treatment work-up, participants will undergo a baseline PET-CT and PFT, and then repeat studies 3-4 months after completion of the SBRT treatment. The PFTs will include forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) will be measured.

13.4 Blood Tests

Each participant will have a BUN and creatinine sent within three weeks of each of the four DCE-MRI scans to document eligibility to receive gadolinium contrast based on renal clearance per the eligibility criteria (Section 3.2.4). If the estimated glomeular filtration rate is < 30 mL/min/1.73 m^2 the participant will not receive gadolinium contrast and will not undergo the scheduled DCE-MRI at that time point and will be re-evaluated

with repeat BUN and creatinine at the next time point. A serum pregnancy test will be obtained in the baseline blood tests if the participant is a female of child-bearing age.

13.5 History and Physical Exam

For the baseline visit, a complete history and physical exam will be done to determine eligibility for the study. At subsequent visits, focused history and physical exams will be performed to assess for side effects of SBRT treatment as per standard care.

14. DATA COLLECTION

14.1 Data Reporting Methods

The QACT will collect, manage, and monitor data for this study. Note: All adverse events that have occurred on the study, including those reported through AdEERS, must be reported via CTMS or CDUS.

14.2 QACT Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 21 days of registration
Adverse Event Report Form	Within 14 days of completing last DCE-MRI scan
Off Study Form	Within 21 days of completing last DCE-MRI or being taken off study for any reason

14.3 Study Imaging Data Elements

Pulmonary DCE-MRI and 4D-CT data will be transferred electronically to the Hatabu and Lewis laboratories for analysis of tumor and lung parenchyma perfusion. Additionally, images will be imported into our departmental radiation treatment planning software for further analysis of the utility of the pulmonary DCE-MRI and 4D-CT data for SBRT treatment planning. Images will be identified only by a study ID number. The patient's identifying information (name, MR#, DOB) will be removed before the images are transferred.

Routine clinical data such as demographics, performance status, disease status and treatment characteristics will be obtained at baseline and at each subsequent clinic visit when a research scan is obtained. This clinical data is all collected as part of standard of care for follow-up visits. It does not contain any study-specific procedures or information. Thus, non co-investigator MDs or NPs may perform the exam and collect the data in standard consultation and follow-up notes. The standard of care studies

including PET-CT, PFTs, and pathology reports will be obtained from the electronic medical record.

Radiation treatment for this protocol is exactly the same as it would be if the participant were not enrolled on the protocol. Radiation treatment data such as dose, dose per fraction, number of fractions and dose-volume histogram data will be obtained from the radiation oncology electronic archives.

14.4 Timing of Collection of Data Elements

Scan data will be transferred to the cooperating labs for analysis within a month of the scan date. All other data will be transcribed from the clinical records within a month of the last protocol-related treatment/examination.

14.5 Data Storage and Protection

Non-image data will be maintained in a web-based REDCap database developed specifically for this study. The REDCap database is password-protected. The PI will grant permission for specific study staff to have access to the portion of data pertinent to their role on the study.

Imaging data will be securely transferred to the Hatabu and Lewis laboratories, where they will be stored in a password protected data archive housed behind the Partner's firewall. The MRI data to be transferred will be coded with the subject's study ID and not by name, to ensure confidentiality.

14.6 Data and Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet annually and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

The primary objective of this study is to determine the feasibility of utilizing pulmonary DCE-MRI to assess changes from baseline in tumor perfusion during SBRT treatment

(after 1 fraction of SBRT), and 1-2 weeks and 3-4 months after completion of SBRT treatment for stage I NSCLC. **Feasibility (success) is defined as successfully enrolling patients, processing the pulmonary DCE-MRI data, and observing an analyzable change in tumor perfusion between the pre-treatment DCE-MRI and any of the DCE-MRI scans during SBRT (after 1 fraction) or after completion of SBRT treatment. Analyzable change will be defined as a 20% change in tumor perfusion. A recent publication by Ng et al reported the rate of reproducibility of DCE-MRI parameters was between 10-20% (Ng, Raunig et al. 2010), and we have chosen the upper limit of this range to be conservative.**

A total of 20 participants with stage I NSCLC will be enrolled on this study, and a two-stage design will be used. Seven eligible participants in the first stage and 10 eligible participants in the second stage will be accrued. To allow for participants that are unable to complete scans and/or are ineligible to continue on the study, 3 additional participants will be accrued, so up to 8 participants in stage I and 12 participants in stage II will be accrued to this study. If at least 5 successes are observed among the 7 eligible participants in the first stage, up to an additional 12 participants (10 eligible) will be entered. If 14 or more successes are observed among the 17 eligible participants, utilizing pulmonary DCE-MRI to assess changes in tumor perfusion will be considered feasible for this group. With this design, there is a 90% probability of declaring the pilot study feasible if the true feasibility rate is 90%, and a 10% probability of declaring the DCE-MRI worthy of further study if the true feasibility rate is 65%. With 17 eligible participants, we have 90% power to detect a difference of 0.75 standard deviation in the change of tumor perfusion from baseline (prior to SBRT treatment) to post treatment (either right after SBRT treatment or 3-4 months after SBRT treatment) using a 0.1 level two-sided Wilcoxon signed-rank test.

After stage I accrual is met, the pulmonary DCE-MRI data will be reviewed. If the changes in tumor perfusion could only be observed in one or two of the scans during and after treatment compared to the pre-SBRT scan, patients enrolled in the 2nd stage won't be required to undergo all three during and after treatment pulmonary DCE-MRIs and only the time points with useful information will be obtained to save resources.

15.2 Sample Size/Accrual Rate

Twenty participants will be enrolled in this pilot study. We estimate that approximately 20 patients a year would meet the eligibility criteria for enrollment on this study. Assuming that one third of the eligible patients would consent to enrolling on the study, the accrual rate would be 6 patients per year and accrual will be complete within 3.5 years. After the last post-treatment DCE-MRI scan (3-4 months after treatment), participants will be off study, but will continue to undergo follow-up per standard care. Thus, the study will be complete after 4 years.

15.3 Stratification Factors

None

15.4 Analysis of Secondary Endpoints

Secondary endpoints include the feasibility of pulmonary DCE-MRI in characterizing acute and subacute radiation-induced lung injury after SBRT as well as the feasibility of using pulmonary DCE-MRI to identify regions of functional lung for SBRT treatment planning. The feasibility rates of these two endpoints will be calculated along with a 95% confidence interval based on the binomial distribution, and the confidence interval will be no wider than 50%.

15.4.1 To evaluate the feasibility of pulmonary DCE-MRI in characterizing acute (1-2 weeks) and subacute (3 months) radiation-induced lung injury after SBRT, and correlate these findings with clinical outcomes. **Feasibility (success) is defined as successfully enrolling patients, processing the pulmonary DCE-MRI data, and observing an analyzable change in lung perfusion on the 3-month scan.**

15.4.2 To evaluate the feasibility of integrating 4D-CT ventilation imaging with DCE-MRI perfusion imaging in characterizing subacute (3 months) radiation-induced lung injury after SBRT. **Feasibility (success) is defined as successfully enrolling patients, processing the pulmonary DCE-MRI and 4D-CT data, and observing an analyzable change on the 3-month scan.**

15.4.3 To determine the feasibility of using pulmonary DCE-MRI to identify regions of functional lung for planning SBRT for peripheral lung tumors. **Feasibility will be defined as the ability to perform a retrospective comparative treatment planning study using the DCE-MRI images acquired prior to treatment for each participant.** Regions of functional and non-functional lung will be defined on each MRI, and the images will be registered to the 4DCT used for treatment planning. The functional-lung contours will be transferred to the 4D-CT based on this registration. The target volume and other critical structures will be defined as per standard treatment protocol, as described in Section 6 of this document. In addition to the normal-tissue constraints outlined in Section 6, the treatment plan will attempt to maximize sparing of functional-lung regions while maintaining adequate target coverage and not exceeding other normal-tissue constraints. The functional-lung based treatment plans generated in this manner will be compared to the corresponding standard plans that were used to treat the patient. Changes in the functional-lung V20 and V5 will be used to analyze changes in functional-lung sparing.

15.5 Reporting and Exclusions

15.5.1 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first DCE MRI.

15.5.2 **Evaluation of primary endpoint.** All participants who undergo a pre-treatment DCE-MRI and at least one post-treatment DCE-MRI will be included in the study.

15.5.3 **Stopping Rules**. There is no experimental component to the radiation treatment or radiological imaging (both SBRT and the DCE-MRI are utilized in routine clinical care). However, the study will be stopped if preliminary study results determine that it is not feasible to utilize DCE-MRI to achieve any of the primary or secondary objectives including assessing tumor perfusion (primary objective) and lung injury or assisting SBRT treatment planning.

16. REGULATORY CONSIDERATIONS

16.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

16.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

16.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

16.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

16.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

17. PUBLICATION PLAN

We intend to publish the results of this study in a peer-reviewed journal, and the principal investigator will be responsible for publication of the study results. The preliminary results, which may be presented in an abstract at a professional meeting, will be made public within 24 months of the end of data collection. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

18. REFERENCES

Abratt, R. P. and P. A. Willcox (1995). "The effect of irradiation on lung function and perfusion in patients with lung cancer." Int J Radiat Oncol Biol Phys **31**(4): 915-919.

Allen, A. M., M. Albert, et al. (2011). "Can Hyperpolarized Helium MRI add to radiation planning and follow-up in lung cancer?" J Appl Clin Med Phys **12**(2): 3357.

Bates, E. L., C. M. Bragg, et al. (2009). "Functional image-based radiotherapy planning for non-small cell lung cancer: A simulation study." Radiother Oncol **93**(1): 32-36.

Boersma, L. J., E. M. Damen, et al. (1995). "Estimation of overall pulmonary function after irradiation using dose-effect relations for local functional injury." Radiother Oncol **36**(1): 15-23.

Cai, J., R. McLawhorn, et al. (2011). "Helical Tomotherapy Planning for Lung Cancer Based on Ventilation Magnetic Resonance Imaging." Med Dosim.

Cai, J., K. Sheng, et al. (2007). "Evaluation of Lung Tumor Response to Stereotactic Body Radiotherapy using Contrast Enhanced Perfusion MR." Int J Radiat Oncol Biol Phys **69**(3): S514-S515.

Castillo, R., E. Castillo, et al. (2010). "Ventilation from four-dimensional computed tomography: density versus Jacobian methods." Phys Med Biol **55**(16): 4661-4685.

Cheikh, A. B., N. Girouin, et al. (2009). "Evaluation of T2-weighted and dynamic contrast-enhanced MRI in localizing prostate cancer before repeat biopsy." Eur Radiol **19**(3): 770-778.

Christian, J. A., M. Partridge, et al. (2005). "The incorporation of SPECT functional lung imaging into inverse radiotherapy planning for non-small cell lung cancer." Radiother Oncol **77**(3): 271-277.

Graham, M. V., J. A. Purdy, et al. (1999). "Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC)." Int J Radiat Oncol Biol Phys **45**(2): 323-329.

Grills, I. S., V. S. Mangona, et al. (2011). "Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer." J Clin Oncol **28**(6): 928-935.

Guerrero, T., K. Sanders, et al. (2006). "Dynamic ventilation imaging from four-dimensional computed tomography." Phys Med Biol **51**(4): 777-791.

Hall, E. J. and A. J. Giaccia (2006). Radiobiology for the radiologist. Philadelphia, Lippincott Williams & Wilkins.

Hernando, M. L., L. B. Marks, et al. (2001). "Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer." Int J Radiat Oncol Biol Phys **51**(3): 650-659.

Ireland, R. H., C. M. Bragg, et al. (2007). "Feasibility of image registration and intensity-modulated radiotherapy planning with hyperpolarized helium-3 magnetic resonance imaging for non-small-cell lung cancer." Int J Radiat Oncol Biol Phys **68**(1): 273-281.

Ireland, R. H., O. S. Din, et al. (2010). "Detection of radiation-induced lung injury in non-small cell lung cancer patients using hyperpolarized helium-3 magnetic resonance imaging." Radiother Oncol **97**(2): 244-248.

Ireland, R. H., N. Woodhouse, et al. (2008). "An image acquisition and registration strategy for the fusion of hyperpolarized helium-3 MRI and x-ray CT images of the lung." Phys Med Biol **53**(21): 6055-6063.

Keall, P. J., G. Starkschall, et al. (2004). "Acquiring 4D thoracic CT scans using a multislice helical method." Phys Med Biol **49**(10): 2053-2067.

Kwa, S. L., J. V. Lebesque, et al. (1998). "Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients." Int J Radiat Oncol Biol Phys **42**(1): 1-9.

Lavrenkov, K., J. A. Christian, et al. (2007). "A potential to reduce pulmonary toxicity: the use of perfusion SPECT with IMRT for functional lung avoidance in radiotherapy of non-small cell lung cancer." Radiother Oncol **83**(2): 156-162.

Lavrenkov, K., S. Singh, et al. (2009). "Effective avoidance of a functional spect-perfused lung using intensity modulated radiotherapy (IMRT) for non-small cell lung cancer (NSCLC): an update of a planning study." Radiother Oncol **91**(3): 349-352.

Low, R. N., D. B. Fuller, et al. (2011). "Dynamic gadolinium-enhanced perfusion MRI of prostate cancer: assessment of response to hypofractionated robotic stereotactic body radiation therapy." AJR Am J Roentgenol **197**(4): 907-915.

Marks, L. B., D. P. Spencer, et al. (1993). "The utility of SPECT lung perfusion scans in minimizing and assessing the physiologic consequences of thoracic irradiation." Int J Radiat Oncol Biol Phys **26**(4): 659-668.

National Council on Radiation Protection and Measurements., National Council on Radiation Protection and Measurements. Scientific Committee 6-2 on Radiation Exposure of the U.S. Population., et al. (2009). Ionizing radiation exposure of the population of the United States. Bethesda, Md., National Council on Radiation Protection and Measurements.

Ng, C. S., D. L. Raunig, et al. (2010). "Reproducibility of perfusion parameters in dynamic contrast-enhanced MRI of lung and liver tumors: effect on estimates of patient sample size in clinical trials and on individual patient responses." AJR Am J Roentgenol **194**(2): W134-140.

Nyeng, T. B., J. F. Kallehauge, et al. (2011). "Clinical validation of a 4D-CT based method for lung ventilation measurement in phantoms and patients." Acta Oncol **50**(6): 897-907.

Onishi, H., T. Araki, et al. (2004). "Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study." Cancer **101**(7): 1623-1631.

Seppenwoolde, Y., K. De Jaeger, et al. (2004). "Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer." Int J Radiat Oncol Biol Phys **60**(3): 748-758.

Timmerman, R., R. Paulus, et al. (2010). "Stereotactic body radiation therapy for inoperable early stage lung cancer." Jama **303**(11): 1070-1076.

Tofts, P. S., G. Brix, et al. (1999). "Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols." J Magn Reson Imaging **10**(3): 223-232.

Tokuda, J., H. Mamata, et al. (2011). "Impact of nonrigid motion correction technique on pixel-wise pharmacokinetic analysis of free-breathing pulmonary dynamic contrast-enhanced MR imaging." J Magn Reson Imaging **33**(4): 968-973.

Wang, S., Z. Liao, et al. (2006). "Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT)." Int J Radiat Oncol Biol Phys **66**(5): 1399-1407.

Yamamoto, T., S. Kabus, et al. (2011). "Investigation of four-dimensional computed tomography-based pulmonary ventilation imaging in patients with emphysematous lung regions." Phys Med Biol **56**(7): 2279-2298.

Yamamoto, T., S. Kabus, et al. (2011). "Four-dimensional computed tomography pulmonary ventilation images vary with deformable image registration algorithms and metrics." Med Phys **38**(3): 1348-1358.

Yamamoto, T., S. Kabus, et al. (2011). "Impact of four-dimensional computed tomography pulmonary ventilation imaging-based functional avoidance for lung cancer radiotherapy." Int J Radiat Oncol Biol Phys **79**(1): 279-288.

Yuan, S. T., K. A. Frey, et al. (2011). "Semiquantification and classification of local pulmonary function by V/Q single photon emission computed tomography in patients with non-small cell lung cancer: potential indication for radiotherapy planning." J Thorac Oncol **6**(1): 71-78.

19.0 Appendices

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: Adverse Event Reporting Requirements

Definitions

Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to protocol Sections 6 and 7 for a listing of expected adverse events associated with the study therapy.

Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below

Reporting to the Study Sponsor

Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined above, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Raymond H. Mak, M.D.
[redacted]

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Raymond H. Mak, M.D.
[redacted]

[redacted]

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.