Improving Pulmonary Function Following Radiation Therapy
NCT02843568

PI: Carri K Glide-Hurst, PhD
Version Date: 6/9/2022

UW16037 Improving Pulmonary Function Following Radiation Therapy

Principal Investigator: Carri K. Glide-Hurst, PhD, DABR, FAAPM
Director, Radiation Oncology Physics
Department of Human Oncology
University of Wisconsin Madison
Office: (608) 262-5319
glidehurst@humonc.wisc.edu

Co-Investigators:

Andrew M. Baschnagel, MD
Bethany M. Anderson, MD
Paul M. Harari, MD
Mark Ritter, MD
Greg Cooley, MD
Jessica Schuster, MD
Michael Bassetti, MD
Kristen Bradley, MD
Steven P. Howard, MD
Randy Kimple, MD
Matthew Witek, MD

Collaborator Albert van der Kogel, PhD
Joseph M. Reinhardt, Ph.D.
Gary E. Christensen, PhD

Biostatistician: Rick Chappell, PhD
Professor
Depts. of Statistics and of Biostatistics & Medical Informatics

Data Manager: Lisa Sanchez
Clinical Coordinator
Department of Human Oncology
(608) 265-3281
sanchez@humonc.wisc.edu

Improving Pulmonary Function Following Radiation Therapy

SCHEMA

All patients	Pre-RT 4DCT scans
All patients	Pre-RT weight, labs, morbidity scores, and PFTs

↓

STRATIFY	**Conventional Fractionation** 60* subjects (A total of 60-66 Gy, in daily fractions of 1.8-2.0 Gy/fx, nominally 5 fx/week) **Hypo-fractionation** 60* subjects Stereotactic body radiation therapy (40-60 Gy total, in 3-8 fx, using standard schemes at UWHCC) or 12Gy x 4 fx, 10Gy x 5 fx, 5Gy x 8 fx, or 20Gy x 3 fx *To achieve primary objective, subjects must complete 3 month post RT assessments. If this does not occur, the subject will be replaced.	**RANDOMIZE**	**Arm 1:** Create treatment plan that meets standard dose specifications **Arm 2:** Optimize treatment plan meet standard dose specifications and to minimize pulmonary function damage based on predictive model

↓

All patients	Receive full course of RT, as prescribed

↓

All patients	4DCTs @ 3, 6, & 12 months post-RT
All patients	PFTs @ 3, 6, & 12 months post-RT
All patients	Weight and RTOG Late morbidity scores @ 3, 6, & 12 months post-RT

↓

All patients	Weight and RTOG Late morbidity scores every four months in year 2, then six months from year 3 to 5 post-RT, then annually

TABLE OF CONTENTS

PAGE

1. OBJECTIVES

1.1. Primary Objective

This clinical trial sets out to determine if subjects who have been treated with radiation therapy plans designed to spare high ventilation regions have superior preservation of pulmonary function compared to those treated with standard radiation dose distributions. Four dimensional computed tomographic imaging (4DCT) will be used to determine lung tissue elasticity, as required for ventilation. Lung tissue elasticity maps at 3 months after RT will be compared to those prior to RT, and used to quantify the change in the lung elasticity maps. Reduced lung tissue elasticity is defined in this study as a >6% reduction in expansion when compared to the baseline; the amount of lung tissue showing a >6% reduction is the metric for our primary endpoint, and will be tested for a significant difference between the two arms.

1.2. Secondary Objectives

1. Characterize and correlate temporal changes in lung tissue elasticity with delivered radiation doses to anatomical and functional regions within the thorax.
2. Quantify global changes following radiation therapy (RT) for lung cancer, including those observed from Pulmonary Function Tests (PFTs) and inflammation markers in blood plasma for subjects who voluntary consent to provide their blood. These too will be correlated with the delivered radiation doses to anatomical and functional regions within the thorax, and with the maps of post-radiation therapy changes in lung tissue elasticity.
3. Quantify the repeatability of 4DCT based measures of lung tissue elasticity to demonstrate the changes following radiation therapy are greater than the expected variation from the procedure itself and determine the expected variance in longitudinal studies.

2. BACKGROUND

2.1. Lung Cancer and Current Therapy

In the year 2015, over 221,200 new cases of lung cancer were diagnosed and 158,040 deaths were attributed to this disease.[1] Of these, approximately 13% are small cell lung cancers with the remainder being non-small cell lung cancer.[1] Treatment can involve combinations of surgery, chemotherapy, and radiation therapy (both conventional and hypo-fractionation).[2]

Radiation therapy is typically used for small cell lung cancer and the total dose is typically between 45 and 70 Gy. This depends upon the extent of disease, the number of fractions, and the daily delivery technique (once daily *versus* twice daily). Small cell cancers, however, represent the *minority* of treatments for lung cancer and employ different treatment schema.

Radiation therapy for non-small cell lung cancer is dependent upon operative status of the patient. Those patients treated primarily with surgery have radiation and chemotherapy post-operatively as determined by margin status and extent of disease pathologically.[2] Those with slightly more advanced disease are treated with neoadjuvant concomitant chemoradiotherapy. The pre-operative radiation dose is typically limited to 45-50 Gy, based on the hope that reduction of tumor burden will rend the patient operable. Patients

with more advanced non-small cell lung cancer are most commonly treated with definitive high dose combination chemotherapy and radiation, the radiation dose ranging from 60-70 Gy. Finally, an increasing number of patients may have limited disease but poor pulmonary function (limiting their operative status). These patients are being treated with stereotactic radiosurgery (generally 3-5 fractions and total dose from 36-60 Gy). This same approach is being used for a number of other patients with recurrent lung cancer or metastatic disease in the lung.

In conclusion, a majority of patients receive radiation therapy as a component of their lung cancer management and the tolerance to this irradiation is limited by the detrimental impact of that treatment (or its potential) on lung function. While tolerance of lung to radiation is generally considered to be 20 Gy there is little data analyzing the anatomic heterogeneity of lung function in the subject prior to treatment so that the radiation may be tailored to minimize impact on function nor is there any significant data analyzing the impact of radiation therapy across lung function globally that takes into account the biomechanical principles that are critical for lung function.

Radiation Side Effects

Radiation to the tumor and nodal targets (commonly hilar and mediastinal) is complicated by respiratory motion. This requires a larger area of normal lung and mediastinal tissue to be treated to ensure that these targets are within the treatment beams used to deliver the dose. Additionally, lung tumors require radiation doses far in excess of the tolerance of normal lung tissue. Common toxicities include radiation pneumonitis, radiation fibrosis, and ultimately altered respiratory capacity. Dose escalation studies show a clear increase in tumor control with increasing radiation dose for primary lung tumors, but that toxicity also increased with dose. Quantification of lung function after radiotherapy has been limited although recognition of its significance is apparent. Spirometry indices as well as DLCO have been shown to be altered following radiotherapy.

In particular, radiation pneumonitis has been loosely correlated to the fraction of the volume of lung irradiated[3] to doses of 10 – 50 Gy.[4-7] The volume of lung receiving 20 Gy or more has a good correlation with radiation pneumonitis in some studies,[3, 5, 8] but not in others.[9, 10] The mean radiation dose to the lung has also provided conflicting results, showing good[3, 7, 11] and poor correlation between a mean dose > 20 Gy and radiation pneumonitis.[6, 12] All of these analyses ignore two factors we believe to be important: 1) the spatial distribution of pulmonary function within the lung is unlikely to be uniform, so the spatial location of the radiation dose matters, and 2) the changes in lung function may be caused by radiation dose both directly and indirectly, where changes occur in regions of the lung receiving what is currently believed to be “sub toxic” doses due to toxic doses in neighboring tissues. Fundamentally, we do not know the cause of this indirectly produced reduced lung function.

2.2. Preliminary Study and Rationale

The relationship between radiation dose and normal lung tissue toxicity has been thoroughly investigated since CT based planning became commonplace over a decade ago,[6] yet the clear indicators for toxicity remain elusive.[7, 13-20] It has been broadly accepted that radiation dose has a direct effect on treated lung tissue and the lung in the treatment field shows radiographic changes consistent with fibrosis.[21] It is largely

assumed that this is the predominant and in some cases only significant effecter of altered lung function despite known changes in inflammatory cells outside the treated area. All current avoidance methods for lung tissue depend on direct dose/volume relationships with treated lung.[6, 16, 22, 23]

The present treatment-planning dosimetry constraints for the lung are based on studies that assume lung tissue is homogeneous in its response to toxicity, irrespective of its location or underlying function. Furthermore, it is well known lung function is not distributed uniformly, especially in diseased lungs.[24, 25] Because most patients with lung cancer have a history of smoking or other lung disease it is clear that a majority of patients will have other underlying lung issues such as chronic obstructive pulmonary disease. This will further exacerbate this anatomically relevant heterogeneity of lung function.

No human studies have investigated the relationships between local lung function, spatial radiation dose distribution, and radiation induced lung function changes. However, rat studies are investigating changes in pulmonary function based on irradiation of different regions of rat lung. Luijk et al. showed structural changes in rat lung were only correlated with changes in breathing rate when irradiating lateral lung regions (shielding the mediastinum),[26] and then that greater lung damage was observed when irradiating the heart [27] while holding mean lung dose and volume of lung irradiated constant. They've also shown irradiation of larger volumes to smaller doses causes greater toxicity than treating smaller volumes to larger doses,[28] a result confirmed by others.[29] A common yet unspecified thread in the rat studies is radiation treatments including the mediastinum caused a greater change in pulmonary function. The reasons for these findings is mechanistically undefined.

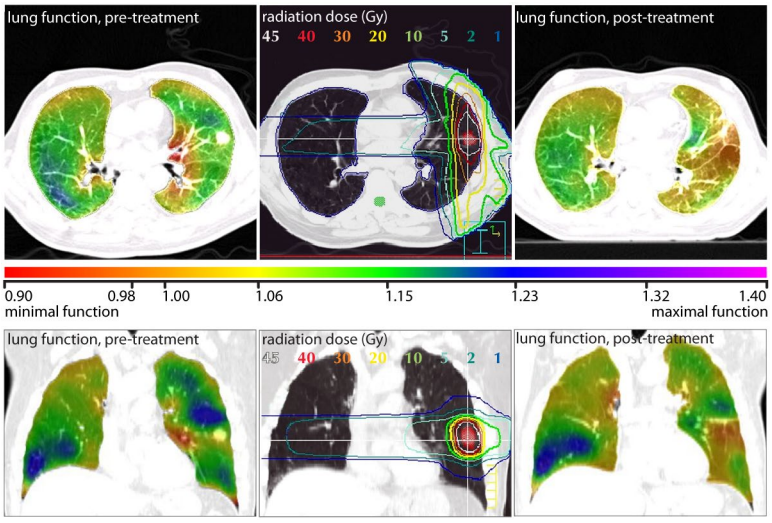

Figure 1. Planned radiation dose distribution (middle) and pulmonary function image before (left) and after (right) radiation therapy. All images are for the same patient. The top row is a transverse cut, the bottom row is a coronal cut. The tumor is located in the left lung on the pre-treatment pulmonary function image and the computed dose distribution image, but absent in the post-treatment images. Post treatment images show a reduction of pulmonary function in the treatment location, when compared to the pre-treatment image.

Our preliminary data is a retrospective analysis of in human subjects (University of Iowa IRB 200805754 from the University of Iowa). Using 4DCT and image registration, we examined the amount of lung expansion (function) in irradiated and non-irradiated lung tissue. What began as a study to evaluate whether we might be able to avoid the most well-functioning lung tissue became something far more exciting once our first set of retrospective data analysis began. Figure 1 shows changes in pulmonary function correlating with calculated 3D radiation dose for a single patient. This patient had two 4DCT studies: the

first was prior to RT for the tumor shown in the left lung, the second was 16 months post RT. The first row is an axial imaging and the second row is a coronal image. The middle image shows the radiation dose distribution (represented by colored lines) while the first and third image show pulmonary function images. The pulmonary function images are color-coded: green and blue indicate normally functioning (expanding) lung tissue with a value > 1.1, while orange and red regions show decreased lung function with a value < 0.95.

The right lung, which was un-treated, shows minimal changes in lung function, while the treated region in the left lung changes from significant expansion (green before RT) to little to no expansion (orange to red after RT). The functional changes observed in the lung appear to correlate well spatially with the delivered radiation dose distribution. A second example is shown in Figure 2, where the top three images show the computed dose distribution and the bottom images show the pulmonary function images. In this case the only pulmonary function images shown are after RT. An extremely interesting and unexpected finding is shown in Figure 2, where regions of decreased pulmonary function extend outside of the applied therapeutic radiation dose. In this case the therapeutic radiation dose is delivered to the tumor in the left lung, but also extends over the mediastinum just 1-2 cm beyond the vertebral bodies of the thoracic spine. Note in this case the change in pulmonary function extends all the way across both lungs even though the therapeutic radiation dose does not, unlike the first clinical case shown above. The numerical value of pulmonary function in a 2x2x2cm volume within the "streak" is 0.96 ± 0.04, while the value in the normal lung is 1.25 ± 0.02. In a third patient (not shown) the pulmonary function values prior to RT were 1.29 ± 0.08 and 1.26 ± 0.01 in the lower lobe and 1.07 ± 0.01 and 1.05 ± 0.02 in the upper lobe of the right and left lung, respectively. These observed differences in un-irradiated areas of lung do not correlate with lower dose scatter patterns and cannot be explained by direct radiation dose effects.

These preliminary results show that we are able to observe radiation induced changes in lung tissue function using 4DCT and image registration. Surprisingly, we see that in the second case, lung function deficits extend well beyond the irradiated tissue. In this project, we will quantify the extent of radiation-induced functional change to irradiated and non-irradiated lung, and correlate these changes with dose delivery plans.

Standard indices for tracking pulmonary toxicity are highly subjective and, predicting RT-quantitative

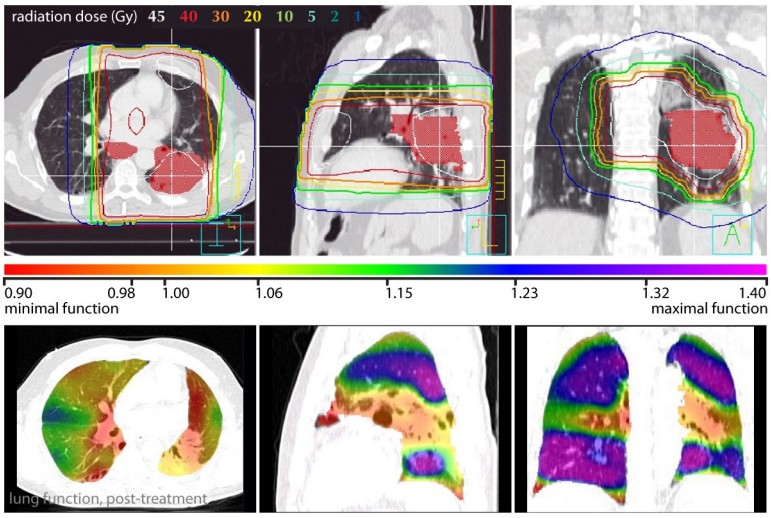

Figure 2. Planned radiation dose distribution (top) and pulmonary function image after radiation therapy (bottom). Both rows of images display a transverse, sagital, and coronal cut. The tumor is located in the left lung. Post treatment lung function images show a reduction of pulmonary function in the treatment location, and an additional "streak" of function reduction across the right lung beyond the treated volume. This observation is consistent with non-spatial functional tests in the rat model and never before shown spatially in humans.

endpoints, as the most common approaches rely on subjective and ambiguous endpoints: shortness of breath, pulmonary function tests, blood gases, exercise capacity, and radiographic abnormalities. Functional imaging is being recognized as having the potential to provide biomarkers as objective endpoints. A nearly two decades of research in this area is based on single photon emission computed tomography (SPECT) perfusion scans to quantify functional lung by measuring blood content within the alveolar capillary network.[13, 25, 30-38] Other investigators are pursuing pulmonary function measurement using novel MRI techniques[38-40] including hyperpolarized helium-3 detected MRI.[38, 40-45] These approaches are challenged by limited spatial resolution, motion correction, and accurate image registration with treatment planning CT scans. We have chosen to utilize CT based image-registration methods to compute local lung expansion from respiratory gated 4DCT, and have shown its correlation with ventilation.[46] Others have investigated 4DCT based pulmonary function assessment also finding favorable results.[47-54] CT has several practical advantages over SPECT and MRI as a tool to measure regional lung injury. CT is more readily available, more directly quantitative, has higher spatial and temporal resolution, is easier to perform with RT positioning devices, faster, and less expensive.

Scores of investigators have worked to establish a relationship between radiation dose-volume parameters and pneumonitis.[14, 36, 37, 48, 50-76] The most substantial datasets used to establish the correlation of radiation dose with pulmonary toxicity are from Washington University in Saint Louis and RTOG trial 9311. The statistical model derived from the combined datasets identified greater risk for mean lung dose (MLD), and irradiation of the inferior lung. Unfortunately, two lessons from these results are unused in clinical practice: high doses to normal lung and the anatomic distribution of dose within the lung are relevant. Instead, the clinical RT paradigm for pulmonary toxicity modeling is driven by the dose-volume relationship of lung volume treated.

This proposed clinical trial will elucidate the complex inter-relationship between RT treatment and the resultant changes in pulmonary function. While other groups have hypothesized the value of dose rearrangement to limit lung toxicity, we will carefully apply this information systematically in this prospective clinical trial to demonstrate its impact.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Histologic diagnosis of a non-small cell lung cancer or lung metastasis from a solid tumor. One biopsy site is adequate for multiple sites of thoracic disease.

3.1.2. Treatment includes localized radiation therapy with or without chemotherapy

3.1.3. Age ≥ 18 years

3.1.4. Karnofsky ≥ 60%

3.1.5. Not pregnant per radiation oncology standard procedures

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

3.2. Exclusion Criteria

3.2.1. Prior (within last 6 months) or future planned therapeutic surgery for the treatment of the existing lung cancer

3.2.2. Prior thoracic radiotherapy

3.2.3. Severe COPD defined as disease requiring an inpatient stay for respiratory deterioration within the past 3 months

3.2.4. Oxygen dependence of > 2 L/min continuously throughout the day at baseline

3.2.5. Known underlying collagen vascular disease or intrinsic lung disease that could complicate expected sequelae of radiation (idiopathic pulmonary fibrosis, Wegener's granulomatosis)

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

3.3. Inclusion of Women and Minorities

Female and male patients of all ethnic groups will be eligible for treatment in these protocols.

4. RANDOMIZATION PROCEDURES

Patients may not undergo protocol procedures prior to signing consent. All patients must meet eligibility criteria listed in Section 3 and provide written informed consent. The study coordinator will verify eligibility, assign a case number, and register the patient in the UWCCC ONCORE database after simulation and after all eligibility criteria have been met. Information to be recorded

The following information will be recorded for each subject enrolled:

- Protocol number
- Patient's name and initials
- Patient's medical record number
- Patient demographic data including gender, birth date and race.
- Signed patient consent forms
- HIPAA authorization form

4.1. Randomization between Therapy Arms 1 & 2

Patients will be randomized between two arms. Subjects in the first arm will receive conventional treatment planning as described in sections 5.5.1 through 5.5.3. Subjects in the second arm will also receive treatment plans that meet all the criteria of the first arm, but their treatment plans will include strategies to reduce pulmonary function damage following radiation therapy as described in section 5.5.4. Randomization will be performed by the data management team using a random number generator application (developed by Randomness and Integrity Services Ltd., Dublin, Ireland) that is a web based application that can also run on an Apple iPhone, iPad, or iPod touch running iOS 5.1.1 or later.

Amend 3/15/22

The Hypo-fractionation patient cohort has reached accrual of 60 subjects (30 conventional treatment planning, and 30 optimized planning).

The Conventional Fractionation cohort has accrued 46/60, however the treatment assignment of conventional treatment planning versus optimized planning is unbalanced, with 27 assigned to the standard dose specification planning and 19 assigned to the optimized treatment planning.

Accrual has significantly slowed and we are accruing 1 subject every 4-8weeks. In light of the extremely low accrual we will assign the next 8 subjects to to the optimized treatment plan to balance the study arms to ensure each arm has adequate enrollment for proper statistical analysis. When the arms are balanced, we will proceed with randomization via random.org until one arm reaches 30, then the remaining subjects will be placed in the remaining open arm.

5. PROCEDURES

Potential subjects will be identified through multidisciplinary lung tumor board, consults, and the radiation oncology clinic. Consent will be obtained prior to initial radiotherapy treatment simulation. One biopsy site is adequate for multiple sites of thoracic disease, as the primary endpoint of the study is the assessment of normal lung tissue response to delivered radiation.

5.1. Baseline Standard of Care Assessments

5.1.1. **4DCT**. For standard of care radiation treatment planning

5.1.2. **Pulmonary function tests.** Include spirometry, diffusion capacity (DLCO), and lung volumes (FEV, FEV1)

5.2. Baseline Research Assessments

5.2.1. **4DCT**. This is ordered in addition to the standard 4DCT performed for RT-simulation

5.2.2. **Patient self-assessment.** Assessment is based on a modified Borg scale, which has a history of use in pulmonary labs, with a scale of 1 (resting comfortably in a chair with no effort) to 10 (the most exertion and difficult breathing ever experienced)

5.2.3. **RTOG defined acute toxicity evaluation.** Evaluate both lung and esophageal toxicity (Appendix B)

5.2.4. **RTOG late toxicity evaluation**. Evaluate lung, esophageal, skin, subcutaneous tissue, spinal cord, heart, and bone (Appendix C)

5.2.5. **Constitutional assessment:** quantify nausea, vomiting, diarrhea and other symptoms prior to initiating chemoradiation and any medications used for these symptoms

5.3. 4-Dimensional Computed Tomography (4DCT) Imaging

4DCT imaging is performed at simulation (treatment planning) in all patients. This first 4DCT is clinically indicated for radiation simulation as a standard procedure. This clinical imaging data will also be used for research in this protocol to evaluate the biomechanical tissue elasticity of the lungs. Lung tissue elasticity is being used as a surrogate for ventilation, which in turn is a component of pulmonary function. Because the goal of the research arm is to reduce pulmonary function damage, changes in lung tissue elasticity will be quantified using 4DCT and it's essential the changes observed be distinguished from random changes in our measurement. Consequently, each subject will receive two 4DCT scans at each time point in order to quantify the repeatability of the measure of tissue elasticity and to demonstrate the changes following RT are greater than the expected variation from the procedure itself. The results from both 4DCT scans will

be used by taking the geometric mean of the tissue elasticity measures of scan 1 and scan 2 at each time point.

Subjects will undergo a total of 7 research-ordered 4DCT scans: one at simulation, and two scans at each of the 3 post-radiation therapy time points (3, 6, and 12 months). Each 4DCT scan delivers approximately 75 mSv, which is the average value observed over 10 patients in our clinic using the newly installed Siemens Edge scanner. The Background Equivalent Radiation Time (BERT) is 25 years for each 4DCT scan, where the background radiation is assumed to be 3 mSv per year. To place this radiation exposure into further context, the radiation dose from the 7 research-ordered 4DCT scans (0.53 Gy) represents less than 1% of the radiation dose the patient will receive from their radiation therapy treatments. In an effort to make the radiation doses from the 4DCT scans "as low as reasonably achievable," the radiation dose subjects receive for each 4DCT scan has recently been reduced by 2-3 times LOWER than prior care at UWHC. This reduction has been made possible by the improved radiation detection technology on the Siemens Edge CT scanner in Radiation Oncology. If further dose reduction can be accomplished by additional technologies or software development, these too will be implemented.

5.4. Localization

Either portal imaging, daily cone beam, and/or optical surface tracking is acceptable for this study according to standard care. If cone beam imaging is prescribed by the treating radiation oncologist, the cone beam images will be utilized for correlative studies.

5.5. Radiation Therapy

The criteria and specifications below in sections 5.5.1 through 5.5.3 are applicable for both the standard of care arm (Arm 1) and the research arm (Arm 2), while those in section 5.5.4 are applicable to the research arm only.

5.5.1. **Dose specification.** Radiation doses between 60-66 Gy using standard fractionation (1.8-2.0 Gy/fx) and stereotactic body radiation therapy (SBRT) hypofractionation schemes used at UWHCC will be utilized. 60 subjects of each fractionation type (standard and hypofractionation) will be included. Treatment volumes will be at the discretion of the treating radiation oncologist and should follow standard of care at UWHC.

5.5.2. **Treatment planning and target volumes**. The critical structures will be in accordance with RTOG 0617.

5.5.3. **Radiation dose limits for critical structures**. Normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, skin, esophagus and spinal cord. Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart

Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 50.5 Gy for standard fractionation. Doses for hypofractionation will follow recommendations in RTOG 0618, 0813, or 0915 based on fraction size.

Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. For standard

fractionation, the volume of both lungs that receive more than 20 Gy (the V20) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be ≤ 20 Gy. (By total lung volume we mean the total lung minus the CTV). Doses for hypofractionation will follow recommendations in RTOG 0618, 0813, or 0915 based on fraction size.

Brachial Plexus: Brachial plexus doses should be kept <66 Gy for standard fractionation. Doses for hypofractionation will follow recommendations in RTOG 0618, 0813, or 0915 based on fraction size.

Esophagus: The mean dose to the esophagus is optimally kept below 34 Gy.[47] This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force the situation. The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient for standard fractionation. Doses for hypofractionation will follow recommendations in RTOG 0618, 0813, or 0915 based on fraction size.

Heart: The following limits are recommended: 60 Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart for standard fractionation. Doses for hypofractionation will follow recommendations in RTOG 0618, 0813, or 0915 based on fraction size.

5.5.4. Research Arm (Arm 2) Only - Planning strategy to reduce pulmonary function damage.

Subjects in the second arm will also receive treatment plans that meet all the criteria of the first arm, but their treatment plans will include strategies to reduce pulmonary function damage following radiation therapy. The strategy to reduce pulmonary function damage, described below, will be implemented during treatment planning. In brief, radiation dose distributions will be designed to "redistribute" the radiation dose away from lung regions with high tissue elasticity. Lung tissue elasticity is calculated from measures of tissue expansion that occurs during respiration. Specifically, the Jacobian determinant of the transformation matrix between the CT scan acquired when the subject has reached the end of exhale and the scan acquired when the subject has reached the end of inhale. These images, which are extracted from the 4DCT data, allow the creation of lung tissue elasticity maps like the ones shown in Figure 3 below.

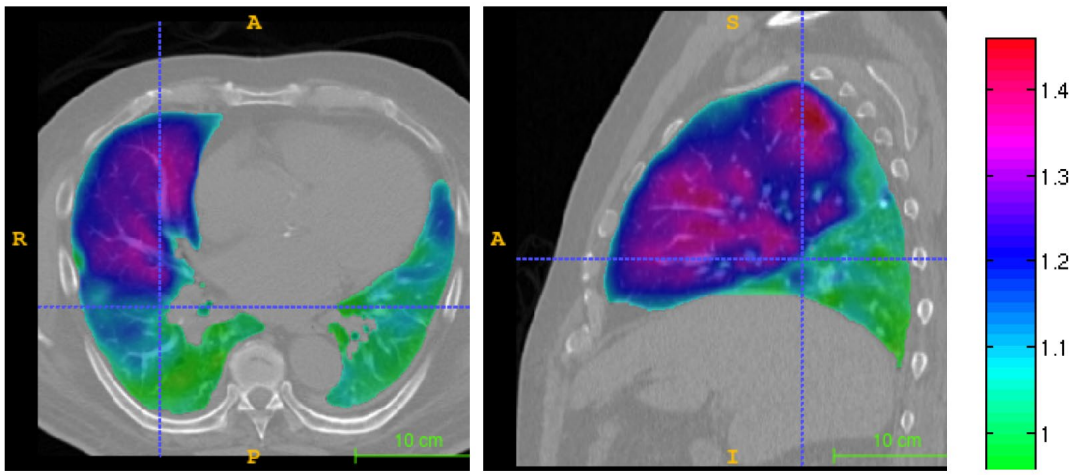

Figure 3. Map of lung tissue elasticity, where a Jacobian value of 1.0 (green) indicates no tissue expansion. The higher the Jacobian value (red end of scale) the greater tissue expansion.

Subjects randomized to this arm of the trial will have the same prescribed radiation dose to the tumor volume and held to the same radiation dose criteria as the subjects in the standard of care arm. The fundamental difference will be radiation doses for these subjects will be redistributed away from regions predicted to cause the greatest reduction in pulmonary function if damaged. For example, to treat the tumor in the images above (slightly medial to the dashed blue lines), circumferential radiation beams restricted to the lower lobes of the lung (green regions) would be chosen over beams that enter or exit the higher tissue expansion regions of the right middle lobe or right upper lobe (blue & purple regions).

Pre-radiation therapy 4DCT images (Section 5.3.1) will be used to identify regions-of-interest (ROI) uniquely utilized in this planning strategy. These ROIs including anatomical regions (airway tree, pulmonary vasculature, heart, and lobar regions of the lung) and functional regions (regions of the lung discretized by the amount of tissue expansion that occurs during ventilation). Although tissue expansion is determined at a $1mm^3$ resolution, the ROIs will be grouped in 0.05 bins of expansion (typically from 1.05 up to 1.5). Airway tree branches and pulmonary vasculature supporting lung regions of high tissue expansion will be preferentially avoided as well. Radiation therapy treatment planning will be calculated using an inverse optimization technique, relying on dose objectives specified for each ROI. The penalty or "cost function" for failing to meet the specified dose objective will increase linearly with radiation dose, while the weight for each cost function will be determined from the slope of the dose response curve for each ROI. The inverse optimization algorithm will minimize the sum of the cost functions for all dose objectives created in the treatment plan. These dose objectives will be added to the dose objectives utilized in the conventional arm of this study (Sections 5.5.1 – 5.5.3).

5.6. Chemotherapy

Chemotherapy is at the discretion of the treating physician and will follow standard of care. The chemotherapeutic agents, dosing and the number of cycles during and after RT will be recorded.

5.7. Study Procedures and Walkthrough

5.7.1. **Radiation therapy planning simulation.** RT simulation will consist of 4DCT imaging as per Department of Human Oncology's standard of care. A second research 4DCT will be acquired at this time point.

5.7.2. **Pulmonary function tests**. The subject will be sent to the pulmonary function lab for spirometry, and DLCO. The pulmonary function tests may be done on the same day, but must be completed before the subject receives the first fraction of radiation therapy.

5.7.3. **Dosimetric planning.** Performed according to standard of care.

5.7.4. **Treatment**. Subjects will be treated once daily or every other day if receiving SBRT. The respiratory surrogate systems will be used daily during radiation therapy treatment per standard clinical practice to monitor respiratory motion.

5.7.5. **Post-treatment 4DCTs**. Three more 4DCT imaging sets will be obtained, at 3 months, 6 months, and 12 months after the last radiation treatment (10 week window: – 2 weeks/+8weeks). These 4DCT must be performed on the Radiation Oncology Siemens Edge. These are research-designated 4DCTs and will not be used for clinical care.

5.7.6. **Post-treatment PFT.** Subjects will undergo PFT at the 3 month, 6 month, and the 12 month imaging to obtain spirometric, and DLCO measurements. These will be performed for research purposes.

5.7.7. **Follow-up.** Subjects will have follow-up appointments with their radiation oncologist every 3 months for the first year, every 4 months for year two, and every 6 months for years 3-5. Follow-up mirrors that of RTOG-0117, enabling time-point comparisons. Data to be collected are outlined in section 11 (measurement of effect). The follow-up time points are consistent with standard of care post radiation disease monitoring.

5.8. General Concomitant Medication and Supportive Care Guidelines

Concomitant care is not affected by this study. Subjects may receive full concomitant and supportive care.

5.9. Duration of Therapy

Therapy will consist of 60-66 Gy in subjects receiving conventional radiation therapy and 40-60 Gy in subjects receiving SBRT. All therapeutic doses delivered on this protocol are consistent with standard of care radiation therapy dosing.

Subjects will have research 4DCT scans and research pulmonary functions performed 3, 6, and 12 months post completion of radiation therapy. These visits will coincide with the standard of care clinic visits which occur every 3 months during year one.

5.10. Duration of Follow Up

Subjects will have life-long follow-up for this study to prospectively quantify radiation-related sequelae. The follow-up schedule is consistent with standard of care follow-up schedules for this patient population. The first study-defined follow-up appointment will be 3 months (10 week window: – 2 weeks to +8weeks) after completing radiation therapy. With approval of PI, subjects can miss this follow-up appointment and continue on the study.

Long term, follow-up will follow standard of care based on subjects disease status at each follow-up. Pertinent late radiation toxicities will be dictated by the treating physician and subsequently graded.

5.11. Adjuvant Therapy

Subjects who have left study, or who have completed their chemo-radiation treatment, may continue therapy at the discretion of their treating medical and radiation oncologists. This treatment is beyond the scope of the protocol, as these patients have completed participation in the protocol. Adjuvant therapy information will be collected for statistical purposes.

5.12. Assessments

5.12.1. **Lung tissue elasticity evaluation using 4DCT**. Subjects will undergo research-ordered 4DCT scans at simulation, 3 months, 6 months and 12 months post-radiation.

5.12.2. **Patient self-assessment** will be documented using a modified Borg scale, which has a history of use in pulmonary labs, with a scale of 1 (resting comfortably in a chair with no effort) to 10 (the most exertion and difficult breathing ever experienced).

5.12.3. **Pulmonary Function Tests** will include FEV1, FVC, DLCO measurements

5.12.4. **RTOG defined acute toxicity evaluation**. Evaluate both lung and esophageal toxicity. (Appendix B). Radiation Oncologist evaluation weekly during chemoradiation, at radiation therapy *fini*, and at 3-month follow-up.

5.12.5. **RTOG late toxicity evaluation.** Evaluate lung, esophageal, skin, subcutaneous tissue, spinal cord, heart, and bone (Appendix C). Evaluation by Radiation Oncologist at 6 month follow-up and beyond.

5.12.6. **Constitutionalassessment**: quantify nausea, vomiting, diarrhea and other symptoms and any medications used for these symptoms. Done weekly during chemoradiation and at follow-up appointments.

6. DOSING DELAYS/DOSE MODIFICATIONS

Not applicable. If radiation dose needs to be modified or delayed, this is per standard of care and beyond the scope of this study. A note will be made in the study chart regarding any changes to radiation dose and any breaks in radiation therapy.

7. ADVERSE EVENTS:

The risks of harm for those subjects randomized to the research arm (arm 2) is equivalent to the control arm: optimized treatment plans in the research arm will be designed to meet the same dose specifications to organs-at-risk. In other words, when comparing the control and research arm:

- the same radiation doses will be delivered to the tumors
- the same radiation dose limits will be achieved for all normal tissues

There are minimal additional risks associated with the research procedures of 4DCT and PFT's.

The most significant risk from 4DCT is the increased radiation exposure which will be less than 1% of the dose received from the prescribed radiation therapy. Subjects may experience

discomfort from laying on their back during additional 4DCT scans. Each 4DCT scan will last 90 seconds. It is anticipated that patients will spend approximately 10-15 minutes on their back to position and collect the scans.

PFT's have the following associated risks: the test requires subjects to breathe in and out quickly, which may cause them to feel dizzy or faint. The test may increase the risk of asthma attack in those with asthma. In very rare cases, PFTs may cause a collapsed lung.

Patients will receive standard of care therapeutic radiation therapy dosing as part of this study. Toxicities associated with therapeutic radiation include: Reversible or permanent alopecia, bone marrow toxicity, skin reactions, and esophagitis are expected side effects of radiation therapy. Radiation-induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving first 6-12 months after initiation of treatment.

Acute (within 90 days post RT completion) and late radiation toxicities (> then 90 days post RT completion) will be recorded with special attention to the toxicities listed in appendix B and C. Any treatment interruption will be based on treating physician judgement and be documented as part of the study toxicity assessments.

7.1. Adverse Events Characteristics

This trial will be focused on the radiation toxicities experienced by patients who receive either SOC radiation treatment planning or the "optimized" treatment planning thus the toxicities recorded in this protocol will focus only on toxicities that can be at least possibly attributed to the radiation treatment.

RTOG (Radiation Therapy Oncology Group) has developed both acute and late radiation toxicities that occur in lung cancer patients. These toxicities and grading criteria are outlined in appendix B (acute toxicities) and Appendix C (late radiation toxicities).

In addition, 15% subjects who undergo chest radiation experience rib fractures. We will track rib fractures using the CTACAE 4.03 term "fracture" to ensure that "optimized" or experimental arm patients frequency and severity of fractures don't exceed control arm subjects or historical frequency.

Changes in Pulmonary function tests

We will utilize the criteria used in RTOG0813 to quantify changes in pulmonary function testing.

RTOG0813 Criteria
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. See appendix D

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 3 event in the original CTCAE version 4 criteria; however, under this modified PFT toxicity classification for patients with abnormal baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:

- 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.

Adverse Event Reporting

Adverse events (AEs) and serious adverse events (SAEs) will be recorded in study database. All SAEs will be reported to the lung DOWG, UWCCC, and UW HS-IRB per policy. Reporting criteria are summarized in Table 1.

An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after initiation of the investigational product whether or not it is considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment. =

Expected events - Expected events are those that have been previously identified as resulting from treatment of lung cancer with radiation. These are defined above for

acute and late toxicities (section 8, appendix B and C). For purposes of this study, reporting requirements are determined by the assessment of the following adverse event characteristics: the type or nature of the event; the severity (grade); the relationship to the study therapy (unrelated, not likely, possibly, likely, or definitely related), and whether the event is expected or unexpected.

Recommended assessment steps include:

- Identification of adverse event.
- Determine whether the adverse event is expected or unexpected.
- Grading the severity of the adverse event using the appropriate set of criteria; CTCAE v.4.03 (General, unexpected).
- Determination as to whether the adverse event is related to the study therapy using the following categories: Unrelated, Possible, Probable, and Definite

For the purpose of this study acute radiation adverse event information will be collected through 90 day (3 month) post radiation visit. After the 90 day (3 month visit) visit only events specific late radiation treatment effects will be collected (appendix C) and any adverse events that result from the 4DCT and PFT's.

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

- Is fatal
- Is life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "other significant hazard" regulatory reporting serious criteria
- Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Note: All deaths on treatment require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On treatment" is defined begins with the radiation simulation planning session and ends 30 days post completion of radiation therapy.

All adverse events deemed to be related by the investigator to the radiation therapy as listed in section 8, appendix B and C will be collected and recorded throughout the study period beginning with the signing of the informed consent through the day patient is removed from the study or the date of death or 5 years after completion of the radiation therapy.

All serious adverse events that occur after the subject has signed the informed consent form must be reported to University of Wisconsin Carbone Cancer Center Data Safety and Monitoring Board and other regulatory agencies.

Grade 4 and 5 serious adverse events occurring greater then 30 days post RT AND thought to be possibly related to the RT or study procedures (4DCT's and/or PFT's) will be collected and submitted within 24 hrs with a full report within 10 working days of discovery or notification of the event via the same mechanism.

Table 1. Expedited reporting requirements for adverse events that occur within 30 days of the last dose of protocol RT and thought to be at least possibly related to protocol RT

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators MUST immediately report to the PI, UWCCC and UW IRB per policy ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). FDA Med Watch (3500A) will be submitted for grade 4 and 5 events at the discretion of the sponsor-investigator.

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

- Death.
- A life-threatening adverse event.
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 Time Frames	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	Not required	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

- See section 8.0, appendix B ,C and D for listing of toxicities
- Grade 3 toxicities resulting in hospitalization with attribution of probably or definitely related to chemotherapy will be exempt from expedited reporting

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of

the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the RT dose and have an attribution of possible, probable, or definite related to radiation or other study procedures (4DCT and PFTs) require reporting as follows:

Expedited 24-hour notification followed by complete report within 10 working days for:

- All Grade 4, and 5 AEs

8. CORRELATIVE/SPECIAL STUDIES: CLOSED TO ADDITIONAL SAMPLE COLLECTIONS

8.1. Correlative Objective

Changes in inflammation blood markers at 3, 6, 9 and 12 months after radiation therapy when compared to baseline. Plasma TGF-β1 will be measured by molecular specific Enzyme Linked Immune Sandwich Assay (ELISA). The levels of plasma cytokines will be measured by ready to use kits for the concentrations of 29 proinflammatory cytokines, including G-CSF, IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1, TGF-α, and TNF-α.

8.2. Correlative lab study

Patients will be offered the opportunity to participate in the correlative components of the study, however participation will be optional. Whole blood, plasma, and serum samples will be drawn within 2 weeks prior to radiation therapy and then drawn 3, 6, 9 and 12 months after radiation therapy.

Platelet-poor plasma will be obtained for cytokine assays; serum samples will be used for, cell death assays and other markers as indicated; buffy coat will be used for genomic studies including methylation analysis. Plasma TGF-β1 will be measured by molecular specific Enzyme Linked Immune Sandwich Assay (ELISA). The levels of plasma cytokines will be measured by ready to use kits, such as LINCOplex (microsphere-based sandwich immunoassay) for the concentrations of 29 proinflammatory cytokines, including G-CSF, IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1, TGF-α, and TNF-α. RILT will be diagnosed and graded based on CTCAE 4. For genomic studies, we will focus our efforts on (but not limited to) global SNP and DNA methylation as well as SNP and methylation analysis of TGFβ1, tissue plasminogen activator (tPA) and angiotensinconverting enzyme (ACE), which are associated with radiation-induced thoracic toxicity such as radiation induced lung injury. Genetic variations within functional locus of these genes will be assessed for in each patient by using gene specific PCR technology. Such SNP studies will be performed using polymerase chain reaction (PCR) and allele specific primers. Genome wide methylation profiling will be performed using the Illumina Infinium HumanMethylation450 BeadChip array which examines the methylation status of 485,577 CpG sites distributed throughout the whole genome, covering 96% of CpG islands and 99% of RefSeq genes. Methylation status of select genes of interests will also be validated using pyrosequencing. Bioinfomatic methodology may be applied for data analysis. Blood markers (cytokine and genomics)

during early course of treatment will be correlated to clinical outcome including tumor control.

Blood (whole blood, plasma and serum) will be processed by the UWCCC BioBank (Translational Science BioCore). 30 ml peripheral blood (two 10 ml EDTA tubes and one 10 ml SST tube) will be taken from each patient at each time point.

Blood—Plasma: 10 ml of blood will be collected in one EDTA (purple top) tube twice. Blood will be inverted 6-7 times to ensure adequate mixing with anticoagulant, then centrifuged within one hour of collection in a standard clinical centrifuge at 3000g at 4°C for 10 minutes. If the interval between specimen collection and processing is anticipated to be greater than one hour, the specimens are kept on ice until centrifuging can begin. Samples will be carefully pipetted in up to ten 1.5 ml cryovials as 1.0 ml aliquots of plasma. Care will be taken to avoid pipetting any blood cells or buffy coat (red/white blood cells). Plasma samples will be labeled and cryovials will be stored at -80°C.

Blood–Serum: 10 ml of blood will be collected without coagulants in one SST (red top) tube. Blood will sit at room temperature for 30 min to allow clot formation, then centrifuged in a standard clinical centrifuge at 3000g at 4°Cfor 10 minutes. Samples will be transferred into up to ten 1.5 ml cryovials as ~1ml aliquots of separated serum. Serum samples will be labeled and cryovials will be stored at -80°C.

Blood—Whole Blood: 10 ml of blood will be collected in one EDTA (purple top) tube. Blood will be inverted 6-7 times to ensure adequate mixing with anticoagulant and then carefully pipetted into three to five 1.5 ml cryovials as 0.5 ml aliquots of whole blood. Samples will be labeled and cryovials will be stored at -80°C.

Initial collected specimens will be labeled with the patient name, date, time and time point collected. A completed specimen collection flow sheet will accompany each specimen.

In an effort to protect the patient's identity in the laboratory, the stored frozen samples will be identified by a code that can be linked back to the patient by the investigators, but not other laboratory personnel.

Blood collections will be scheduled at baseline, which will be within 2 weeks of radiation therapy beginning, and then 3 months, 6 months, 9 months, and 12 months after the completion of radiation therapy.

8.3. Correlation with daily localization imaging

Images acquired for daily localization may show changes in lung tissue that occur during therapy. These images may also be investigated as described in secondary endpoints (Section 10.2)

9.

STUDY CALENDAR

	Pre study[1]	Simulation	Weekly during Rt	3 mo post	6 mo post	12 mo post

H & P	**X**			**X**	**X**	**X**
KPS	**X**		**X**	**X**	**X**	**X**
Weight	**X**		**X**	**X**	**X**	**X**
Informed Consent	**X**					
4DCT		**X**[3]		**X**	**X**	**X**
PFT's[2] and pt self assessment		**X**[4]		**X**[5]	**X**[5]	**X**[5]
Toxicity Assessment	**X**		**X**	**X**	**X**	**X**

10. MEASUREMENT OF EFFECT

The aims of this proposal are to use quantitative imaging to characterize pulmonary biomechanics, improve pulmonary function following RT by utilizing per-RT pulmonary function data to avoid regions of the lung with high function, and gather outcomes data to further refine our radiation dose response model. The primary endpoint is changes in pulmonary function, based on changes in tissue elasticity measured from 4DCT. Secondarily we will evaluate global measures of change using routine pulmonary function tests.

10.1. Primary endpoint

Lung tissue elasticity changes. The primary endpoint of this study will be the ratio of the tissue elasticity map following RT to the elasticity map before RT (i.e., the Jacobian ratio of (post RT /pre RT)) calculated from 4DCT at 3 months post-RT. Based on the randomness of our measurement technique, diminished expansion (i.e. substantial change) is defined as a Jacobian ratio <0.94 (i.e., less than 94% of the pre-RT value).

10.2. Secondary endpoints

10.2.1. Lung tissue elasticity changes

Temporal changes in reduced elasticity. Since the differences in expansion may increase with time, we will investigate these same changes during therapy (using localization images acquired per 5.4) and at 6 and 12 months post-RT.

10.2.1.1. Temporal changes in increased elasticity. At 3, 6 and 12 months post-RT we will determine the volume of lung where expansion is improved (Jacobian ratio (post-RT/pre-RT) > 1.06)

10.2.1.2. Temporal changes in fraction of expanding lung. At 3, 6 and 12 months post-RT we will determine the volume of lung where "meaningful" expansion occurs (Jacobian post-RT > 1.1).

10.2.1.3. Validation of dose response model. Validation in consistency of tissue elasticity changes measured with values predicted based on existing radiation dose response curves.

10.2.2. Global measures of change

10.2.2.1. Pulmonary Function Tests. Changes in patient self-assessment, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusion lung capacity for carbon monoxide (DLCO). All metrics will be evaluated at 3, 6, and 12 months post-RT in comparison to values pre-RT.

10.2.2.2. Inflammation. Plasma TGF-β1 will be measured by molecular specific Enzyme Linked Immune Sandwich Assay (ELISA). The levels of plasma cytokines will be measured by ready to use kits for the concentrations of 29 proinflammatory cytokines, including G-CSF, IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1, TGF-α, and TNF-α.

10.2.3. Repeatability of 4DCT based measures of lung tissue elasticity

10.2.3.1. Variation of the tissue elasticity calculated between scan 1 and scan 2 at each time point will be quantified and compared to longitudinal changes in tissue elasticity.

10.3. Data collection

10.3.1. 4DCT data and radiation dose distribution data

10.3.2. Respiratory surrogate data. Collected from standard treatment techniques, used to assess tumor motion through time and space.

10.3.3. Daily images acquired for patient alignment and motion management. Collected from standard treatment techniques.

10.3.4. RTOG toxicity data and constitutional symptoms

10.3.5. Pulmonary function tests, including FEV, FEV1 and DLCO.

10.3.6. Patient self-assessment

10.3.7. RTOG acute radiation morbidity scoring scheme. Utilized for RTOG 9311, these criteria will be reviewed at radiation therapy *fini* and at the 3-month post-radiation follow-up appointment.

10.3.8. RTOG late radiation morbidity scoring scheme. Utilized for RTOG 0117, these side effects will be collected at follow-up visits after 90 days post-radiation.

11. STATISTICAL CONSIDERATIONS

11.1. Study Design/Endpoints

The primary endpoint of this study will be the ratio of the tissue elasticity map following RT to the elasticity map before RT (i.e., the Jacobian ratio of (post RT /pre RT)) calculated from 4DCT at 3 months post-RT. Based on the randomness of our measurement technique, diminished expansion is defined as a Jacobian ratio <0.94 (i.e., less than 94% of the pre-RT value). Data for the analysis will consist of the voxel-specific ratios of tissue elasticity measures from scans being compared. The primary and secondary endpoints at 3, 6, and 12 months post-RT include: (i) the volume of lung where diminished expansion occurs (Jacobian ratio (post RT /pre RT)<0.94), (ii) the volume of lung where expansion is improved (Jacobian ratio (post RT /pre RT)>1.06), (iii) the volume of lung where “meaningful” expansion occurs (Jacobian post-RT > 1.1), and (iv) clinically observed pulmonary toxicity determined by PFT endpoints, and (v) changes in inflammation as determined from blood serum.

Some subjects may have multiple sites of disease treated within the thorax. Since these subjects will be treated at all sites with either the control (Arm 1) or experimental (Arm 2) treatment plan, and since the primary endpoint of the study is the assessment of normal lung tissue response to delivered radiation, these subjects represent a single sample within our analysis.

Power analysis shows the planned enrollment of 60 subjects per cohort will ensure 90% power to detect mean difference of 4% in the lung tissue elasticity (percentage of the lung with a Jacobian ratio post-RT/pre RT < 0.94), based on 6.3% deviation in this measure from 13 subjects in our preliminary data. If the normality assumptions of ANOVA are not satisfied, nonparametric rank-based tests will be used instead. All statistical tests will be two-sided and assessed for significance at the 5% level, and will be performed by the UW-Madison Department of Biostatistics and Medical Informatics.

Update as of 2/3/2021: The statistics are based on 30 subjects reaching the 3 month followup time point. To date 106 have been enrolled but 14 did not complete the 3 month imaging time point. Therefore we are adding numbers to replace those subjects and to allow an addtional 5 subjects to ensure we complete the protocol and meet the study objectives.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta: American Cancer Society; 2015.
2. National Comprehensive Cancer Network (NCCN) Quick Guide, *Non-Small Cell Lung Cancer*. 2015.
3. Martel, M.K., et al., *Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis.* Int J Radiat Oncol Biol Phys, 1994. **28**(3): p. 575-81.
4. Armstrong, J.G., et al., *Strategy for dose escalation using 3-dimensional conformal radiation therapy for lung cancer.* Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 1995. **6**(7): p. 693-7.
5. Claude, L., et al., *A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: clinical and dosimetric factors analysis.* Radiother Oncol, 2004. **71**(2): p. 175-81.
6. Graham, M.V., et al., *Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC).* International Journal of Radiation Oncology*Biology*Physics, 1999. **45**(2): p. 323-329.
7. Hernando, M.L., et al., *Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer.* Int J Radiat Oncol Biol Phys, 2001. **51**(3): p. 650-9.
8. Jenkins, P., et al., *Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART).* Int J Radiat Oncol Biol Phys, 2003. **56**(2): p. 360-6.
9. Allen, A.M., et al., *Do dose-volume metrics predict pulmonary function changes in lung irradiation?* Int J Radiat Oncol Biol Phys, 2003. **55**(4): p. 921-9.
10. Rodrigues, G., et al., *Prediction of radiation pneumonitis by dose - volume histogram parameters in lung cancer--a systematic review.* Radiother Oncol, 2004. **71**(2): p. 127-38.
11. Oetzel, D., et al., *Estimation of pneumonitis risk in three-dimensional treatment planning using dose-volume histogram analysis.* Int J Radiat Oncol Biol Phys, 1995. **33**(2): p. 455-60.
12. Rancati, T., et al., *Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study.* Radiother Oncol, 2003. **67**(3): p. 275-83.
13. Fan, M., et al., *Relating radiation-induced regional lung injury to changes in pulmonary function tests.* International Journal of Radiation Oncology, Biology, Physics, 2001. **51**(2): p. 311-317.
14. Ghafoori, P., et al., *Radiation-induced lung injury. Assessment, management, and prevention.* Oncology (Williston Park), 2008. **22**(1): p. 37-47; discussion 52-3.
15. Gopal, R., et al., *The relationship between local dose and loss of function for irradiated lung.* International Journal of Radiation Oncology*Biology*Physics, 2003. **56**(1): p. 106-113.
16. Kwa, S.L.S., et al., *Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients.* International Journal of Radiation Oncology*Biology*Physics, 1998. **42**(1): p. 1-9.
17. Miller, K.L., et al., *Long-term changes in pulmonary function tests after definitive radiotherapy for lung cancer.* International Journal of Radiation Oncology*Biology*Physics, 2003. **56**(3): p. 611-615.
18. Nielsen, M., O. Hansen, and W. Vach, *Attempts to predict the long-term decrease in lung function due to radiotherapy of non-small cell lung cancer.* Radiother Oncol, 2006. **78**(2): p. 165-8.
19. Pelagia, G.T. and I.K. Michael, *Radiation pneumonitis and fibrosis: Mechanisms underlying its pathogenesis and implications for future research.* International Journal of Radiation Oncology, Biology, Physics, 2006. **66**(5): p. 1281-1293.
20. Seppenwoolde, Y., et al., *Comparing different NTCP models that predict the incidence of radiation pneumonitis.* International Journal of Radiation Oncology*Biology*Physics, 2003. **55**(3): p. 724-735.
21. Mehta, V., *Radiation pneumonitis and pulmonary fibrosis in nonâ€“small-cell lung cancer: Pulmonary function, prediction, and prevention.* International Journal of Radiation Oncology, Biology, Physics, 2005. **63**(1): p. 5-24.

22. Olivier, C., A.F. Benedick, and K.T.H. Randall, *Multiple fields may offer better esophagus sparing without increased probability of lung toxicity in optimized IMRT of lung tumors.* International Journal of Radiation Oncology, Biology, Physics, 2006. **65**(1): p. 255-265.
23. Yorke, E.D., et al., *Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy.* International Journal of Radiation Oncology*Biology*Physics, 2002. **54**(2): p. 329-339.
24. McGuire, S.M., et al., *A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung.* International Journal of Radiation Oncology, Biology, Physics, 2006. **66**(5): p. 1543-1552.
25. Quan-Sing, N., et al., *Acute tumor vascular effects following fractionated radiotherapy in human lung cancer: In vivo whole tumor assessment using volumetric perfusion computed tomography.* International Journal of Radiation Oncology, Biology, Physics, 2007. **67**(2): p. 417-424.
26. Luijk, P.v., et al., *Relation between radiation-induced whole lung functional loss and regional structural changes in partial irradiated rat lung.* International Journal of Radiation Oncology, Biology, Physics, 2006. **64**(5): p. 1495-1502.
27. Luijk, P.V., et al., *The Impact of Heart Irradiation on Doseâ€"Volume Effects in the Rat Lung.* International Journal of Radiation Oncology, Biology, Physics, 2007. **69**(2): p. 552-559.
28. Novakova-Jiresova, A., et al., *Changes in Expression of Injury After Irradiation of Increasing Volumes in Rat Lung.* International Journal of Radiation Oncology, Biology, Physics, 2007. **67**(5): p. 1510-1518.
29. Semenenko, V.A., et al., *Irradiation of Varying Volumes of Rat Lung to Same Mean Lung Dose: a Little to a Lot or a Lot to a Little?* International Journal of Radiation Oncology, Biology, Physics, 2008. **71**(3): p. 838-847.
30. Marks, L.B., et al., *Quantification of radiation-induced regional lung injury with perfusion imaging.* International Journal of Radiation Oncology*Biology*Physics, 1997. **38**(2): p. 399-409.
31. Seppenwoolde, Y., et al., *Optimizing radiation treatment plans for lung cancer using lung perfusion information.* Radiotherapy and Oncology, 2002. **63**(2): p. 165-177.
32. Woel, R.T., et al., *THE time course of radiation therapy-induced reductions in regional perfusion: a prospective study with >5 years of follow-up.* International Journal of Radiation Oncology*Biology*Physics, 2002. **52**(1): p. 58-67.
33. McGuire, S.M., et al., *A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung.* International Journal of Radiation Oncology*Biology*Physics, 2006. **66**(5): p. 1543-1552.
34. Roach, P.J., et al., *SPECT/CT in V/Q scanning.* Semin Nucl Med, 2010. **40**(6): p. 455-66.
35. Zhang, J., et al., *Radiation-Induced Reductions in Regional Lung Perfusion: 0.1-12 Year Data From a Prospective Clinical Study.* International Journal of Radiation Oncology*Biology*Physics, 2010. **76**(2): p. 425-432.
36. Yuan, S.T., et al., *Changes in global function and regional ventilation and perfusion on SPECT during the course of radiotherapy in patients with non-small-cell lung cancer.* Int J Radiat Oncol Biol Phys, 2011. **82**(4): p. e631-8.
37. Farr, K.P., et al., *Loss of lung function after chemo-radiotherapy for NSCLC measured by perfusion SPECT/CT: Correlation with radiation dose and clinical morbidity.* Acta Oncol, 2015. **54**(9): p. 1350-4.
38. Norberg, P., et al., *Does quantitative lung SPECT detect lung abnormalities earlier than lung function tests? Results of a pilot study.* EJNMMI Res, 2015. **4**(1): p. 39.
39. Cai, J., et al., *Reproducibility of Interfraction Lung Motion Probability Distribution Function Using Dynamic MRI: Statistical Analysis.* International Journal of Radiation Oncology*Biology*Physics, 2008. **72**(4): p. 1228-1235.
40. van Beek, E.J.R. and E.A. Hoffman, *Functional Imaging: CT and MRI.* Clinics in Chest Medicine, 2008. **29**(1): p. 195-216.
41. Stavngaard, T., et al., *Hyperpolarized 3He MRI and 81mKr SPECT in chronic obstructive pulmonary disease.* Eur J Nucl Med Mol Imaging, 2005. **32**(4): p. 448-57.

42. Cai, J., et al., *Direct Measurement of Lung Motion Using Hyperpolarized Helium-3 MR Tagging.* International Journal of Radiation Oncology*Biology*Physics, 2007. **68**(3): p. 650-653.
43. Ireland, R.H., et al., *Feasibility of Image Registration and Intensity-Modulated Radiotherapy Planning With Hyperpolarized Helium-3 Magnetic Resonance Imaging for Non-Small-Cell Lung Cancer.* International Journal of Radiation Oncology*Biology*Physics, 2007. **68**(1): p. 273-281.
44. Hodge, C.W., et al., *On the Use of Hyperpolarized Helium MRI for Conformal Avoidance Lung Radiotherapy.* Medical Dosimetry, 2010. **35**(4): p. 297-303.
45. Ireland, R.H., et al., *Detection of radiation-induced lung injury in non-small cell lung cancer patients using hyperpolarized helium-3 magnetic resonance imaging.* Radiotherapy and Oncology, 2010. **97**(2): p. 244-248.
46. Reinhardt, J.M., et al., *Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation.* Medical Image Analysis, 2008. **12**(6): p. 752-763.
47. Roland, T., et al., *A method for deriving a 4D-interpolated balanced planning target for mobile tumor radiotherapy.* Med Phys, 2012. **39**(1): p. 195-205.
48. Vinogradskiy, Y.Y., et al., *Use of weekly 4DCT-based ventilation maps to quantify changes in lung function for patients undergoing radiation therapy.* Med Phys, 2012. **39**(1): p. 289-98.
49. Cole, A.J., et al., *Investigating the potential impact of four-dimensional computed tomography (4DCT) on toxicity, outcomes and dose escalation for radical lung cancer radiotherapy.* Clin Oncol (R Coll Radiol), 2013. **26**(3): p. 142-50.
50. Vinogradskiy, Y., et al., *Spatial and dose-response analysis of fibrotic lung changes after stereotactic body radiation therapy.* Med Phys, 2013. **40**(8): p. 081712.
51. Hoover, D.A., et al., *Functional lung avoidance for individualized radiotherapy (FLAIR): study protocol for a randomized, double-blind clinical trial.* BMC Cancer, 2014. **14**: p. 934.
52. Santyr, G., et al., *Anatomical, functional and metabolic imaging of radiation-induced lung injury using hyperpolarized MRI.* NMR Biomed, 2014. **27**(12): p. 1515-24.
53. Vinogradskiy, Y., et al., *Comparison of 4-dimensional computed tomography ventilation with nuclear medicine ventilation-perfusion imaging: a clinical validation study.* Int J Radiat Oncol Biol Phys, 2014. **89**(1): p. 199-205.
54. Hardcastle, N., et al., *Accuracy and Utility of Deformable Image Registration in (68)Ga 4D PET/CT Assessment of Pulmonary Perfusion Changes During and After Lung Radiation Therapy.* Int J Radiat Oncol Biol Phys, 2015. **93**(1): p. 196-204.
55. Kocak, Z., et al., *Prospective assessment of dosimetric/physiologic-based models for predicting radiation pneumonitis.* Int J Radiat Oncol Biol Phys, 2006. **67**(1): p. 178-86.
56. Oguz, A., et al., *Long-term pulmonary function in survivors of childhood Hodgkin disease and non-Hodgkin lymphoma.* Pediatr Blood Cancer, 2007. **49**(5): p. 699-703.
57. De Ruysscher, D., et al., *Dyspnea evolution after high-dose radiotherapy in patients with non-small cell lung cancer.* Radiother Oncol, 2008. **91**(3): p. 353-9.
58. Ma, J., et al., *Association between RT-induced changes in lung tissue density and global lung function.* Int J Radiat Oncol Biol Phys, 2008. **74**(3): p. 781-9.
59. Vagane, R., et al., *Radiological and functional assessment of radiation-induced pulmonary damage following breast irradiation.* Acta Oncol, 2008. **47**(2): p. 248-54.
60. Zhang, G., et al., *Functional lung imaging in thoracic cancer radiotherapy.* Cancer Control, 2008. **15**(2): p. 112-9.
61. Cho, J., et al., *High dose-per-fraction irradiation of limited lung volumes using an image-guided, highly focused irradiator: simulating stereotactic body radiotherapy regimens in a small-animal model.* Int J Radiat Oncol Biol Phys, 2010. **77**(3): p. 895-902.
62. Ding, K., et al., *4DCT-based measurement of changes in pulmonary function following a course of radiation therapy.* Med Phys, 2010. **37**(3): p. 1261-72.
63. Downing, L., et al., *A simple quantitative method for assessing pulmonary damage after x irradiation.* Radiat Res, 2010. **173**(4): p. 536-44.
64. Yuan, S.T., et al., *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, 2010. **6**(1): p. 71-8.

65. Bertelsen, A., et al., *Radiation dose response of normal lung assessed by Cone Beam CT - a potential tool for biologically adaptive radiation therapy.* Radiother Oncol, 2011. **100**(3): p. 351-5.
66. Sanchez-Nieto, B., et al., *Predictive models for pulmonary function changes after radiotherapy for breast cancer and lymphoma.* Int J Radiat Oncol Biol Phys, 2011. **82**(2): p. e257-64.
67. Agarwal, R., et al., *The effect of CyberKnife therapy on pulmonary function tests used for treating non-small cell lung cancer: a retrospective, observational cohort pilot study.* Cancer Manag Res, 2012. **4**: p. 347-50.
68. Lopez Guerra, J.L., et al., *Changes in pulmonary function after three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy for non-small-cell lung cancer.* Int J Radiat Oncol Biol Phys, 2012. **83**(4): p. e537-43.
69. Ng, A., et al., *Individualized 3D reconstruction of normal tissue dose for patients with long-term follow-up: a step toward understanding dose risk for late toxicity.* Int J Radiat Oncol Biol Phys, 2012. **84**(4): p. e557-63.
70. Preston, R.J., *Radiation effects.* Ann ICRP, 2012. **41**(3-4): p. 4-11.
71. Vogelius, I.R. and S.M. Bentzen, *A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis.* Acta Oncol, 2012. **51**(8): p. 975-83.
72. Wang, D., et al., *Functional and biologic metrics for predicting radiation pneumonitis in locally advanced non-small cell lung cancer patients treated with chemoradiotherapy.* Clin Transl Oncol, 2012. **14**(12): p. 943-52.
73. Zhang, W., et al., *Quantitative study of lung perfusion SPECT scanning and pulmonary function testing for early radiation-induced lung injury in patients with locally advanced non-small cell lung cancer.* Exp Ther Med, 2012. **3**(4): p. 631-635.
74. Zhang, X.J., et al., *Prediction of radiation pneumonitis in lung cancer patients: a systematic review.* J Cancer Res Clin Oncol, 2012. **138**(12): p. 2103-16.
75. Thind, K., et al., *Detection of radiation-induced lung injury using hyperpolarized (13)C magnetic resonance spectroscopy and imaging.* Magn Reson Med, 2013. **70**(3): p. 601-9.
76. Siva, S., et al., *Respiratory-gated (4D) FDG-PET detects tumour and normal lung response after stereotactic radiotherapy for pulmonary metastases.* Acta Oncol, 2015. **54**(8): p. 1105-12.

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	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: Radiation Therapy Oncology Group Acute toxicity (baseline, during RT, 3 month post-RT)

Lung	0	None
	1	Mild symptoms of dry cough or dyspneal on exertion
	2	Persistent cough requiring narcotic, antitussive agents; or Dyspnea with minimal effort but not at rest
	3	Severe cough unresponsive to narcotic antitussive agent; or Dyspnea at rest; or, Clinical or radiographic evidence of pneumonitis; or, Intermittent oxygen or steroids may be required
	4	Severe respiratory insufficiency; or, Continuous oxygen or assisted ventilation required
	5	Death

Esophageal	0	None
	1	Mild dysphagia or odynophagia; or, Requires topical anesthetic or non-narcotic analgesics; or, Requires soft diet
	2	Moderate dysphagia or odynophagia; or, Requires narcotic analgesics; or, Requires puree or liquid diet
	3	Severe dysphagia or odynophagia with dehydration or weight loss (>15% from pretreatment baseline) requiring nasogastric feeding; or, I.V. fluids; or, Hyperalimentation
	4	Complete obstruction, ulceration, perforation, or fistula
	5	Death

Weight loss	0	None
	1	5 to <10% form baseline; intervention not indicated
	2	10 - <20% from baseline; nutritional support indicated
	3	≥ 20% from baseline; tube feeding or TPN indicated

APPENDIX C: Radiation Therapy Oncology Group Late toxicity (6 months post-RT and beyond)

Lung	0	None
	1	Mild symptoms (dry cough); or, Slight radiographic appearances
	2	Moderate symptomatic fibrosis or pneumonitis (severe cough); or, Low-grade fever; or, Patchy radiographic appearance
	3	Severe symptomatic fibrosis or pneumonitis; or, dense radiographic changes
	4	Severe respiratory insufficiency; or, continuous oxygen or assisted ventilation required
	5	Death

Esophageal	0	None
	1	Mild fibrosis; or, slight difficulty in swallowing solids (no pain on swallowing)
	2	Unable to take solid food normally; or, Swallowing semi-solid food Dilation indicated
	3	Severe fibrosis; or, Able to swallow only liquids; Pain upon swallowing; Dilation required
	4	Necrosis/perforation
	5	Death

Skin	0	None
	1	Slight atrophy; or, Pigmentation change; or, Some hair loss
	2	Patchy atrophy; or, Moderate telangiectasia; or, Total hair loss
	3	Marked atrophy; or, Gross telangiectasia
	4	Ulceration

Subcutaneous tissue	0	None
	1	Slight induration (fibrosis) and loss of subcutaneous fat
	2	Moderate fibrosis but asymptomatic; or, Slight field contracture (<10% linear reduction)
	3	Severe induration and loss of subcutaneous tissue; or, Field contracture (>10% linear measurement)
	4	Necrosis

Radiation Therapy Oncology Group Late toxicity
(6 months post-RT and beyond)

Spinal cord	0	None
	1	Mild L'Hermitte's syndrome
	2	Severe L'Hermitte's syndrome
	3	Objective neurological findings at or below cord level treatment
	4	Mono, para, quadriplegia

Heart	0	None
	1	Asymptomatic or mild symptoms; or, Transient T-wave inversion & ST changes; Sinus tachycardia >110 (at rest)
	2	Moderate angina on effort; or, Mild pericarditis (normal heart size); or, Persistent abnormal T-wave and ST changes; or, Low ORS
	3	Severe angina; or Pericardial effusion; or Constrictive pericarditis; or Moderate heart failure; or Cardiac enlargement; or EKG abnormalities
	4	Tamponade; or Severe heart failure; or Severe constrictive pericarditis

Bone Fracture	0	None
	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic but non-displaced; immobilization indicated
	3	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated
	4	Life-threatening consequences; urgent intervention indicated

APPENDIX D: RTOG PULMONARY FUNCTION TOXICITY CRITERIA

(baseline and at 3, 6 and 12 months; coinciding with 4DCT scans)

The SBRT Pulmonary Toxicity Scale

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

APPENDIX E: PATIENT SELF ASSESSMENT CRITERIA

Modified Borg Scale

G. Borg, Psychophysical bases of perceived exertion, Med Sci Sports Exerc, 14 (1982), pp. 377–381

0	No breathlessness* at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximal)
10	Maximal

Figure 1

Modified Borg scale. (Note: The word "breathlessness" was added in our version of the scale for clarification.) (From Burdon JGW, Juniper EF, Killian KJ, Hargrave FE, Campbell EJM. The perception of breathlessness in asthma. Am Rev Respir Dis 1982;126:825-8. Official Journal of the American Thoracic Society. © by the American Lung Association.)

APPENDIX F: UWCCC DATA SAFETY MONITORING PLAN

Oversight And Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports)
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

Monitoring And Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Intermediate Monitoring Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOWG meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOWG meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

Review and Oversight Requirements

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-

up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database. The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators. For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators

Serious Adverse Event-Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database. The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators. For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

Sponsor-Investigator Responsibilities for SAE Review

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) suspectedness (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) unexpectedness in the context of theis study. SAE with suspected causality to study intervention deemed unexpected are reported as IND safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study intervention will be reported by the UWCCC PI to the FDA, all participating investigators on the study within 7 calendar days.

Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external

monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC

Expedited Reporting Of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list. Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

SAE Requiring *[24]* Hour Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 5 days of the initial *[24]* hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu

b) *John Bayouth, Ph.D., UWCCC PI*

c) *Diana Trask, UWCCC Radiotherapy PM*

d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. **Report to the IRB:**

Consult the UW-IRB website for reporting guidelines

SAE Requiring *[10]* Day Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOWGs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[10]* day reports.

For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu

b) Any appropriate parties listed on SAE Routing Form

2. Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Table 1. Expedited reporting requirements for adverse events that occur within 30 days of the last dose of protocol RT and thought to be at least possibly related to protocol RT

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators MUST immediately report to the PI, UWCCC and UW IRB per policy ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). FDA Med Watch (3500A) will be submitted for grade 4 and 5 events at the discretion of the sponsor-investigator.

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

- Death.
- A life-threatening adverse event.
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 Time Frames	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	Not required	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

- See section 8.0, appendix B, C and D for listing of toxicities
- Grade 3 toxicites resulting in hospitalization with attribution of probably or definitely related to chemotherapy will be exempt from expedited reporting

Expedited AE reporting timelines are defined as:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-

hour report.

- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the RT dose and have an attribution of possible, probable, or definite related to radiation or other study procedures (4DCT and PFTs) require reporting as follows:

Expedited 24-hour notification followed by complete report within 10 working days for:

- All Grade 4, and 5 AEs