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Protocol #: 14-1856

Protocol Title: **Early phase clinical trial incorporating lung function imaging into radiation therapy for lung cancer patients**

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Lead Site: University of Colorado

Participating Site: Beaumont Health System, Royal Oak, MI

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Definitions

UCCC	University of Colorado Cancer Center
Beaumont	William Beaumont Hospital
Lead PI	Yevgeniy Vinogradskiy
Site PI	Inga Grills
PFT	Pulmonary Function Testing
CT	Computed Tomography
4DCT	4-Dimensional Computer Tomography
4DCT-Ventilation	4DCT based ventilation imaging
PET	Positron Emission Tomography
Nuclear Medicine VQ	Nuclear Medicine Ventilation-Perfusion
CTCAE	Common Terminology Criteria for Adverse Events
QOL	Quality of life
DVH	Dose-volume histogram
AE	Adverse Event
SAE	Serious Adverse Event

1.0 Objectives

1.1 Primary Objective

The proposed study is in the field of thoracic radiation oncology where radiation therapy is used to treat lung cancer. The primary objective of the early phase clinical trial will be to evaluate the safety and preliminary efficacy of performing functional avoidance radiation therapy for lung cancer patients using 4DCT-ventilation imaging. 4DCT-ventilation is an imaging modality that uses anatomical CT imaging data acquired as part of routine clinical care for lung cancer patients[1] to calculate lung function images[2, 3] (Figure 1). We propose to use 4DCT-ventilation for thoracic functional avoidance. Functional avoidance implies placing and optimizing the radiation treatment beams to avoid the functional portions of the lung as displayed by the 4DCT-ventilation. Standard radiation therapy does not take into account the patient's regional variation in lung function and treats the lung as a homogenous organ when delivering radiation. 4DCT-ventilation measures which areas of the lung are used for breathing and functional avoidance will allow physicians to spare these regions when delivering radiation. The idea is that avoiding functional portions of the lung will decrease the rate of thoracic side-effects from radiation. Our goal will be to accrue 67 lung cancer patients from 2 institutions (University of Colorado and Beaumont Health System) for an early phase prospective study evaluating functional avoidance. As noted in section 7.3, patients will count towards study accrual if they have a thoracic toxicity evaluation 3 months after completing radiotherapy. To account for screen fails and patient dropout we anticipate we will need to consent 110 patients to reach our 67 patient clinical trial goal. Our primary objective will be to determine whether functional avoidance is safe and results in acceptable thoracic clinical toxicity.

1.2 Secondary Objectives

A list of secondary objectives is shown below. In addition to the primary objective of clinical toxicity, in secondary objectives 1 and 2 we will assess radiation treatment response using imaging-based changes and pulmonary function test (PFT) data. In objective 3 we plan to compare our novel imaging modality, 4DCT-ventilation, to other forms of lung function imaging in a prospective setting. Objectives 4 and 5 will aim to develop preliminary results for the design of a large scale, randomized trial.

1. Assess imaging-based changes in the lung due to the radiation therapy

2. Assess changes in PFT due to the radiation therapy
3. Compare 4DCT-ventilation with other lung function assessment methods
4. Assess the percentage of patients that are eligible for functional avoidance in a prospective setting
5. Assess preliminary efficacy results for the generation of data for a large scale, randomized, multi-institutional clinical trial

1.3 Study Design

The schema for the proposed study is shown in Figure 2 including whether the procedure is considered standard of care (SOC) or research (R).

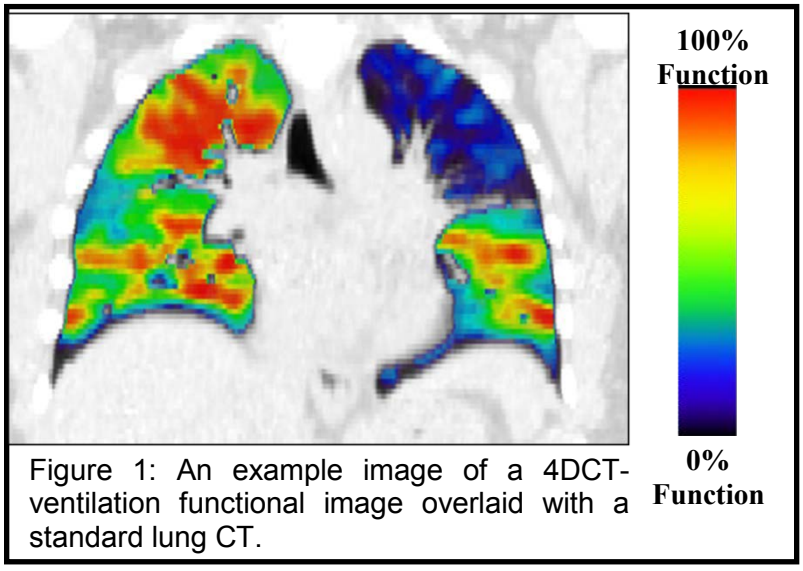

Figure 1: An example image of a 4DCT-ventilation functional image overlaid with a standard lung CT.

Step 1: Subject Enrollment and Screening: Biopsy proven lung cancer patients receiving definitive radiation therapy (defined as receiving 45-75 Gy) will be eligible to be enrolled in the study. As part of routine clinical care each patient will undergo 4D computed tomography (4DCT) imaging. We will use the 4DCT data to calculate 4DCT-ventilation images. The 4DCT-ventilation images will be assessed for lung function defects. Patient receiving definitive radiation therapy and who display a clinically significant reduction in regional ventilation will be eligible for the trial.

Step 2: Functional avoidance plan generation: Subjects will have a functional avoidance plan generated under the guidance of a radiation oncologist and a radiation physicist. We will use the subject's 4DCT-ventilation imaging to design radiation treatment plans that avoid functional portions of the lung while still delivering the prescribed dose to the target and respecting dose tolerance limits for other thoracic organs at risk.

Step 3: Pre-treatment lung function assessment: Subjects will undergo pre-treatment lung function assessment including: clinical assessment by a radiation oncologist using the NCI's Common Terminology Criteria for Adverse Events (CTCAE) toxicity scoring system[4], thoracic quality of life (QOL) questionnaires, 4DCT-ventilation imaging, nuclear medicine ventilation-perfusion (VQ) imaging, Positron Emission Tomography (PET) imaging, radiographic injury assessment using CT imaging, and PFTs.

Step 4: Radiation therapy treatment: The functional avoidance radiation therapy plan will be delivered using a standard course of radiation treatment on a linear accelerator. The subject will be assessed each week by a radiation oncologist for side effects from the radiation treatment.

Step 5: Post-treatment lung function assessment: After completion of radiation therapy the subject will undergo post-treatment lung function assessment using all modalities used to assess function during pre-treatment. Assessment will include: clinical assessment by a radiation oncologist using the CTCAE scoring system, thoracic QOL questionnaire, PFTs, CT imaging, 4DCT-ventilation imaging, nuclear medicine VQ imaging, and PET imaging. The clinical assessment and subject questionnaire will be done on the last day of treatment and at 3, 6, and 12 months post therapy. The imaging and PFT studies will all be done at 3 months post therapy only (with the exception of the CT study which will be done at 1 year post therapy). The thoracic clinical toxicity for functional avoidance radiation therapy will be assessed using clinical end points (clinical CTCAE toxicity grade and subject questionnaire) and quantitative pulmonary assessment studies (PFT and imaging).

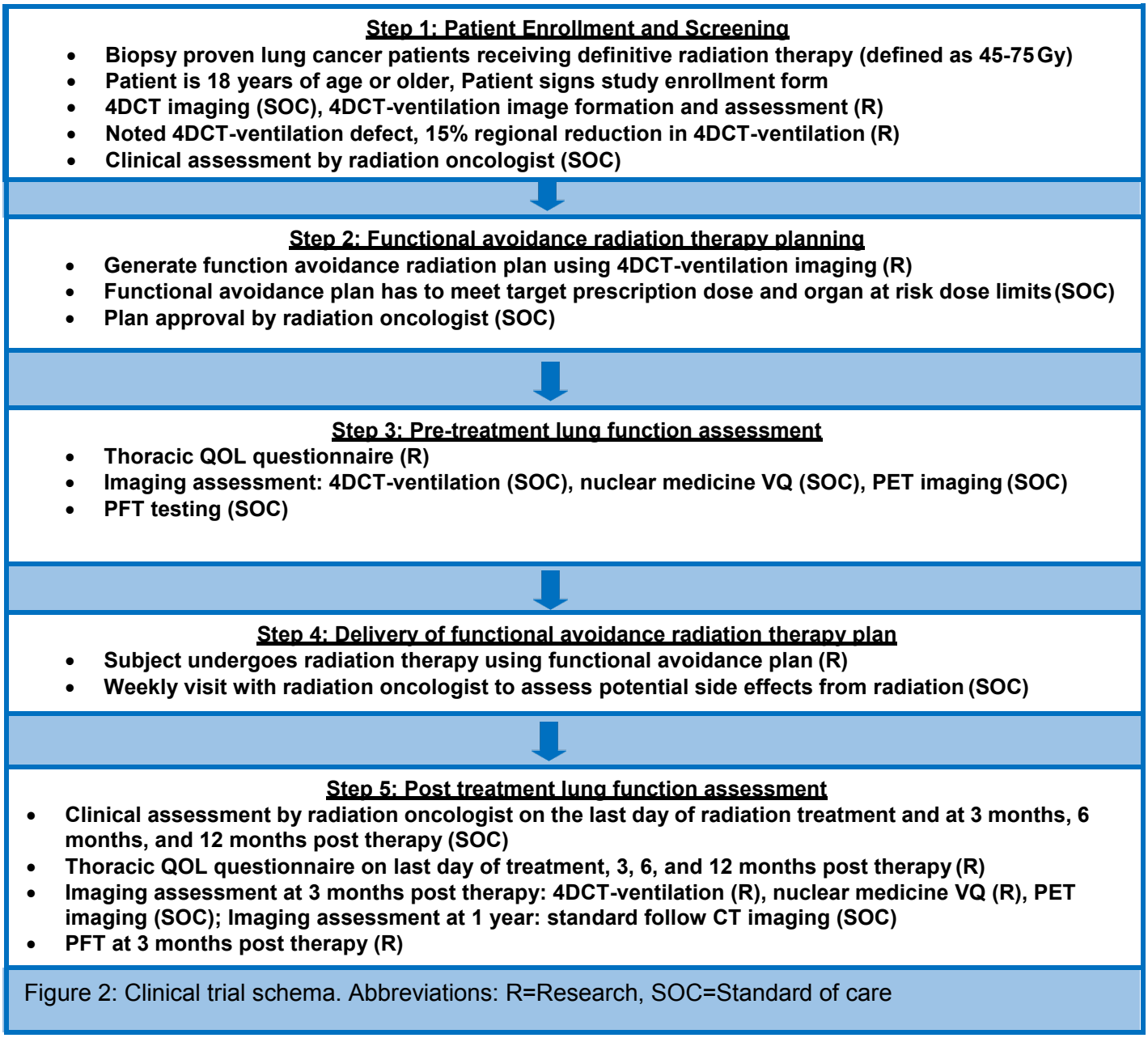

Figure 2: Clinical trial schema. Abbreviations: R=Research, SOC=Standard of care

2.0 Background and Significance

2.1 Radiation therapy for lung cancer

Lung cancer remains a major public health problem. There will be an estimated 240,000 new lung cancer cases in 2014. Lung cancer is the number one cause for cancer related deaths in the United States. Five year survival rates for patients with lung cancer have been reported to be as low as 15%[5]. Radiation therapy is considered one of the primary definitive treatment options for patients with lung cancer. Up to 80% of patients with lung cancer receive radiation therapy. The success of radiation therapy in the lung has been limited by normal tissue radiation dose tolerance limits. In other words, the dose that can be delivered to the tumor is limited

by the radiation tolerance of the surrounding healthy lung. Serious and sometimes life-threatening thoracic side effects from radiation therapy generally occur in 25% of patients with rates as high as 50% cited[6]. The thoracic side-effects are a serious limitation to the patient's quality of life following radiation treatment. Additionally, the fear of causing these life threatening thoracic side effects limits radiation doses that physicians are able to safely deliver to the tumor.

2.2 Imaging in radiation therapy

The current standard of care in thoracic radiation therapy does not take into account the patient's regional lung function distribution. In other words, the radiation treatment plan is designed assuming homogenous lung function throughout the lung. However, studies have shown that is not the case, and up to 70% of lung cancer patients can have spatial ventilation defects due to their tumor, areas of prior irradiation, or non-oncologic lung conditions such as chronic obstructive pulmonary disease (COPD)[6-8]. There is emerging evidence to suggest that incorporating lung function imaging into radiation therapy can reduce the risk of thoracic side effect[7, 9-12].

Our proposed new lung function imaging, which we refer to as 4DCT-ventilation, is especially suited for radiation therapy and has great potential to improve quality of life for lung cancer patients. 4DCT-ventilation imaging is accomplished via an algorithm that uses data acquired as part of routine clinical care. Nearly every one of our lung cancer patients undergoes four-dimensional computed tomography (4DCT) imaging[1, 13]. 4DCT images provide a 'movie' of the moving lung anatomy and help clinicians design radiation treatment plans that account for the patient's breathing motion. Our algorithm uses the 4DCT data to calculate 4DCT-based lung ventilation images by calculating a density-change between different phases of the breathing cycle[2, 3]. The theory behind this algorithm is that the density in a given voxel is proportional to the amount of air present and therefore the difference in density provides the amount of air movement; which is the definition of ventilation. The result of the algorithm is a 3D spatial map of ventilation (Figure 1). 4DCT-ventilation provides an excellent way to visualize which portions of the lung are functional and used for breathing. 4DCT-ventilation has been validated against other ventilation imaging modalities (nuclear medicine and Magnetic Resonance Imaging for example) with promising results[14-18].

The major advantage of 4DCT-ventilation is that the functional information is obtained with no extra imaging procedures necessary; our proposed imaging modality only requires software processing on already obtained 4DCT images. Because 4DCTs are acquired as part of routine care, 4DCT-ventilation imaging does not burden the patient with an extra imaging procedure, reduces the imaging related cost, and spares the patient from any unnecessary radiation exposure. 4DCT-ventilation has superior spatial resolution (compared to nuclear medicine ventilation) and by definition combines function information (ventilation) with anatomic information (CT).

2.3 4DCT-Ventilation based functional avoidance

Our group, as well as others, have proposed to use 4DCT-ventilation for functional avoidance radiation therapy planning[7, 19, 20]. Functional avoidance means placing and optimizing the radiation treatment beams to avoid the functional portions of the lung. The idea is that if functional portions of the lung received less radiation dose, thoracic side effects from the radiation treatment would decrease. 4DCT-ventilation measures which areas of the lung are used for breathing and can allow for avoidance of these regions when delivering radiation. The concept of functional avoidance is demonstrated in Figure 3. Two different radiation treatment plans are shown for the same patient. Each image shows the CT scan, overlaid 4DCT-ventilation functional information, tumor location, and the radiation isodose lines. The ventilation image shows which portions of the lung are used for breathing with the bright colors representing functional portions and the dark tones displaying ventilation defect areas. The presented patient displays a ventilation defect posterior to the tumor and functional portions in areas lateral to the tumor. The patient's clinically used plan is shown on the left and demonstrates that the 25 Gy isodose line (shown in green) engulfs functional lung. The functional avoidance plan is shown on the right and is able to successfully avoid the functional portion of the lung with the 25 Gy isodose line by placing more dose posterior to the tumor.

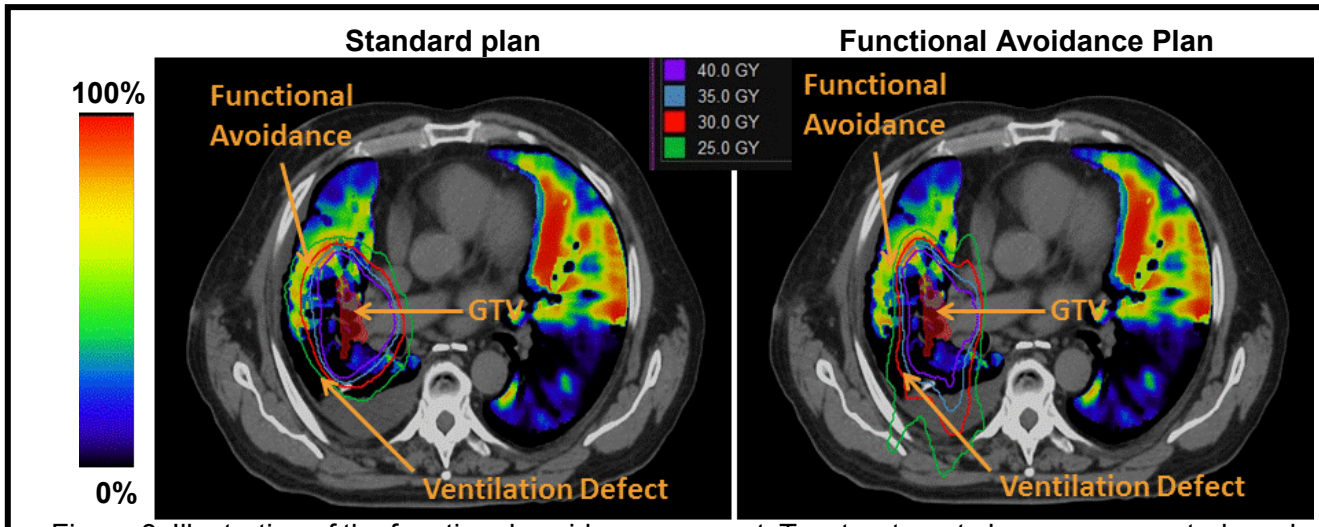

Figure 3: Illustration of the functional avoidance concept. Two treatment plans are presented, each shows the CT, overlaid 4DCT-ventilation functional image, tumor location, and radiation isodose distribution. The plan on the left is the clinically used plan and displays dose in the functional portions of the lung while the plan on the right is the functional avoidance plan which spares functional lung.

3.0 Preliminary data

3.1 4DCT-ventilation method development:

Our retrospective results demonstrate that 4DCT-ventilatin is ready to be prospectively used on human subjects. The image calculation techniques have been developed, 4DCT-ventilation has been validated, and functional avoidance has been retrospectively demonstrated.

Our group presented the initial work for the 4DCT-ventilation calculation concept [21]. Since then, our team [2, 3, 22] as well as others [23, 24] have extensively developed 4DCT-ventilation imaging techniques. We will briefly describe the image formulation process. The input into the algorithm is a data set of 4DCT images [13, 25]. 4DCT images provide a 'movie' of the moving lung anatomy and help clinicians design radiation treatment plans that account for the patient's breathing motion. Our method uses the 4DCT data to map lung voxels from the inhale to exhale phases [26] of the breathing cycle and calculate a density change between the 2 phases. The theory is that the density in a given voxel is proportional to the amount of air present and therefore the difference in density provides the amount of air movement; which is the definition of ventilation. The result is a 3D spatial map of ventilation that provides an excellent way to visualize which portions of the lung are functional and used for breathing (Figure 1). 4DCT-ventilation is ready to be prospectively used on patients because there will be no change to the imaging procedure as seen by the patient; our novel imaging method only requires software processing on already clinically established imaging.

3.2 Validation of 4DCT-ventilation: Before 4DCT-ventilation can be implemented clinically it needed to be validated. In a retrospective study we compared 4DCT-Ventilation imaging to the established method of nuclear medicine ventilation imaging with promising results[18]. Nuclear medicine VQ images, although limited in certain aspects, are considered the current gold standard for ventilation imaging. Nuclear medicine VQ images are generated with the patient inhaling a radioactive aerosol with radiation detectors capturing the photons emitted from the patient. A patient example with good agreement between nuclear medicine ventilation and 4DCT-ventilation image is shown in Figure 4. Both the 4DCT-ventilation imaging and the nuclear medicine ventilation image demonstrate a major ventilation defect in the left upper lobe. Overall, our study demonstrated good agreement between 4DCT-ventilation imaging and nuclear medicine VQ imaging using radiologist observations and quantitative metrics. We performed another validation by comparing 4DCT-ventilation to PFT data and

showed a good correlation between the two methods of measuring lung function[27]. PFTs present an established way of a lung function and our study demonstrated that 4DCT-ventilation is able to reliably predict global lung function. Other studies have shown similar promising validation results comparing 4DCT-ventilation to nuclear medicine[14, 16], helium based MRI[17], PET imaging using gallium[28], xenon based CT[15], and PFT data[14]. The validation work has demonstrated that 4DCT-ventilation can reliably demonstrate global lung function and is ready to be used prospectively in the treatment of lung cancer patients

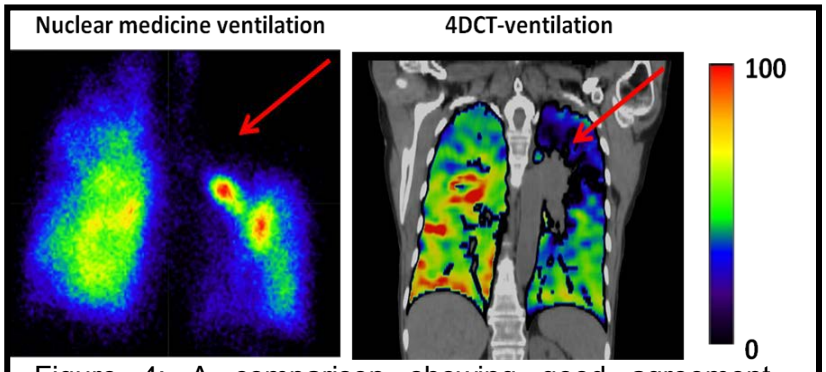

Figure 4: A comparison showing good agreement between nuclear medicine ventilation (left) and 4DCT-ventilation (right).

3.3 Functional avoidance: Studies have proposed the concept of functional avoidance[7, 8, 10, 12, 19, 29, 30]. Early studies suggested performing functional avoidance using nuclear medicine ventilation imaging [8, 12, 29]. However, these theoretical studies did not result in clinical trials because of the inherent limitations of nuclear medicine (VQ) imaging which has limited spatial resolution, suffers from a significant artifact where the aerosol gets stuck in the airways, and is not readily available to all oncology clinics [18]. 4DCT-ventilation addresses these shortcomings with improved spatial resolution, no aerosol requirement, and the convenience of being able to calculate images using data acquired as part of routine care in radiation oncology clinics.

Three important findings have come out of functional avoidance work focused on 4DCT-ventilation [2, 7]. First, studies have demonstrated that it is possible to avoid functional portions of the lung without reducing dose to the tumor or compromising on tolerance limits for significant thoracic organs (spinal cord, heart, and esophagus)[9, 10]. These results assure that by using functional avoidance we will not sacrifice any current standards of care for lung cancer patients. Second, in a novel study we showed that 4DCT-ventilation functional information predicts for clinically significant radiation toxicity[31]. The concept is illustrated in Figure 3, which shows one patient who developed clinically significant radiation side effects and another patient who did not. Both patients received identical radiation doses to the lung. Patient 2, who received radiation dose to functional portions of the lung, developed serious lung toxicity, while patient 1, who received dose to the non-functioning portions, did not develop any pulmonary complications. Our retrospective results suggest that prospectively incorporating 4DCT-ventilation imaging can reduce clinical toxicity.

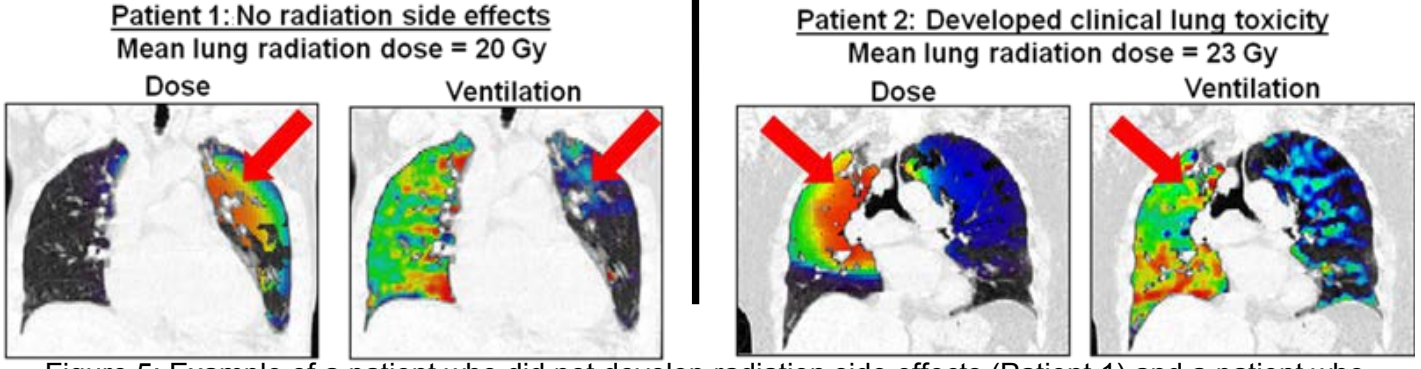

Figure 5: Example of a patient who did not develop radiation side effects (Patient 1) and a patient who developed clinical lung toxicity (patient 2). The red arrow highlights that the patient that developed toxicity received dose to the functional portions of the lung while the patient who did not develop side-effects received dose to the non-functioning lung.

The third important finding is that up to 70% of lung cancer patients treated with radiation therapy can have regionally variant (non-homogenous) lung function with major ventilation defects; suggesting that a significant portion of the lung cancer population could benefit from functional avoidance[32].

3.4 Toxicity assessment:

There has been significant effort in the field of radiation oncology to assess thoracic toxicity after radiation therapy. The primary toxicity for thoracic radiation therapy is radiation pneumonitis. Radiation pneumonitis results in cough, shortness of breath, and can be fatal if left untreated. Clinically significant radiation pneumonitis (as defined by the NIH[4]) generally occurs in 25% of patients with rates as high 50% published[6, 33, 34]. In addition to clinical toxicity, studies have characterized lung function changes using QOL questionnaires[35], PFTs[36], and lung imaging[2, 31, 37-40]. The toxicity work demonstrates that the radiation response of the lung can be very complex as the radiation damage can be juxtaposed with functional improvement due to tumor regression. We provide two significant examples from our work of differing lung responses for 2 different patients (Figure 4). In the images on the left we use 4DCT-ventilation to demonstrate improvement in lung function throughout therapy as the tumor shrinks and on the right we use PET imaging to demonstrate significant radiation damage (9, 43). The toxicity studies provide the necessary methods for us to assess our hypothesis that functional avoidance reduces the rate of toxicity and underline the importance of obtaining a complete set of lung function data to assess treatment response.

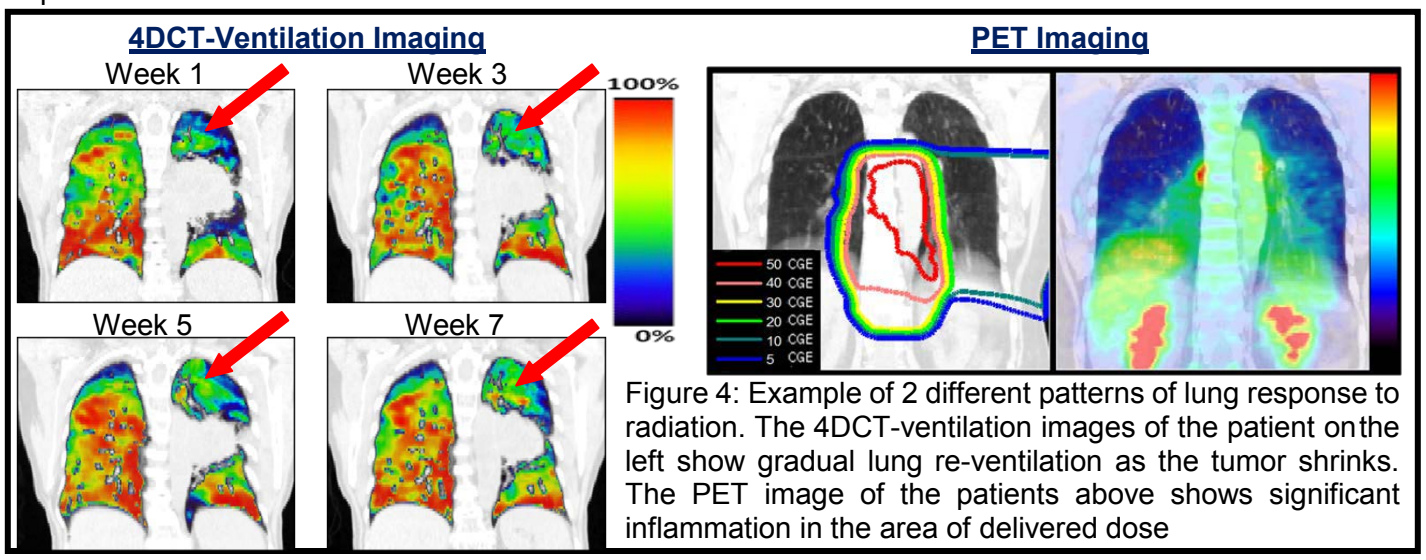

Figure 4: Example of 2 different patterns of lung response to radiation. The 4DCT-ventilation images of the patient on the left show gradual lung re-ventilation as the tumor shrinks. The PET image of the patients above shows significant inflammation in the area of delivered dose

We believe the necessary retrospective work in 4DCT-ventilation has been complete: the imaging calculation techniques have been optimized[2, 3, 16, 41], 4DCT-ventilation has been retrospectively validated[14-16, 18], the functional avoidance concept has been retrospectively demonstrated[32], and tools have been developed to quantitatively and qualitatively evaluate lung function. The next logical step in the progress of 4DCT-ventilation is to prospectively incorporate the imaging modality into radiation therapy through a functional avoidance clinical trial. Our clinical trial proposes an important pilot study incorporating 4DCT-ventilation into clinical practice. 4DCT-ventilation presents many exciting applications in radiation therapy, all without burdening the patient with an extra imaging procedure. Our project proposes a rigorous study to evaluate the safety of functional avoidance.

4.0 Research Methods

4.1 Outcome Measures

1. Primary outcome measure: To assess safety we will evaluate the rate of CTCAE defined radiation pneumonitis
2. Primary outcome measure: CTCAE toxicity for the spinal cord, esophagus, and heart.
3. Primary outcome measure: Changes in subject reported thoracic QOL outcomes from pre-treatment to post-treatment.

4. Primary outcomes measure: Overall survival at 1 year post radiation therapy.

5. Secondary outcome measure: Quantitative and qualitative changes in 4DCT-ventilation imaging from pre-treatment to post-treatment.
6. Secondary outcome measure: Quantitative and qualitative changes in nuclear medicine VQ imaging from pre-treatment to post-treatment.
7. Secondary outcome measure: Quantitative and qualitative changes in PET imaging from pre-treatment to post-treatment.
8. Secondary outcome measure: Quantitative and qualitative changes in 1 year follow up CT imaging. We will determine whether the subject had grade 2+ CTCAE defined radiation fibrosis which is determined as radiographic fibrosis in 25-50% of the ipsilateral lung.
9. Secondary outcome measure: Changes in PFT assessment from pre-treatment to post-treatment.
10. Secondary outcome measure: The percentage of subjects who have significant ventilation defects as defined in section 5.4.

4.2 Subject Eligibility and Description of Enrolled Population

The subject has to meet the trial inclusion and exclusion criteria in Table 1 to be eligible for the study.

Table 1: List of trial inclusion and exclusion criteria.

Inclusion criteria
1. Diagnosis of pathologically confirmed lung cancer by tumor biopsy and/or fine-needle aspiration
2. Lung Cancer patients that will undergo definitive radiation therapy defined as 45-75 Gy as part of standard of care for their disease.
3. 18 years of age or older
4. Signed informed consent
5. Planned curative intent chemotherapy, delivered either concurrently or sequentially in combination with radiotherapy
6. The patient's 4DCT-ventilation image meets the heterogeneity criteria outlined in section 5.4
Exclusion criteria
1. Patients receiving Stereotactic Body Radiation Therapy
2. Patient receiving palliative radiation therapy (defined as less than 45 Gy)

Inclusion criteria 1-4 above represents patient and clinical factors. Inclusion criteria 5 above represents the functional imaging status. Consultation with a multi-disciplinary team including a physicist, radiation oncologist, radiologist, and pulmonologist is encouraged.

Subjects enrolled in the study will be biopsy proven lung cancer patients receiving definitive radiation therapy. The definitive radiation therapy criteria is designed to rule out any patients receiving palliate care. The enrolled subjects will have a lung function profile that displays a significant ventilation defect. The idea is that if the subject has homogenous lung function, there is no basis to preferentially spare any regions, and functional avoidance is not necessary. On the other hand, if the subject has spatially variant lung function, functional avoidance can be used to avoid the active portions of the lung. Our inclusion criteria will ensure that the population enrolled in the trial will be the group of patients that can benefit most from functional avoidance. If the patient does not fit either clinical or imaging trial inclusion criteria, or is found to be ineligible due to exclusions criteria, it will in no way affect their ability to receive appropriate care from their chosen providers.

4.3 Research plan

The study schema is shown in Figure 1 and a table of the procedures experienced by the patient/subject is shown in Table 2. The table in Appendix A provides a snapshot of the study assessments. We will divide our clinical protocol into 5 steps: 1) Screening 2) Functional avoidance planning 3) Pre-treatment lung function assessment 4) Radiation therapy treatment delivery 5) Post-treatment lung function assessment.

4.4 Step 1: Screening

The start of the screening process will occur when a patient is referred to radiation oncology for radiation treatment. The patient will have to have a diagnosis of pathologically confirmed lung cancer by tumor biopsy and/or fine-needle aspiration. Patients with both non-small cell lung cancer (NSCLC) (all histologies) and small cell carcinomas will be eligible to enroll in the trial. The patient will undergo a standard consultation with the radiation oncologist. During consultation it will be determined if the patient meets clinical criteria which includes a prescription of definitive radiation treatment (defined as 45-75 Gy), is 18 years of age or older. Patients will be offered the study and asked to sign consent after the initial consultation occurs. Patients at any stage of disease will be eligible; however, based on our definitive radiation therapy inclusion criteria our subject cohort will primarily consist of stage III lung cancers. The definitive radiation treatment criteria of doses ranging from 45 to 75 Gy is specifically designed to exclude patients receiving Stereotactic Body Radiation Therapy (SBRT). While patients receiving SBRT may benefit from functional avoidance; there are unique demands in the treatment planning aspects of SBRT and we believe it would be prudent to evaluate functional avoidance in patients treated with conventional fractionation prior to implanting functional avoidance in patients receiving SBRT.

The patient will also undergo 4DCT imaging as standard of care. The 4DCT data will be used to calculate 4DCT-ventilation images and the patient's 4DCT-ventilation image will be assessed for image heterogeneity using the criteria defined in section 5.4. Patients have to meet both clinical and imaging criteria to proceed with functional avoidance radiation therapy.

There are other patient and clinical factors that need to be considered with respect to radiation pneumonitis: chemotherapy regimen, immunotherapy status, smoking status, baseline lung function, and tumor location. There is no consensus in the literature regarding the effect of chemotherapy regimen, smoking status, baseline lung function, and tumor location on toxicity. For example, some studies note that certain chemotherapy agents (carboplatin/paclitaxel)[42] increase risk of radiation pneumonitis, while other studies do not find any relationship between chemotherapy regimen and risk of toxicity[43-45]. Similarly, the effect of smoking status on the risk of developing radiation pneumonitis is inconclusive. Certain studies site that smoking decreases risk of toxicity[6, 46, 47], some studies suggest inconclusive results[45, 48], while another cohort of studies suggests smoking increases chances of radiation pneumonitis[49, 50]. Generally, baseline lung function has been shown not to have an impact on the chances of developing toxicity[45, 51] with a few counter-examples suggesting that toxicity and baseline lung function may be related[52]. Several early studies suggested that patients with tumors located in the lower lobe maybe at an increased risk of toxicity[53], however, other work has shown no correlation between tumor position and toxicity[54]. Similar to other co-variates, there has been mixed data on whether immunotherapy has an impact on toxicity. We have decided to not exclude patients from the protocol based on chemotherapy regimen, immunotherapy status, smoking status, baseline lung function, and tumor position due to the inconclusive results presented in the literature. We will record these patient and clinical factors (along with other metrics) and evaluate whether each factor had an impact on the risk of developing radiation pneumonitis using analysis of variance (ANOVA).

To homogenize the study population, one of the study inclusion criteria is that there must be a planned curative intent chemotherapy, to be delivered either concurrently or sequentially in combination with radiotherapy. However, there will be situations where the decision to administer chemotherapy will change after consent has been administered. Whether the patient is receiving chemotherapy does not increase any risk to the subject in the study and functional radiotherapy has been found to have a theoretical benefit for patients being treated both with and without chemotherapy[7, 10, 14]. The study will perform a 2nd chemotherapy eligibility check prior to the start of radiation treatment to check whether the patient is still scheduled to receive chemotherapy. In the event that the chemotherapy plan changes after the consent, it will be up to discretion of the PI whether to have the patient remain in the study.

4.5 Step 2: Functional avoidance plan generation

A functional avoidance plan will be generated under the guidance of a radiation oncologist and a radiation physicist. The plan will use the patient's 4DCT-ventilation image to design radiation treatment that avoid functional portions of the lung. The functional avoidance plan will be quantitatively and qualitatively assessed using the criteria outlined in section 5.5. The calculation and evaluation of the 4DCT-ventilation image and functional avoidance plan generation will be done within a 2 week time frame and will not require any additional actions from the patient.

Table 2: Timeline of clinical protocol events experienced by the patient.

Study phase	Suggested Timeline	Procedure Seen by Subjects	Standard of care (SOC) or research (R)
Screening	-28 days from time subject signs consent form	Consultation with Radiation Oncologist	SOC
		4DCT imaging	SOC
		Patient signs consent form	R
Pre-treatment lung function imaging	Prior 3 months or as late as 1 week into radiation therapy	QOL questionnaire	R
		Nuclear medicine VQ scan	SOC/R
		PET imaging	SOC
		PFT testing	SOC
Treatment	3-8 weeks	Delivery of radiation therapy	SOC
End of treatment visit	Within the final week of radiation therapy	Visit with Radiation Oncologist	SOC
		QOL questionnaire	R
3 month follow up visit	1-5 months from the completion of radiation therapy	Appointment with Radiation Oncologist	SOC
		QOL questionnaire	R
3 month follow up lung function assessment	2-9 months from the completion of radiation therapy	4DCT-ventilation imaging	R
		Nuclear medicine VQ imaging	R
		PET imaging	SOC
		PFT testing	R
6 month follow up visit	5-9 months from the completion of radiation therapy	Appointment with Radiation Oncologist	SOC
		QOL questionnaire	R
12 month follow up visit and imaging	9-14 months from the completion of radiation therapy	Visit with Radiation Oncologist/Clinical Toxicity Assessment	SOC
		QOL questionnaire	R
		CT imaging	SOC

4.6 Step 3: Pre-treatment lung function assessment

Once the subject has enrolled in the study they will undergo a series of lung function evaluations to establish a baseline. Lung function evaluation will include CTCAE clinical toxicity assessment, thoracic QOL questionnaire (SOC), PET imaging (SOC), nuclear medicine VQ imaging (SOC/R), and PFT testing (SOC). If the subject had imaging or PFT testing done within the prior 3 months, it will be acceptable to use those data for the study. Otherwise, the testing and imaging studies should be done as close as possible to study registration. It should be noted that although the primary objective of the proposed study is to evaluate clinical toxicity, the

QOL questionnaire, PFT testing, and imaging studies will enable us to evaluate subclinical toxicity and provide further details for the subjects that do experience clinical toxicity.

4.7 Step 4: Radiation therapy treatment delivery

The subject will undergo a standard course of radiation therapy (SOC). The radiation treatment plan used to treat the subject will be the functional avoidance plan. The subject will be treated with external beam radiation therapy using a linear accelerator. On-board imaging on the linear accelerator will be used to set-up the subject to the same daily treatment position. Each week the subject will have a standard visit with the radiation oncologist to manage any side effects that may arise while the subject is undergoing radiation therapy.

4.8 Step 5: Post-treatment lung function assessment

At various time points after the completion of therapy the subject will undergo a complete evaluation of lung function status using all modalities applied to assess lung function prior to therapy. These lung function assessments will include clinical toxicity assessment using the CTCAE scoring system, QOL questionnaire, 4DCT-ventilation imaging, nuclear medicine VQ imaging, PET imaging, CT imaging, and PFT testing. On the last day of treatment the subject will have a visit with the radiation oncologist which will include a clinical assessment of lung function using CTCAE criteria (SOC) and a thoracic QOL questionnaire (R). At 3 months from completion of radiation therapy the subject will have a visit with the radiation oncologist which will include CTCAE clinical assessment of lung function (SOC) and fill out the QOL questionnaire (R). In addition, at 3 months post therapy the subject will undergo 4DCT-ventilation imaging (R), PET imaging (SOC), nuclear medicine VQ imaging (R), and PFT testing (R). The 3 month time point was chosen for follow up imaging because the highest probability of developing radiation pneumonitis occurs at 3 months after the completion of radiation therapy [55]. We will evaluate radiographic fibrosis using 1 year follow up CT imaging (SOC). Radiographic fibrosis will be defined as 25-50% of the ipsilateral lung having fibrotic presentation on 1 year follow up CT imaging. At 6 and 12 months from completion of radiation therapy the subject will have a visit with the radiation oncologist which will include a CTCAE clinical assessment of lung function (SOC) and fill out the QOL questionnaire (R).

5.0 Description of events

5.1 Subject enrollment and initial visit with radiation oncologist

The subject will have a pre-treatment, standard of care work-up visit with the radiation oncologist. During the visit, the radiation oncologist will perform a standard work-up to assess whether the subject is a good candidate for radiation therapy. The radiation oncologist will also determine whether the subject meets clinical criteria for trial enrollment. The subject will be clinically eligible if they have biopsy proven lung cancer, are prescribed definitive radiation therapy (defined as 45-75 Gy), are at least 18 years of age, and sign the informed consent. The radiation oncologist will perform a baseline clinical assessment of pre-treatment lung function using the CTCAE V4.0 toxicity scoring system[4]. The primary end-point will be the rate of CTCAE defined grade 2+ radiation pneumonitis[6]. Radiation pneumonitis is the most serious and prevalent toxicity after radiation therapy, is a severe impairment on the subject's quality of life, and can result in treatment related death. CTCAE defined radiation pneumonitis is the standard clinical metric used to evaluate thoracic toxicity and was one of the main end-point in a recent seminal national lung cancer clinical trial (RTOG 0617). CTCAE grading criteria for radiation pneumonitis is provided in Table 3.

Table 3: CTCAE grading criteria for radiation pneumonitis.

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental Activities of Daily Living (ADL)

3	Severe symptoms; limiting self-care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g.,tracheotomy or intubation)
5	Death

5.2 CT and 4DCT Imaging

Two sets of CT imaging will be acquired during the subject's initial visit as standard of care: a non-gated CT and a gated-4DCT. 4DCTs are standard CT images resolved into different phases of the breathing cycle and provide physicians with a 'movie' of the moving lung anatomy. 4DCTs allow physicians to account for breathing motion throughout the course of radiation therapy by enabling them to evaluate and encompass the motion of the tumor throughout the breathing cycle. As standard of care, every lung cancer subject receiving definitive radiation treatment will undergo standard 4DCT imaging in our department. In add to 4DCT imaging, the subject will undergo a standard non-gated CT scan to be used for treatment planning and dose calculations. During both sets of imaging, the subject will be placed in radiation treatment position and be immobilized using an alpha cradle or any other immobilization techniques deemed necessary by the radiation oncologist. Abdominal compression will be allowed at the discretion of the radiation oncologist.

5.3 4DCT-ventilation image generation

4DCT-ventilation images will be generated from the already acquired 4DCT data. It should be underlined that 4DCT-ventilation image generation will not require any additional action from the subject; we will use 4DCT data already acquired as part of the treatment process. We will use our software to generate ventilation images from the acquired 4DCT data[2, 3, 7, 18, 22]. Briefly, our algorithm calculates a density-change between different phases of the breathing cycle. The theory behind the algorithm is that the density in a given CT voxel is proportional to the amount of air present and therefore the difference in density provides the amount of air movement; which is the definition of ventilation. The result of the algorithm is a 3D spatial map of the ventilation (Figure 1) which provides information about which portions of the lung are used for breathing.

5.4 4DCT-ventilation image assessment criteria

The 4DCT-ventilation image will be assessed for image defect presence. Subjects will be allowed to proceed with functional avoidance only if they have a significant ventilation defect. Ventilation defects are indicated by a heterogeneous image with distinct areas of low and high lung function (examples shown in Figures 1, 3, and 4). The idea is that if the subject has homogenous lung function, there is no basis to preferentially spare any regions, and functional avoidance is not necessary. On the other hand, if the subject has regionally variant lung function, functional avoidance can be used to spare functional lung. We will apply both quantitative and clinical image heterogeneity criteria. The eligibility criteria for the 4DCT-ventilation image assessment will be:

1) Noted ventilation defect (scored as a binary yes or no) by the radiation oncologist and
2) 15% reduction in regional lung function.

Consultation with a multi-disciplinary team including a physicist and nuclear medicine radiologist will be encouraged. The radiation oncologist, physicist, and nuclear medicine radiologist have extensive experience with interoperation of 4DCT-ventilation images[18]. For a quantitative assessment, we will calculate the percent ventilation in each lung third (superior, middle, and inferior portions for each lung). These metrics are used clinically to assess ventilation and are intended to reflect regional and lobar ventilation[18]. If the subject's 4DCT-ventilation image shows a regional reduction in ventilation of 15% in one of the lung thirds the subject will be eligible for the trial. The 15% reduction in regional lung function was taken from our previous work which showed 15% reduction to be indicative of significant ventilation defects[32]. The 4DCT-ventilation image inclusion criteria are designed to include subjects with heterogeneous ventilation that can benefit from functional avoidance. It should be noted that 4DCT-ventilation image assessment will not require any additional effort from the subject.

5.5 4DCT-ventilation functional avoidance plan generation

A functional avoidance radiation therapy plan will be generated using the 4DCT-ventilation image. The generation of the plan will not require any action from the subject. The first portion of the planning process will be done in the same manner as a standard radiation therapy plan for lung cancer patients. The following steps describe the standard of care portion for the treatment planning process for lung cancer patients:

Radiation therapy will be delivered using external beam radiation. Allowed delivery techniques include 3D conformal techniques, intensity modulated radiation therapy (IMRT), arc therapy, or non-coplanar techniques at the discretion of the treating radiation oncologist.

Target volumes will be approved by the treating radiation oncologist, using the information obtained through clinical examination, the CT and 4DCT scan acquired within the radiation oncology department, and histologic specimens when available. When feasible and necessary, the subject's diagnostic images (CT scan, MRI study, or PET/CT imaging) will be fused with the simulation scan to delineate standard International Commission on Radiation Units[56] target volumes described below.

Gross Tumor Volume (GTV) – All known disease (including nodal disease) detected by the above methods.

Internal Gross Tumor Volume (iGTV) – GTV plus margin for the tumor motion assessed from the 4DCT imaging.

Clinical Target Volume (iCTV) – iGTV plus the region at risk for microscopic spread. This target volume will be added at the physician's discretion.

Planning Target Volume (PTV) – iGTV or iCTV plus a margin to account for subject movement and daily setup error.

Organ at Risk (OAR) Volumes – Delineation of the pertinent organs at risk will include the lung, heart, esophagus, and spinal cord. Other OARs may be delineated at the discretion of the radiation oncologist.

The radiation doses to the PTV and OARs will be in line with current standards of care for lung cancer noted in the National Comprehensive Cancer Network Guidelines[57]. Doses will range from 45-75 Gy and be delivered in 15-35 fractions. Prescriptions will be made such that 95% of the PTV will receive at least 95% of the prescription dose. Guidelines for OARs are listed in Table 4 and are in line with national recommendation[57, 58]. Final treatment radiation dose and regimen along with OAR constraints will be at the discretion of the radiation oncologist.

Table 4: Organ at risk dose constraints

Target	Dose-volume constraint
Total Lung (defined as Total Lung minus GTV)	Mean Lung Dose ≤ 20Gy
Spinal Cord	Max dose ≤ 50 Gy
Esophagus	V50Gy≤40%, mean ≤35 Gy
Heart	V40Gy≤40%, mean ≤34 Gy

The following portion provides a description of the functional avoidance portion of the planning process which is novel to the proposed protocol and is currently not standard of care. The first step will be to use 4DCT-ventilation images to create a contour of the functional portions of the lung. The contour will be created using semi-automated methods and will be called the 'functional avoid contour.' The functional avoid contour will represent the most active portions of the lung. The functional avoid contour, PTV, and other OAR contours will then be imported into the treatment planning system and used in the optimization process for the radiation treatment plan. Effort will be made to reduce dose to the functional avoid contour while still delivering the

prescribed dose to the PTV and respecting dose limits to other OARs. Optimizing and shaping the dose distribution throughout different anatomy is a standard operation within the treatment planning system software. The unique aspect of functional avoidance is that the functional avoid contour will be included in the optimization process. It should be noted that the goals of delivering the total dose to the PTV and not-exceeding doses to OARs will not be sacrificed in favor of reducing dose to the functioning lung. The priority for the optimization will be 1) Deliver the prescribed dose to the PTV 2) Meet the dose limits for OARs 3) Reduce dose to functional lung. This prioritization is designed to ensure that every functional avoidance plan will meet current standards of care.

Final radiation dose calculations for the functional avoidance plan will be done with heterogeneity corrections. Once a functional avoidance plan is made we will calculate standard dose metrics for the PTV, OARs, and functional regions. Standard dose metrics include the 3D isodose distribution, dose volume histograms (DVHs), mean doses, max doses, and volume receiving a certain dose (Vdose). For example, we will calculate the mean lung dose (MLD), max spinal cord dose, and the volume of the PTV receiving at least 95% of prescription.

In addition to standard metrics, we will calculate the combination of dose and function descriptive metrics that will allow us to evaluate how much of the functional lung was spared. Rather than evaluating dose alone, these metrics will combine dose and function. One of the metrics we will evaluate is the functional mean lung dose (fMLD). To calculate the fMLD, at each point in the lung the dose will be multiplied by the ventilation weighting and the functionally weighted doses in the lung will be averaged to calculate fMLD. The dose will be 'de-valued' in regions of poor ventilation and be 'emphasized' in regions of functional lung. The physician will review the dose-function metrics along with the rest of treatment plan and dose criteria and assess final approval of the treatment plan.

5.6 Pre-treatment lung function assessment, imaging, and PFT testing

Subjects will undergo a full pre-treatment lung function evaluation to establish a baseline. Subjects will undergo clinical, imaging, and PFT based testing. During the initial visit, the radiation oncologist will assess subject clinical lung function status using the standard CTCAE toxicity scoring system[4]. The primary end-point evaluated will be grade 2 or higher (referred to as grade 2+) radiation pneumonitis which is defined as Symptomatic; medical intervention indicated; limiting instrumental Activities of Daily Living. Although we do not expect the subject to have clinical toxicity before treatment, it will be important to establish a baseline.

In addition, it is imperative to collect subject reported outcomes to aide with the interoperation of the study, identify potential toxicity interventions (6), evaluate cost effectiveness, and because there may be a disconnect between physician and patient reported outcomes. Furthermore, a recent analysis of a recent national lung cancer clinical trial (RTOG 0617) revealed subject report QOL predicted for the worsening overall survival results in the high dose arm (7). To evaluate QOL, we will use the lung cancer subscale (LCS) of the FACT-Trials Outcome Index (FACT-TOI). FACT-TOI is a measure that sums the functional well-being, physical well-being, and the lung cancer subscale. The questionnaire is brief, user friendly, and has been validated. Most importantly, the FACT-TO1 questionnaire has been extensively used for measuring QOL for subjects with lung cancer, including in the RTOG 0617 protocol.

The subject will undergo nuclear medicine VQ imaging. Pre-treatment nuclear medicine VQ imaging is standard of care for lung cancer patients and used to evaluate pre-treatment lung function. Nuclear medicine ventilation images are generated with the subject inhaling a radioactive aerosol (technetium diethylene triamine pentaacetic acid) and radiation detectors capturing the photons emitted from the subject. Nuclear medicine perfusion is generated with intravenous injection of a radioactive technetium macro aggregated albumin and radiation detectors capturing the photons emitted from the subject. The nuclear medicine imaging will be done in the department of radiology and will be supervised by the radiologist involved with the protocol who has previously been involved with the proposed[18].

Subjects will undergo pre-treatment PET imaging to perform tumor staging. All PET imaging will be done on a PET/CT scanner and will include a CT for attenuation correction and for anatomical information overlay. PET imaging will be done in the department of radiology and be supervised by the radiologist involved with the

protocol. We will use the staging PET to assess image features that have been shown to predict for lung toxicity[40]. For either the nuclear medicine VQ imaging or PET imaging, it will be acceptable to use any images acquired within 3 months prior to step 1 enrollment. Otherwise, the subject should have nuclear medicine VQ imaging and PET imaging completed as close as possible to the study enrollment date.

The subject will undergo PFT testing. Pre-treatment PFTs are standard of care for definitive lung cancer patients and are used to assess pre-treatment lung function. PFTs use spirometry to measure air flow. We will acquire standard PFT metrics including: lung volumes, the forced expiratory volume in 1 second (FEV1), the forced vital capacity (FVC), the ratio of FEV1/FVC, and Carbon Monoxide Diffusing Capacity (DLCO). PFT acquisition will be supervised by the pulmonologist involved in the proposed protocol who has previously been involved with the proposed research[27]. Both absolute and relative PFT values will be recorded.

The primary objective of the study is to assess clinical toxicity using the CTCAE scoring system. The QOL, imaging, and PFT data are being collected to provide additional imperative information on the subjects lung function and to help assess our ability to reduce toxicity with functional avoidance.

5.7 Radiation therapy

The patient's functional avoidance plan will be used to deliver radiation therapy treatment. Treatment will be performed on a linear accelerator with on-board imaging capabilities to help align the subject to the same treatment position daily. Throughout treatment, the subject will have a weekly evaluation with the radiation oncologist to help manage health problems should any arise.

5.8 End of treatment visit with radiation oncologist

The subject will have a standard of care end of treatment visit with the radiation oncologist. During the visit the radiation oncologist will assess whether the subject has received any immunotherapy, has any new complications related to radiation treatment and perform a clinical assessment of lung function. Lung function assessment will be performed using the CTCAE scoring system[4]. In addition to pneumonitis for the lung, we will assess CTCAE toxicity for other, less common thoracic conditions including esophagitis, radiation myelopathy, and pericarditis for the esophagus, spinal cord, and heart respectively. During the consultation the subject will also be asked to fill out a thoracic QOL questionnaire designed to evaluate the subject's lung function.

5.9 3 Month follow up visit with radiation oncologist

The subject will have a standard of care 3 month follow up visit with the radiation oncologist. During the consult the radiation oncologist will assess whether the subject has any new complications related to radiation treatment and perform a clinical assessment of lung function. Lung function assessment will be performed using the standard CTCAE V 4.0 toxicity scoring system[4]. CTCAE toxicity will be assessed for the lung as well as other thoracic organs including the esophagus, heart, and spinal cord. During the visit the subject will also be asked to fill out a thoracic QOL questionnaire.

5.10 3 month post therapy lung function imaging

The subject will undergo imaging studies to assess lung function at 3 months post radiation therapy. We will have the subject undergo 4DCT imaging in the department of radiation oncology and calculate 4DCT-ventilation from the 4DCT images. The 3 month follow up 4DCT-ventilation imaging will provide us with an imaging assessment of lung function and enable us to evaluate lung function changes due to the radiation therapy by comparing pre-treatment 4DCT-ventilation images with post-treatment 4DCT-ventilation images. Post treatment 4DCT-ventilation is not standard of care and is specific to the proposed protocol. The risk to the subject is the additional radiation dose from the 4DCT imaging. The radiation dose to the subject from a single 4DCT scan is on the order of 3 cGy[59]. The typical dose used for radiation treatment will be about 6000 cGy (60Gy). Therefore, the 3 cGy additional dose from the imaging represents 0.05% additional dose compared to what the subject will have received during radiation therapy. The additional 0.05% increase in radiation dose can be justified by the lung function information gained from the imaging study.

The subject will also undergo nuclear medicine VQ imaging at 3 months after the completion of radiation treatment. Nuclear medicine VQ imaging will allow us to evaluate changes in lung function due to the radiation therapy and allow us to prospectively compare our way of imaging ventilation to the current clinical standard. Post treatment nuclear medicine VQ imaging is not standard of care and is specific to the proposed research. The only risk to the subject is the additional radiation dose. The radiation doses from nuclear medicine VQ imaging is less than 1 cGy[60]. The 1 cGy additional dose represents a 0.02% increase in dose compared to what the subject received during radiation therapy. The additional 0.02% increase in radiation dose can be justified by the lung function information gained from the imaging.

The subject will undergo PET imaging at 3 months post radiation therapy. Three month follow up PET imaging is standard of care for lung cancer patients and enables clinicians to assess treatment response and evaluate for any distant metastasis[61]. We will use PET imaging to provide an additional assessment of lung function and aid with the evaluation of post-treatment lung function changes. All post-treatment imaging will be done on the same scanner as used for pre-treatment imaging and use the same imaging parameters. The consistency in scanner and imaging parameters will aid in the quantification of changes.

5.11 3 month pulmonary function testing

The subject will undergo PFT testing at 3 months post therapy. We will use the PFT data to provide additional evaluation metrics of lung function changes due to radiation therapy. Post treatment PFTs are not standard of care for lung cancer patients (unless the patient has newly developed respiratory symptoms); however, we do not believe the additional PFT testing poses any increased risk to the subject.

5.12 6 Month follow up visit with radiation oncologist

The subject will have a standard of care 6 month follow up visit with the radiation oncologist. During the visit, the radiation oncologist will determine whether the subject has any issues due to the radiation treatment and perform a clinical assessment of lung function. Lung function assessment will be performed using the standard CTCAE V 4.0 toxicity scoring system[4]. CTCAE Toxicity will be assessed for the lung as well as other thoracic organs including the esophagus, heart, and spinal cord. During the visit the subject will also be asked to fill out a thoracic QOL questionnaire.

5.13 12 Month follow up CT imaging

The subject will undergo standard CT imaging at 12 months post radiation therapy. We will use the CT imaging to determine whether the subject has grade 2+ CTCAE defined radiation fibrosis. Grade 2 radiation fibrosis is defined as 25-50% of the ipsilateral lung having fibrotic presentation. The radiologist involved in the protocol has experience in diagnosing radiographic pulmonary injury.

5.14 12 Month follow up visit with radiation oncologist

The subject will have a standard of care 12 month follow up visit with the radiation oncologist. During the consult, the radiation oncologist will determine whether the subject has any issues due to the radiation treatment and perform a clinical assessment of lung function. Lung function assessment will be performed using the standard CTCAE V 4.0 toxicity scoring system[4]. CTCAE Toxicity will be assessed for the lung as well as other thoracic organs including the esophagus, heart, and spinal cord. During the consultation the subject will also be asked to fill out a thoracic QOL questionnaire.

It should be noted that if the subject is unwilling or unable to attend the 3, 6, or 12 month follow up visit; the protocol will allow for a toxicity assessment over the phone or by reviewing the subject's medical chart.

5.15 Summary of risks and justifications

The unique features of the proposed clinical trial that deviate from standard of care are the 4DCT-ventilation imaging and functional avoidance radiation therapy. We have underlined in the proposal how 4DCT-

ventilation is ready for use in human subjects. 4DCT-ventilation is accomplished with a novel method that uses data acquired as part of routine care. The input into our novel algorithm is 4DCT data. 4DCTs are standard of care and are used to provide a 'movie' of the moving lung anatomy to help clinicians design radiation treatment plans that account for the subject's breathing motion. 4DCT imaging is an established technique in radiation therapy that has been around since 2002. Because 4DCT-ventilation only requires software processing on already obtained 4DCT images, we believe our novel imaging modality does not pose any additional risk to the subject. We have validated 4DCT-ventilation imaging against other forms of ventilation imaging.

We have put multiple measures in place to ensure the safety of functional avoidance radiation therapy. First and foremost we will use strict target and organ at risk evaluation criteria that are standard of care for lung cancer patients; helping ensure that the functional avoidance plan meets the current standards for radiation treatment of lung cancer. The trial also provides the radiation oncologist with final authority over the approval of the functional avoidance plan; therefore, if they do not feel comfortable with any aspect of the plan, the plan will not be used for treatment. The subject will also undergo frequent mid and post-treatment evaluation of lung function; helping ensure that if thoracic toxicity arises it will be caught at an early stage. Study participants will receive involved and complex clinical care within the department, and as such will have constant contact with clinicians who can detect and avoid potential risks related to the study. If the subject does experience radiation pneumonitis, they will be treated with a standard course of steroids and be referred to pulmonology in the event that symptoms do not resolve. It should be noted, if the subject does not fit trial inclusion criteria or they chose to discontinue participation for any reason, it will in no way affect their ability to receive appropriate care from their chosen providers. We will also build in a 2 stage trial design.

The subject will undergo 3 additional follow up examinations that are not considered standard of care: the 3 month follow up nuclear medicine VQ imaging, 3 month follow up 4DCT-ventilation imaging, and PFT testing. The additional PFT testing does not pose any increased risk to the subject. The increased risk to the subject from the nuclear medicine VQ and 4DCT imaging is the increased radiation dose. The radiation dose from a 4DCT scan is 3 cGy and the radiation dose from a nuclear medicine VQ scan is 1 cGy for a total extra radiation dose of 4 cGy. As part of their radiation treatment, the subject typically receives 6000 cGy, therefore 4 cGy represents an increase in 0.07% of the total dose delivered to the subject. We will abide by the principles of ALARA (As Low As Reasonably Achievable) with respect to imaging radiation dose. We believe the ability to quantitatively evaluate lung function with VQ and 4DCT-ventilation imaging justifies the minimal increase in radiation dose to the subject.

6.0 Potential Scientific Problems

A challenge of any clinical trial is whether there will be enough subjects to demonstrate statistically significant results. Our primary objective will be to demonstrate safety by comparing the rate of grade 2+ radiation pneumonitis in our study cohort with the pneumonitis rate of 25% quoted with current standard of care techniques[6] (see section 7.1 for full statistical calculations). There are 3 possible outcomes: our pneumonitis rate is lower than 25%, is not statistically different from 25%, or is significantly higher than 25%. We expected the toxicity rates in our early phase trial to be lower or equivalent to 25%. In the unlikely event that the toxicity rates with our trial are higher than toxicity with standard therapy; we will take that as a strong indication that our proposed imaging based therapy should not be considered for a large scale trial. If the toxicity rates are not statistically different from 25%, we will perform further evaluation using quality of life metrics and imaging based end-points.

One of the challenges of the proposed work is that analyzing lung response to radiation therapy can be complex as the injury due to radiation dose is sometimes juxtaposed by improvement expected from tumor regression. In some instances subjects who do not develop clinical toxicity still develop imaging based changes and subjects who do develop clinical toxicity display important information in their imaging profiles. We hope to address the complexity of treatment assessment by acquiring and analyzing a complete data set of lung function which must include imaging and functional end-points in addition to clinical toxicity.

7.0 Data analysis plan

7.1 Statistics for primary objectives

Our primary objective is to assess the safety and preliminary efficacy of 4DCT-ventialtion functional avoidance. We will assess safety using clinical outcomes. The primary clinical outcome used will be the rate of CTCAE defined grade 2+ radiation pneumonitis. To assess safety, we will calculate the crude rate of grade 2+ radiation pneumonitis in our population and compare the results to a historical control. The rate of grade 2+ pneumonitis with current standard of care techniques has been quoted to be 25%[6] on average. Based on previous studies, we hypothesize we can reduce the radiation pneumonitis rate to 12% with functional avoidance. Using a binomial distribution (given the toxicity/no toxicity end-point), current toxicity rates of 25%, our hypothesized rate of 12%, and a study power of at least 80%, we calculate 67 subjects needed for the study. As noted in section 7.3, patients will count towards study accrual if they have a thoracic toxicity evaluation at the 3 months post radiotherapy follow-up time point. To account for screen fails and patient dropout we anticipate we will need to consent 110 patients to reach our 67 patient clinical trial goal. A Simon's two-stage design will be applied in order to stop the trial early if the rate of radiation pneumonitis is significantly higher than 25%. If there is any dropout during the trial, new subjects will be added in to warrant the evaluable number of subjects as planned. We will aim to evaluate equal number of patients from each institution to mitigate any factors associated with a given institution.

Similar to radiation pneumonitis, we will report toxicity rates for other thoracic organs and their associated binomial exact 95 CIs. In a descriptive manner we will compare our toxicity rates with those noted in the literature. Specifically, we will use historical toxicity rates of 25% for esophagitis[58], 15% for pericarditis[58], 1% for spinal cord radiation myelopathy[58].

Questionnaire QOL changes between pre-treatment and post-treatment will be characterized using standard descriptive metrics: means, medians, ranges, and standard deviations. Our primary hypothesis is that subjects on our trial will have less clinically significant decline in QOL (as measured by FACT-T0I) compared to current standard of care. Clinically significant decline will be defined as percentage of subjects with >2 point difference (out of a 5 point scale) of the LCS. The end-point used for our primary hypothesis will be the 3 month post therapy time point questionnaire. We will compare our results to the QOL results achieved with current standard of care. We will focus particularly on the QOL results from RTOG 0617 which found clinically significant QOL decline in 46% of subjects in the high dose arm and in 31% of subjects in the low dose arm. Although the primary hypothesis centers on the lung cancer subscale, physical and functional well-being data will also be collected and analyzed. We will use a one-sample t-test, Wilcoxon-Mann-Whitney test, and chi-squared distribution to analyze our results. The subject reported QOL questionnaires will provides us with an imperative tool for us to evaluate subject reported outcomes and determine the effectiveness of our novel treatment technique. Finally, we will assess overall survival and progression free survival using the Kaplan-Meier method. Survival (and reason for death) at 12 months will be recorded for the study.

There are several covariates which may influence the risk of radiation pneumonitis including smoking status and type of chemotherapy regimen. We will use analysis of variance for regression to assess the effect of chemotherapy and smoking status on toxicity rates in our study.

We hope to demonstrate safety by showing that functional avoidance results in similar or reduced radiation pneumonitis rates when compared to current standard of care techniques. We aim to show that there are no unintended consequences in using functional avoidance in terms of overall survival and toxicity to other thoracic organs including the cord, heart, and esophagus.

7.2 Statistics for secondary objectives

We will assess imaging and PFT based treatment response using radiologist observations and quantitative regional changes. Regional fibrosis, ventilation, and PET-based changes will be described using descriptive statistics (median, range, standard deviation) and evaluated using correlation coefficients, linear and

logistic regression, and dice similarity analysis. Correlation coefficients and regression analysis will enable us to quantify the magnitude and direction (stable, improvement, regression) of imaging and functional related changes.

One of the secondary objectives will be to compare 4DCT-ventilation to other forms of functional imaging in a prospective setting. We will compare 4DCT-ventilation with both nuclear medicine VQ imaging and PET imaging. Comparisons will be done using radiologist clinical observations and quantitative regional values. Quantitative results will be analyzed using bland-altman plots.

Another secondary objective will be to assess the percentage of subjects that were eligible for functional avoidance. The percentage will be calculated by taking the ratio of subjects that had lung function profiles suitable for functional avoidance and subjects that were clinically eligible (receiving 45-75 Gy). Retrospectively, we have estimated that 70% of subjects receiving 45-75 Gy have heterogeneous lung function profiles and would be eligible for functional avoidance[32]. The data in our clinical trial will enable us to validate the 70% eligibility metric in a prospective setting; which will be critical for the design of a large scale trial.

7.3 Suggested Timeline

We would like to accrue 67 subjects for our study in 2 years with about half (35) of those being accrued at our institution. In total, we see about 150 lung cancer patients a year. About 100 of the 150 patients fit the clinical profile for definitive radiation therapy (receiving 45-75 Gy). Of the 100 patients, 50 will have lung function profiles that fit the criteria outline in section 5.4. Assuming a 60% enrollment rate and a 30% drop out rate we expect approximately 21 subjects per year to enroll and complete our trial. Therefore we believe a conservative estimate for the required 35 subject trial accrual is 2 years. Beaumont Health System sees about 170 lung cancer patients annually. Based on the numbers listed above, they will also be able to accrue the required 35 subjects for the protocol. As detailed below, patients will count towards study accrual if they have a thoracic toxicity evaluation 3 months after completing radiotherapy. To account for screen fails and patient dropout we anticipate we will need to consent 110 patients to reach our 67 patient clinical trial goal.

It should be noted that we will use radiation pneumonitis at 3 months after the completion of therapy as our primary end-point. Therefore, if subjects drop out after the 3 month time point they will still be counted towards accrual and if they drop out prior to the 3 month follow up time point they will not be counted toward accrual. We will record and evaluate radiation pneumonitis at 1 year post therapy as a secondary end-point using the available data. Subjects who wish to discontinue study procedures at any point during the study have the option, as indicated in the consent form, to remain in the study and allow follow-up data to be collected. This choice to discontinue active study participation and only allow follow-up data collection will be documented.

8.0 Summary of knowledge to be gained

The most important knowledge we hope to gain is the evaluation of the safety and preliminary efficacy of 4DCT-ventilation functional avoidance. Specifically, we hope to show that 4DCT-ventilation is safe and does not results in increased toxicity when compared to current standard of care therapy techniques. Theoretically, functional avoidance radiation therapy should be safe because we are meeting current standards of care and should be effective because we are sparing functional portions of the lung. However, the safety of the novel treatment techniques needs to be demonstrated prospectively before functional avoidance can be implemented in a large scale randomized clinical trial. In order to properly assess the efficacy of functional avoidance we estimate a 200 subject, randomized, multi-institutional study is needed. Before resources are committed for a large scale, 200 subject trial, a study is needed that prospectively demonstrates safety and provides preliminary efficacy results. Our clinical trial can demonstrate that 4DCT-ventilation based functional avoidance is safe, develop the evaluation metrics, and provide efficacy results that will pave the way for a large scale randomized study.

Our imaging based secondary end-points will provide an invaluable addition to the primary clinical outcomes and are a must for a complete assessment for functional avoidance. Assessing lung response to radiation is complex as treatment related changes can be juxtaposed with improvement from tumor regression. Our study will provide a complete assessment of lung function including clinical end-points, imaging, and PFTs. With the complete lung function data set we will be able to perform a full characterize of lung response and

analyze each method of assessing lung function. Our clinical protocol proposes a prospective, rigorous, and safe study to evaluate the integration of 4DCT-ventilation functional avoidance into radiation therapy clinical practice.

9.0 Data and safety monitoring plan

The Lead Principal Investigator (PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and subject safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, Serious Adverse Events (SAEs), Unanticipated Problems (UAPs) and reportable Adverse Events (AE)s are reported to the DSMC, IRB, and Lead PI per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the CU Cancer Center DSMC within 5 business days of receiving notification of the occurrence. If the AE or SAE occurs at CU Cancer Center it will be reported to the Lead PI who will then report it to the DSMC and IRB. If the AE or SAE occurs at Beaumont it will be reported to the Site PI, then reported it to the Lead PI, and the Lead PI will report to DSMC and IRB.

Each subject's treatment outcomes will be discussed by the Site PIs and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The Lead PI will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well.

As the Lead PI in this multi-site trial, the Lead PI is responsible for organizing and conducting teleconferences with all participating sites once every 2 months. The Lead PI will also be responsible for including data from all of the participating sites within the overall trial's six month DSM report to the DSMC to include minutes from bi-monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six month review to their IRB of record at the time of continuing review. Each aspect of the clinical trial will undergo quality assurance and quality control. The subject's radiation treatment will be subject to standard radiation therapy quality assurance including an independent treatment plan check by a physicist and radiation oncologist as well as standard quality assurance for the linear accelerators. The protocol team will meet twice a year to discuss and review the data for each subject enrolled on the trial.

All data will be stored in institutional servers with restricted access protocols. Data being analyzed will be recorded and identified by subject code numbers only. Only members of the investigative group will have access to secured files or to the master list for subject code numbers and will be well educated regarding the protection of subjects' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project.

9.1 Procedures for Adverse Events - Definitions and Reporting Criteria

9.1.1 Definitions

The definition of “related” being that there is a reasonable possibility that the treatment caused the adverse event.

An adverse event is UNEXPECTED when the specificity or severity is not consistent with the current expectations of treatment complications.

Adverse Event (AE)

An AE will be defined as any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic testing.
An AE will be recorded for events related to pneumonitis, esophagitis, dyspnea, fistula, events that involved pulmonary or vascular hemorrhage, or cardiac toxicities. Any AEs noted in the patients chart by the radiation oncologist during scheduled study visits will be recorded as AEs.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Events unequivocally due to disease progression, including the development of metastatic disease, will not be reported.

9.2 Discontinuation of treatment

Study patients who have completed all study procedures and have undergone 1 year follow up will have completed the study. At least 3 months follow up is required to count towards enrollment in the study. Study patients may be prematurely terminated from the study for the following reasons:

- Physician, PI, and/or patient decides to discontinue treatment for reasons other than an AE
- Noncompliance with the study protocol
- Development of unrelated illness which compromises further participation in the study
- The subject is lost to follow up (no further data collection or
- submission will be expected)
- The subject withdraws consent (no further data collection or submission will be expected)

At termination, ongoing AEs are to be recorded, including any new AEs reported at the end of the study. Any unresolved AE at discontinuation of the study treatment should be followed until they have resolved or stabilized. Subjects may choose to stop study treatment for any reason without jeopardizing their relationship with healthcare providers.

10.0 Study Monitoring and Frequency of Monitoring Visits

The monitoring for this trial will be carried out in full compliance with all Good Clinical Practice (GCP) Guidelines, COMIRB policies and regulations and all applicable federal regulations. This study will monitored for its entire duration until the investigation is completed.

A site initiation visit (SIV) will be conducted for all participating sites prior to enrolling any subjects into this trial to document full training of all study personnel who will be delegated any specific task on the study. This visit includes but is not limited to training on the IRB approved study protocol, regulatory requirements for study conduct including but not limited to GCP guidelines, reporting of adverse events, the review of study personnel's roles and responsibilities, completion of the Delegation of Authority Log and Protocol Training, review of the monitoring plan as outlined in the protocol, and to review data collection and proper source documentation procedures.

The monitor will perform both on-site interim monitoring visits and remote monitoring off-site for all participating sites in this study. Data that is collected during the duration of this trial will be reviewed by the sponsor to identify data discrepancies, inconsistencies or any unclear information both on-site and remotely. In order to reconcile data discrepancies, queries will be sent electronically to the site(s) for data that requires clarification.

Due to the nature of this trial being a multi-center IIT (Investigator-Initiated Trial) with the CU Cancer Center as the coordinating site, as well as an early phase radiation therapy trial, this study is considered to be high risk and will need consistent routine monitoring visits. An initial monitoring visit will be performed within 2- 4 weeks of the first subject being enrolled into the trial. Subsequently, this study will then be monitored every 8-12 weeks on-site, with remote monitoring in-between scheduled on-site visits, as necessary based on the study needs, at all participating sites.

The monitor will perform routine on-site monitoring visits that include but are not limited to:

- Interface with the PI at each visit if possible, to discuss any findings, address concerns, and to update the PI and site staff on current study progress.
- Subject source documentation verification and subject eligibility
- Informed Consent review
- Verify radiation treatment
- Protocol adherence
- Review Case Report Forms and the Redcap electronic database
- Regulatory documents review
- Review and determine if all Adverse Events and Serious Adverse Events have been appropriately reported within the specified time periods required by the protocol, GCP, the IRB and any other applicable regulatory requirements

The Monitor may remotely review the following but is not limited to in-between interim visits:

- Query follow-up and resolution from on-site monitoring visits
- Adverse event and Serious adverse event review
- Electronic database verification and data clarification
- Communication between Monitor, the PI and study personnel via email and/or telephone

After monitoring visits are completed, the monitor will evaluate and summarize the results after each monitoring visit in a written report. This report will include all pertinent findings during the monitoring visit including all identifiable and reportable data and non-compliant problems ongoing in the study and recommend resolutions for noted deficiencies. Any noted deficiencies that are in need of resolution will need a corrective plan of action by the PI and/or research staff.

The PI will receive a post interim monitoring visit follow-up letter 7 to 10 business days following the completion of the monitoring visit, documenting study progress and any pertinent findings and outstanding action items that need to be resolved. The PI will need to sign and date the letter after reviewing, and keep the original on site. The Monitor may review the letter at the next subsequent visit to ensure it has been reviewed, signed and dated by the PI in a timely manner.

Upon completion or termination of the study, the sponsor will ensure that each participating site undergo a site Close-out Monitoring visit prior to final closure of the study. The Monitor will assure that all necessary site close-out procedures and activities have been completed which include but are not limited to query resolution, Case Report Form completion, notification to local IRB and regulatory authorities of study closure, record retention arrangements finalized, AE and SAE resolution, and all essential documents are available and present in the PI's file. The Monitor will complete a final close-out report documenting completion of the Close-out Monitoring visit and forward a study Close-out follow up letter to the PI(s) at the participating site(s) to be reviewed, signed and dated, and file a copy on site for record retention.

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Appendix A – A snapshot of study assessments

Study Procedures	**Screening**	**Pre-treatment lung function imaging**	**Treatment**	**End of treatment Visit**	**Follow up**			
					3 month follow up visit	3 month follow up lung function assessment	6 month follow up visit	12 month follow up visit and imaging
Suggested timelines	*-28 days from time of consent*	*Prior 3 months or as late as 1 week into radiation therapy*	3-8 weeks	Within the final week of radiation therapy	*1-5 months from completion of radiation therapy*	*2-9 months from completion of radiation therapy*	*5-9 months from completion of radiation therapy*	*9-14 months from completion of radiation therapy*
Procedures								
Informed consent	X							
Confirm eligibility (Inclusion/exclusion criteria)	X							
Radiation Oncologist visit (Adverse Event Assessment)	X			X	X		X	X
QOL questionnaire		X		X	X		X	X
PFT		X				X		
4DCT Imaging	X					X		
Nuclear medicine VQ scan		X				X		
PET Imaging		X				X		
CT Imaging		X						X
Radiation therapy			X					