Official Study Title:	Novel Lung Functional Imaging for Personalized Radiotherapy
ClinicalTrials.gov ID:	NCT02308709
Secondary ID:	CCRO030
Protocol Version:	Version 19: October 22, 2020

Novel Lung Functional Imaging for Personalized Radiotherapy

Protocol #: CCRO030

Principal Investigator:
Tokihiro Yamamoto, Ph.D.
Assistant Professor
Department of Radiation Oncology
UC Davis Comprehensive Cancer Center
[redacted]

Co-Principal Investigator:
Megan Daly, M.D.
Assistant Professor
Department of Radiation Oncology
UC Davis Comprehensive Cancer Center
[redacted]

Co-Investigators:
Stanley Benedict, Ph.D.
Professor and Vice Chair of Clinical Physics
Department of Radiation Oncology
UC Davis Comprehensive Cancer Center
Department of Radiation Oncology
[redacted]

Ken Y. Yoneda, M.D.
Professor of Clinical Internal Medicine
Division of Pulmonary and Critical Care
University of California Davis Medical Center
[redacted]

Friedrich D. Knollmann, M.D., Ph.D.
Professor of Clinical Radiology
Department of Radiology
University of California Davis Medical Center
[redacted]

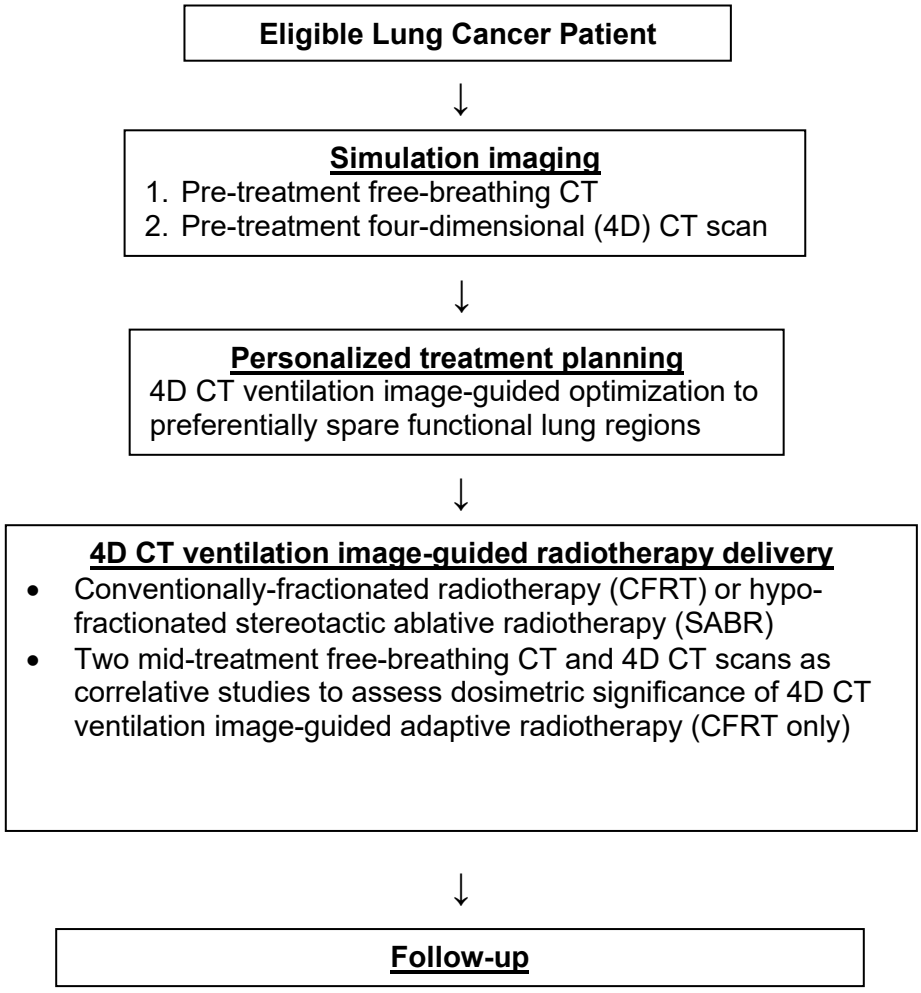
Biostatistics:
Lihong Qi, Ph.D.
Associate Professor
Department of Public Health Sciences
University of California Davis
[redacted]

[redacted]

Protocol Version and Date:	Version 19: October 22, 2020 Version 18: March 11, 2019

Index

SCHEMA


Eligible Lung Cancer Patient
Simulation imaging
1. Pre-treatment free-breathing CT
2. Pre-treatment four-dimensional (4D) CT scan
Personalized treatment planning
4D CT ventilation image-guided optimization to preferentially spare functional lung regions
4D CT ventilation image-guided radiotherapy delivery
• Conventionally-fractionated radiotherapy (CFRT) or hypo-fractionated stereotactic ablative radiotherapy (SABR)
• Two mid-treatment free-breathing CT and 4D CT scans as correlative studies to assess dosimetric significance of 4D CT ventilation image-guided adaptive radiotherapy (CFRT only)
Follow-up

Introduction and Background Data

1.1. Overall survival of lung cancer patients treated with radiotherapy remains disappointing with substantial toxicity

Lung cancer is the leading cause of cancer death in the US and worldwide. In 2011, approximately 221,130 new cases of lung or bronchial cancer were expected to be diagnosed in the US, and 156,940 patients (71%) are estimated to die of this disease (Siegel *et al.*, 2011). Approximately 64% of non-small-cell lung cancer (NSCLC) patients and 54% of small-cell lung cancer (SCLC) patients will require radiotherapy at least once (Tyldesley *et al.*, 2001). Stereotactic body radiotherapy (SBRT) has provided excellent clinical outcomes for early stage NSCLC, *e.g.*, three-year local control, 98%; three-year survival, 56% in the Radiation Therapy Oncology Group (RTOG) 0236 trial (Timmerman *et al.*, 2010). For advanced stage NSCLC, however, Machtay *et al*. have recently reported a five-year survival rate of 15% for patients treated with chemoradiotherapy from seven RTOG trials (Machtay *et al.*, 2012). The maximum tolerated dose is limited by the risk of toxicity, especially for advanced disease. For example, an attempt to escalate the prescribed dose in the early Phase I portion of RTOG 0117 was unsuccessful because of severe toxicity, including Grade 3 and 5 radiation pneumonitis (Bradley *et al.*, 2005b). Radiation pneumonitis is a common, potentially fatal toxicity that occurs in 5-30% of lung cancer patients treated with radiotherapy (Marks *et al.*, 2010; Palma *et al.*, 2013).

1.2. Personalized radiotherapy that avoids high-functional lung regions may reduce toxicity and facilitate safe investigations designed to improve tumor control

To address the critical problem described above, we propose a novel paradigm, *i.e.*, functional image-guided personalized radiotherapy that avoids high-functional lung regions. It may reduce toxicity and facilitate safe investigations designed to improve tumor control. This hypothesis is supported by several findings in the literature. Abratt *et al.* have found that patients whose irradiated lung regions had >35% of the total lung perfusion are significantly more likely to manifest post-treatment decreases in diffusing capacity and worsening of dyspnea score (Abratt *et al.*, 1990). Seppenwoolde *et al*. (Seppenwoolde *et al.*, 2004) and Vinogradskiy *et al.* (Vinogradskiy *et al.*, 2013) have demonstrated better correlations between the function-weighted lung dose and pneumonitis than those between the physical lung dose and pneumonitis.

1.3. Novel lung ventilation imaging based on 4D CT has high translational potential and advantages

4D CT ventilation imaging is a novel promising technique (Guerrero *et al.*, 2005) (Figure 1) that has high translational potential and advantages (*e.g.*, higher resolution, lower cost, and/or greater availability) over competing modalities. Thus, there has been growing interest in using this technology for functional avoidance treatment planning (Yaremko *et al.*, 2007; Yamamoto *et al.*, 2011) and treatment/toxicity assessment (Ding *et al.*, 2010; Vinogradskiy *et al.*, 2012). Animal studies have demonstrated high accuracy, *e.g.*, correlation with xenon (Xe)-CT ventilation as reference (Fuld *et al.*, 2008; Reinhardt *et al.*, 2008; Ding *et al.*, 2012) as well as high reproducibility (Du *et al.*, 2012). Human studies have reported relatively inconsistent results (Castillo *et al.*, 2010; Castillo *et al.*, 2012; Du *et al.*, 2012; Mathew *et al.*, 2012; Yamamoto *et al.*, 2012; Yamamoto *et al.*, 2014), but reasonable correlations with PFT parameters (Yamamoto *et al.*, 2014), SPECT ventilation (Yamamoto *et al.*, 2014), hyperpolarized ^{3}He MR ventilation (Mathew *et al.*, 2012) and SPECT perfusion (Castillo *et al.*, 2012) indicate the potential for 4D CT ventilation imaging to have physiological significance.

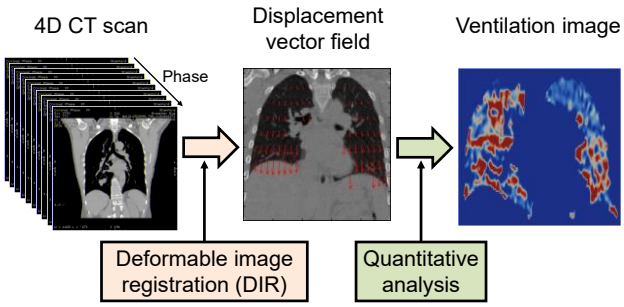


Figure 1. Schematic diagram for 4D CT ventilation imaging through (1) acquisition of 4D CT scans, (2) spatial mapping of different respiratory phases of 4D CT images using DIR, deriving a displacement vector field, and (3) analysis of the resultant displacement vector field to quantify regional volume change, a surrogate for ventilation.

1.4. We propose a novel paradigm, 4D CT ventilation image-guided personalized radiotherapy to improve therapeutic gains

Many investigators have demonstrated a dosimetric benefit of functional image-guided radiotherapy that avoids high-functional lung regions using various modalities, including SPECT perfusion (Marks *et al.*, 1995), hyperpolarized gas magnetic resonance (MR) ventilation (Ireland *et al.*, 2007) and 4D CT ventilation (Yaremko *et al.*, 2007; Yamamoto *et al.*, 2011). We have demonstrated that 4D CT ventilation image-guided radiotherapy planning reduces the mean dose to high-functional lung regions by 2 Gy on average compared to anatomic image-guided planning (Yamamoto *et al.*, 2011), indicating that 4D CT ventilation image-guided radiotherapy is estimated to reduce pneumonitis by 4%, corresponding to over 5,000 patients/year in the US, based on the fact that about 60% (Tyldesley *et al.*, 2001) of 221,130 new lung cancer patients (Siegel *et al.*, 2011) are treated with radiotherapy. It is assumed that the probability of pneumonitis increases with the mean dose to high-functional lung regions in a similar manner to the published data on the mean dose to the total lung (Marks *et al.*, 2010). There have been no attempts to assess the safety/feasibility or clinical significance of such treatment in human subjects. In this clinical trial, we will assess the safety and feasibility of 4D CT ventilation image-guided personalized radiotherapy. We will deliver personalized radiotherapy treatments for lung cancer patients, and follow up patients to assess the safety and feasibility. The hypothesis to be tested is: *4D CT ventilation image-guided personalized radiotherapy can be delivered safely for lung cancer*.

2. Specific Objectives and Hypotheses

2.1. Primary objective and hypothesis

Objective: Assess the safety and feasibility of 4D CT ventilation image-guided personalized radiotherapy that selectively avoids irradiating highly-functional lung regions for lung cancer.
Hypothesis: 4D CT ventilation image-guided personalized radiotherapy can be delivered safely for lung cancer.

2.2. Secondary objectives

1) Assess long-term toxicity from 4D CT ventilation image-guided personalized radiotherapy as scored by the NCI-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
2) Estimate the clinical significance of 4D CT ventilation image-guided personalized radiotherapy by evaluating: (1) clinical and subclinical endpoints for pulmonary toxicity (including symptomatic radiation pneumonitis and post-treatment changes in pulmonary function tests (PFTs), 6-min walk test, and BODE index); (2) correlation between those endpoints and functional dose-volume parameters.
3) Assess local tumor control after 4D CT ventilation image-guided personalized radiotherapy.
4) Quantify the dosimetric significance of 4D CT ventilation image-guided adaptive radiotherapy.

5) Investigate whether in vivo EPID dosimetry can detect clinically significant anatomic changes for patients treated with CFRT.

3. Patient Selection

3.1. Inclusion criteria

1) Primary lung cancer or metastatic disease to the lungs to be treated with either conventionally-fractionated radiotherapy (CFRT) or hypo-fractionated stereotactic ablative radiotherapy (SABR).
2) Age restriction and/or gender/ethnic restrictions: Patients must be ≥18 years of age. There are no gender or ethnic restrictions.
3) Concurrent chemotherapy is allowed, but not required.
4) Life expectancy with treatment should be ≥6 months in the estimation of the treating physicians.
5) Zubrod performance status ≤2
6) Adequate marrow and hepatic function defined as Hgb ≥8; platelets ≥100k; ANC≥1500; LFTs ≤2x upper limit of normal and creatinine ≤2.0 or creatinine clearance of ≥40
7) Patient must be able to provide study specific informed consent prior to study entry.

3.2. Exclusion criteria

1) Prior radiotherapy for thoracic cancer or other malignancy leading to any overlap of planned radiotherapy fields.
2) For patients undergoing definitive CFRT, patients with distant metastatic disease are not eligible.
3) For patients undergoing SABR, both early stage primary lung cancer patients and those with limited metastatic disease to the lungs are eligible; however, patients with oligometastatic disease should have a controlled primary and no more than one other involved organ system.
4) Children (<18 years of age), pregnant women, University of California employees and students, and prisoners will be excluded from this study.
5) We will carefully consider the inclusion of patients with severe artifacts in 4D CT images, which deteriorate the accuracy of ventilation computation.

4. Imaging Procedures

4.1. Scans to be acquired

Patients will be positioned in the supine position on a flat tabletop with immobilization (a customized thermoplastic immobilization cast or a molded foam cradle for stabilization for CFRT; a stereotactic body frame or BodyFIX system for SABR). Abdominal compression will be used for all SABR patients unless tumor motion <1 cm can be reliably demonstrated by fluoroscopy and confirmed by 4D CT without compression. The following scans will be obtained:

Simulation imaging

1) Free-breathing CT extending from the angle of the mandible cranially to the inferior extent of the liver caudally at a slice thickness of ≤3 mm for CFRT and ≤2 mm for SABR. IV contrast to assist in delineation of the mediastinal nodal regions is permitted but not required.
2) Pre-treatment 4D CT scan to include lungs from apices to diaphragm and full disease extent.
3) If abdominal compression is used, an additional 4D CT scan will be acquired without abdominal compression.

During a course of treatment (CFRT only)

1) Two mid-treatment free-breathing CT scans performed at 16-20 Gy and 30-34 Gy to include lungs from apices to diaphragm and full disease extent based on the same method as simulation.
2) Two mid-treatment 4D CT scans performed with the mid-treatment free-breathing CT scans to include lungs from apices to diaphragm and full disease extent.

4.2. 4D CT ventilation computation

4D CT ventilation images at the peak-inhale phase will be created using a software tool developed and provided by a collaborator, Dr. Kabus at Philips Research. This software has not received regulatory clearance. This tool loads anonymized 4D CT images acquired at UC Davis as input, and provides ventilation images calculated based on a non-parametric/volumetric DIR algorithm (Staring *et al.*, 2010) and two classes of ventilation metric: Hounsfield unit (HU)-change (Simon, 2000; Fuld *et al.*, 2008) and Jacobian (Reinhardt *et al.*, 2008) as output.

5. Radiation Therapy

5.1. Dose specifications

CFRT

Patients undergoing CFRT will receive a total of 60 Gy in 30 fractions. The plan will be normalized such that ≥95% of the PTV receives the prescription dose. Minimum dose to the PTV (defined as the dose to the lowest 0.03 cc) must be ≥90% of the prescription dose (≥85% will be scored as a minor deviation) and maximum dose must be ≤115% of the prescription dose to ≤0.03 cc (≤120% will be scored as a minor deviation).

SABR

Patients undergoing SABR will receive a total of 54 Gy in 3 fractions for peripheral tumors or 55 Gy in 5 fractions for centrally located tumors (defined as within 2 cm of the proximal bronchial tree or PTV touching mediastinal structures or pleura; tumors with significant chest wall overlap of PTV can also be treated over 5 fractions at treating physician discretion). The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.

5.2. Technical parameters

Radiotherapy will be delivered by intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) with an Elekta linear accelerator at energies ≥6 MV. The dose behind the patient, i.e., transmission dose images will be acquired with a linear accelerator-mounted electronic portal imaging device (EPID). The acquired data will be analyzed with a research version of the PerFRACTION software (Sun Nuclear, Melbourne, FL) (not FDA-approved/cleared).

5.3. Immobilization and simulation

See section 4.

5.4. Treatment planning

Treatment plans will be created using a research version and a clinical version of the Pinnacle treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI). The research version has not received regulatory clearance, whereas the clinical version has a FDA 510(k) clearance and is routinely used for treatment planning in the Department of Radiation Oncology. First, the research version will be used to create an initial 4D CT ventilation image-guided treatment plan. The initial plan will then be transferred to the clinical version for final dose calculation and evaluation by a radiation oncologist to ensure that the plan quality is clinically appropriate, *i.e.*, target coverage is adequate and critical structures are spared as necessary.

5.4.1. Target volumes

CFRT

1) GTV: Will include visible tumor as identified by diagnostic and/or treatment planning CT or PET, including pathologically enlarged lymph nodes >1 cm in short axis, hypermetabolic by PET (SUV >3), or pathologically confirmed to contain malignant cells. Elective treatment of nodal areas is not permitted.
2) CTV: A CTV margin of 5-10 mm will be added at the discretion of the treating physician to account for potential microscopic spread. This margin may be shaved off overlapping adjacent structures including chest wall, heart, esophagus, great vessels, and vertebral bodies.
3) ITV: Will include the full range of tumor motion of the primary tumor and nodal target as delineated by 4D CT. Depending upon tumor location, a maximum intensity projection or maximal inhale/exhale scans may be used to identify the ITV.
4) PTV: An additional margin of 5-10 mm will be added to account for setup error.

SABR

1) GTV: Will include visible tumor as identified by diagnostic and/or treatment planning CT or PET.
2) CTV: No additional margin for microscopic spread will be used. For purposes of this protocol, ITV=CTV.
3) ITV: Will include the full range of tumor motion of the primary tumor and nodal target as delineated by 4D CT. Depending upon tumor location, a maximum intensity projection or maximal inhale/exhale scans may be used to identify the ITV.
4) PTV: An additional margin of 5 mm will be added to account for setup error.

5.4.2. Lungs

We will create 4D CT ventilation image-guided personalized radiotherapy plans that selectively avoid irradiating highly-functional lung regions. The peak-inhale 4D CT ventilation image will be aligned with the free-breathing CT image (primary image set for treatment planning) by rigid image registration. The overlapped lungs between the free-breathing CT and peak-inhale 4D CT images will be contoured. Note that the final total lung volume for dose-volume analysis will include combined right and left lungs, excluding the GTV, trachea, and main and lobar bronchi. IMRT or VMAT optimization will be performed by setting higher weights to highly-functional lung regions than poorly-functional regions to meet the dose-volume constraints shown below.

CFRT

Tissue	Constraints
Lung (right and left minus CTV)	V_{20} <37% (<40% will be scored as a minor deviation) Mean lung dose (MLD) <20 Gy (<21 Gy will be scored as a minor deviation) Functional V_{20} <30% (Vinogradskiy *et al.*, 2013) (<33% will be scored as a minor deviation) Functional MLD <19 Gy (Vinogradskiy *et al.*, 2013) (<20 Gy will be scored as a minor deviation)

SABR

Tissue	3 fraction			5 fraction		
	Volume	Vol Max	Max to 0.03 cc	Volume	Vol Max	Max to 0.03 cc
Lung (right and left minus CTV)	<1500 cc <1000 cc	10.5 Gy* 11.4 Gy*	NA	<1500 cc <1000 cc	12.5 Gy* 13.5 Gy*	NA
	Functional V_{20} <4% (Barriger *et al.*, 2012) (<7% will be scored as a minor deviation) Functional MLD <4 Gy (Barriger *et al.*, 2012) (<5 Gy will be scored as a minor deviation)					

*Constraints marked by asterisk are guidelines and will not be scored as a protocol deviation if not achieved. For SABR in patients with more than one target, the lung dose-function constraints (functional MLD and V20) are guidelines and will not be scored as a protocol deviation if not achieved. **Other constraints represent absolute limits and treatment delivery that cannot meet these constraints will constitute a major protocol violation**.

5.4.3. Other critical structures

The following other critical structures will be contoured on the free-breathing CT image for both CFRT and SABR patients.

1) Spinal Cord: The spinal cord should be contoured on every axial CT slice as the bony limits of the spinal canal, extending from at least 10 cm superior to the superior-most extent of the PTV, and caudally 10 cm below the inferior-most extent of the PTV.
2) Heart: The heart, along with the pericardial sac, should be contoured from its base to apex, beginning superiorly at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extending inferiorly to the apex of the heart.
3) Esophagus: The entire circumference of the esophagus including the outermost fatty dventitia should be contoured based on mediastinal windowing, and should be contoured on every axial CT slice at least 10 cm cranial and caudal to the PTV.
4) Brachial Plexus: The right and left brachial plexi should be contoured separately. The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.
5) Proximal bronchial tree: Should extend from 2 cm above the carina and include the right and left main bronchi, extending distally to the first bifurcation of the named bronchi.
6) Trachea: Should include the tracheal and cartilage rings extending at least 10 cm superior to the superior extent of the PTV.
7) Great Vessels: Should include the aorta, right and left pulmonary arteries, and superior vena cava at least 10 cm superior and inferior to PTV.
8) Skin: The skin will be defined as a rind encompassing the outer 0.3 cm of the body surface.

CFRT

Tissue	Max Dose to 0.03 cc (Gy)	Other Constraints
Spinal cord	47 Gy	
Esophagus	70 Gy	Mean <34 Gy*
Brachial Plexus	66 Gy*	
Heart/Pericardium	70 Gy	60 Gy to <33%; 45 Gy to <66%
Great Vessels	70 Gy*	
Trachea	70 Gy	
Central Airways	68 Gy	

SABR

Tissue	3 fraction			5 fraction		
	Volume	Vol Max	Max to 0.03 cc	Volume	Vol Max	Max to 0.03 cc
Spinal cord	<0.35 cc	18 Gy	21.9 Gy	<0.35 cc	23 Gy	30 Gy
Esophagus	<5 cc	17.7 Gy*	25.2 Gy	<5 cc	19.5 Gy	35 Gy
Brachial Plexus	<3 cc	20.4 Gy*	24 Gy*	<3 cc	27 Gy*	30.5 Gy*

Heart/Pericardium	<15 cc	24 Gy*	30 Gy	<15 cc	32 Gy*	38 Gy
Great Vessels	<10 cc	39 Gy*	45 Gy	<10 cc	47 Gy*	53 Gy
Trachea	<4 cc	15 Gy*	30 Gy	<4 cc	16.5 Gy*	40 Gy
Central Airways	<0.5 cc	18.9 Gy*	23.1 Gy	<0.5 cc	21 Gy*	33 Gy
Skin	<10 cc	30 Gy*	33 Gy*	<10 cc	36.5 Gy*	39.5 Gy*

*Constraints marked by asterisk are guidelines and will not be scored as a protocol deviation if not achieved. **Other constraints represent absolute limits and treatment delivery that cannot meet these constraints will constitute a major protocol violation**.

6. Pulmonary Function Test, 6-min Walk Test, and BODE Index

We will perform PFTs (including spirometry, lung volumes and diffusing capacity) at pre-treatment and at 6-month follow-up, 6-min walk test (recommended but optional at pre-treatment and follow-up), and calculate the BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index for those who complete the 6-min walk tests.

7. Adverse Event Reporting

7.1. Adverse event monitoring

Subjects will be carefully monitored for adverse events. This monitoring includes clinical and laboratory tests. This study will utilize the NCI-CTCAE version 4.0 for toxicity and Adverse Event Reporting. A copy of the NCI-CTCAE version 4.0 can also be downloaded from http://ctep.cancer.gov/reporting/ctc.html. Adverse events will be assessed each cycle, and the highest grade according to NCI-CTCAE version 4.0 will be recorded. Adverse events will be assessed in terms of seriousness, severity, and relationship to the study procedures.

7.2. Adverse Event Definitions

Adverse Events (AEs)

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).

Serious Adverse Events (SAEs)

Any adverse experience occurring during any part of the protocol treatment and 30 days after that results in any of the following outcomes:

- Results in death.
- Is life-threatening (refers to an AE 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 an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent.

Intensity (Severity) of the Adverse Event

The intensity or severity of AEs will be graded according to the NCI-CTCAE version 4.0 criteria.

Adverse Event Documentation

All AEs occurring after the subject has received the first dose of investigational treatment will be fully recorded in the subject's case record form. Documentation will be supported by an entry in the subject's file. Each event will be described in detail along with start and stop dates, severity, relationship to study treatment, action taken and outcome.

7.3. Study Procedure Adverse Events

Treatment-related AEs will be categorized and graded based on the NCI-CTCAE version 4.0. Treatment should be interrupted for Grade 4 in-field toxicity and resumed when that toxicity has decreased to Grade ≤2 as detailed below. If treatment is interrupted for >2 weeks, the patient should be removed from study treatment. Expected AEs include reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, esophagitis and radiation pneumonitis. Radiation-induced myocarditis or transverse myelitis rarely occurs at doses <50 Gy. Radiographic evidence of density change and subsequent fibrosis of the lung will occur within lung volume receiving ≥20 Gy, usually within the first six months after initiation of treatment.

Esophagitis

Esophageal complaints are common with thoracic radiotherapy. Esophagitis typically manifests as dysphagia, odynophagia, and reflux symptoms. Acute esophagitis occurs during a course of treatment and often persists for several weeks after treatment (Werner-Wasik *et al.*, 2010). The symptoms of severe esophagitis (Grade ≥3) typically peak 4-8 weeks from the beginning of treatment. Late esophageal damage, typically stricture and associated dysphagia, develops ~3-8 months after treatment. Esophagitis does not constitute a reason to interrupt or delay radiotherapy provided oral intake is sufficient to maintain hydration. If Grade 3 or 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less.

Acute esophageal toxicity should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are as follows:

1) Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages.
2) Ketoconazole 200 mg PO q day OR Fluconazole 100 mg PO q day until completion of radiation.
3) Mixture of: 2% viscous lidocaine: 60 cc, Mylanta: 30 cc, sucralfate (1 gm/cc): 10 cc; Take 15-30 cc PO q3-4 hrs prn (Contraindications: pts on Dilantin, Cipro, Digoxin).
4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation.
5) Grade 4 esophagitis: hold radiotherapy until Grade ≤2.
6) Occasionally, narcotics may be required.

Radiation pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Approximately 80% of radiation pneumonitis is clinically manifest within 10 months of treatment (Marks *et al.*, 2010). The clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids,

bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve. At that point, a clinical decision whether to finish therapy will be made by the treating physicians.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be reported to Co-PI, Dr. Daly (or designee).

Reporting Forms:

- SAE Report Form
- Reporting to the FDA: US FDA MedWatch 3500A (http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm)

Each serious AE will be followed up until resolution or stabilization, by submission of updated reports to the Co-PI, Dr. Daly. Both serious and non-serious AEs will be reported in accordance with UCD Institutional Review Board (IRB) Administration and UCD Cancer Center policies. The UC Davis IRB can be reached at (916) 703-9151.

8. Data Review and Management

8.1. Patient Registration

Once signed, informed consent has been obtained and all pre-treatment evaluations have been performed, patients will be entered on study according to UCD Cancer Center policy. To register a patient, the research nurse or data manager will complete the Eligibility Checklist and the Patient Registration Form. A patient accession number will then be assigned. Study biopsy and administration of study drug may not be initiated until the patient is registered. An original signed and dated participant Informed Consent document will reside in a secured location within the UCD Department of Radiation Oncology. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

8.2. Data Collection

All data will be collected using the UCD Database System (eVELOS) forms.

9. Statistical Considerations

9.1. Study endpoints

Primary endpoints

(1) Grade ≥3 radiation pneumonitis, (2) grade ≥3 esophagitis, (3) other grade ≥3 AEs that occur ≤12 months after treatment and drop-out defined as definitely, probably, or possibly related to the protocol treatment.

Secondary endpoints

1) Long-term toxicity, as scored by the NCI-CTCAE version 4.0.
2) Clinical and subclinical endpoints for pulmonary toxicity (including radiation pneumonitis and post-treatment changes in PFTs, 6-min walk test, and BODE index).
3) Correlation between the clinical/subclinical endpoints for pulmonary toxicity and functional dose-volume parameters.

4) Local tumor control.
5) Lung functional dose-volume metrics, including the functional V_x (fV_x) (% volume receiving ≥x Gy) and functional mean lung dose (fMLD).

9.2. Patient accrual

We aim to accrue 34 patients over 1.5 years. Patient accrual will continue until either the projected sample of 34 patients has been enrolled, or the number of patients developing Grade ≥3 AEs or drop-out due to intolerance of treatment exceeds five. Patient follow-up will continue until all patients have at least two years of follow-up, to allow for assessment of longer-term AEs.

9.3. Analysis plan

Primary endpoints: (1) Grade ≥3 radiation pneumonitis, (2) grade ≥3 esophagitis, (3) other grade ≥3 AEs that occur ≤12 months after treatment and drop-out defined as definitely, probably, or possibly related to the protocol treatment.

We will estimate the rates of AEs and tolerability with exact 95% confidence intervals. 4D CT ventilation image-guided personalized radiotherapy will be considered safe if AE rates are lower than the following acceptable rates (determined based on the published toxicity data for locally advanced lung cancer patients): (1) grade ≥3 radiation pneumonitis, 13% (Jiang *et al.*, 2012), (2) grade ≥3 esophagitis, 21% (Wei *et al.*, 2006), and (3) other grade ≥3 AEs and drop-out, 20% (Bradley *et al.*, 2015).

Secondary endpoints

Analyses of secondary endpoints will be primarily descriptive rather than hypothesis testing.

Toxicity will be summarized by frequency and exact 95% confidence intervals, overall and separately by grade and organ system.

The clinical significance of 4D CT ventilation image-guided personalized radiotherapy will be estimated by evaluating: (1) clinical and subclinical endpoints for pulmonary toxicity (including radiation pneumonitis, PFTs, 6-min walk test, and BODE index); (2) correlation between those endpoints and functional dose-volume parameters. Radiation pneumonitis will be assessed at follow-up every 3 months for a minimum of 2 years after treatment using the NCI-CTCAE version 4.0. Post-treatment changes in PFTs (including spirometry, lung volumes and diffusing capacity), 6-min walk test, and the BODE index will be evaluated at the time of 6-month follow-up. Using composite treatment plans, the following lung functional dose-volume parameters will be calculated: functional mean lung dose (fMLD), functional V_{20} (fV_{20}) and functional effective dose (fD_{eff}) (Vinogradskiy *et al.*, 2013), which will be correlated with the endpoints for pulmonary toxicity.

To quantify the dosimetric significance of 4D CT ventilation image-guided adaptive radiotherapy, we will create: (1) 4D CT ventilation image-guided adaptive radiotherapy plan, (2) 4D CT ventilation image-guided non-adaptive radiotherapy plan, and (3) anatomical image-guided non-adaptive radiotherapy plan. We will evaluate the lung functional dose-volume parameters, including the functional V_x (fV_x) (% volume receiving ≥x Gy) and functional mean lung dose (fMLD) for each plan. The lung functional dose-volume parameters of the 4D CT ventilation image-guided adaptive radiotherapy plans will be compared with those of the 4D CT ventilation image-guided non-adaptive radiotherapy plans and anatomical image-guided non-adaptive radiotherapy plans using a paired *t*-test. Furthermore, we will also investigate sensitivity to the number (1 or 2) and time (16-20 Gy and/or 30-34 Gy) of plan adaptation to design an optimal adaptive radiotherapy strategy, *e.g.*, when and how many time(s) to adapt the original plan.

9.4. Sample size

We will examine the safety of 4D CT ventilation image-guided personalized radiotherapy based on AEs during the first 12 months of follow-up and toxicity-related drop-out. With a sample size of 34 patients, we will be able to see grade ≥3 radiation pneumonitis, grade ≥3 esophagitis and other grade ≥3 AEs at least once with 94%, 99% and 99% probabilities, respectively, assuming

true rates of 13%, 21% and 20%, respectively. We can also estimate these AE rates with a standard error of 8%, 9% and 9%, respectively.

Approximately 37% of patients are estimated to die over the first 12 months of follow-up according to the published survival data for patients with locally advanced NSCLC (Machtay *et al.*, 2012). Also 1% of patients are estimated to drop out for reasons unrelated to the protocol treatment. To compensate for possible loss of patients for such reasons, a sample size of 34 (increased by 38% from 20) will be used.

9.5. Interim analysis to monitor study progress

Interim reports will be prepared twice yearly until the final analysis has been completed. In general, reports will describe accrual, projected completion date, pre-treatment characteristics of patients, and frequency and severity of adverse events.

10. Study Timelines

Task	Year 1		Year 2	
Enroll 34 patients and deliver 4D CT ventilation image-guided personalized radiotherapy				
Assess the safety/feasibility of 4D CT ventilation image-guided personalized radiotherapy				
Estimate the clinical significance of 4D CT ventilation image-guided personalized radiotherapy				

11. Patient Assessments

11.1. Pre-treatment assessments

Staging workup will include PET/CT, MRI of the brain (this is only required for locally advanced patients and for other patients, it is optional), and CT of the chest and upper abdomen performed with contrast (recommended, but not required) within 8 weeks prior to registration, as well as histologic or cytologic documentation of lung cancer. PFT to include routine spirometry, lung volumes, and diffusing capacity should be performed within 8 weeks before treatment. CBC with differential and comprehensive metabolic panel will be obtained within 14 days of enrollment to ensure adequate marrow reserve and end organ function.

11.2. Evaluation during treatment

In an effort to improve the capture and consistency of AE reporting, essential AEs commonly associated with lung cancer radiotherapy, including but not limited to esophagitis, pneumonitis, pericarditis, dermatitis, hematologic toxicity, and chest wall pain are to be assessed at baseline and weekly during treatment using the NCI-CTCAE version 4.0. Additional AE terms and grading criteria can be accessed online at http://ctep.cancer.gov/reporting/ctc.html. Guidelines for management of AEs are outlined in section 7. History, physical examination, Zubrod performance status, and body weight will also be obtained weekly during treatment.

11.3. Discontinuation of protocol treatment

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease
- Unacceptable adverse events [at the discretion of the treating physician(s)]
- Patient refusal
- If protocol treatment is discontinued, follow-up and data collection will continue as specified.

11.4. Post-treatment evaluations

In an effort to improve the capture and consistency of AE reporting, essential AEs commonly associated with lung cancer radiotherapy, including esophagitis, pneumonitis, pericarditis, dermatitis, hematologic toxicities, spinal cord injury, chest wall pain, and are to be assessed at follow-up every 3 months for a minimum of 2 years after treatment using the NCI-CTCAE version 4.0. Additional AE terms and grading criteria can be accessed online at http://ctep.cancer.gov/reporting/ctc.html. Post-treatment PFTs will be performed at 6 months post-treatment, to include routine spirometry, lung volumes, diffusing capacity and diffusing capacity.

Disease response and progression will be monitored by the use of contrast-enhanced CT of the chest every 3 months for the first 2 years post-treatment. PET/CT will be obtained at the discretion of the treating physician or to follow up suspicious findings on CT. Patient assessments are outlined in Appendix III.

11.5. Discontinuation of follow-up assessments

Follow-up assessments may be discontinued for either of the following reasons:

- Patient refusal
- Patient's withdrawal of consent; Data for these patients will not be used for analysis.
- Otherwise, patients will be followed at least every three months for two years following treatment.

12. Ethical and Regulatory Considerations

12.1. Ethical conduct of the study

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to (International Conference on Harmonization) ICH guidelines. Specifically, the study will be conducted under a protocol reviewed by the IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2. Informed consent procedures

Informed consent will be obtained before conducting any study-specific procedures (*i.e.*, all of the procedures described in the protocol). The process of obtaining informed consent will be documented in the patient source documents.

All patients will have signed an informed consent for participation in research activities in accordance with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights.

12.3. Protocol deviations

PI, Dr. Yamamoto and Co-PI, Dr. Daly will discuss all protocol waivers and/or treatment deviations immediately, and will submit an amendment to the protocol if the deviation is likely to occur again. All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center policies.

13. Data Safety and Monitoring

In addition to the requirements for AE reporting as outlined in section7, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on AE reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

14. Data Sharing

The anonymized pre- and mid-treatment CT image data acquired in this study will be shared with external investigators upon request for other research activities. To date we have received a request from Dr. Rene Werner (University Medical Center Hamburg-Eppendorf, Germany) who will develop a repeat 4D CT image database that will be publicly accessible for various developments and investigations such as respiratory motion modeling. Anonymized CT image data will be transferred through cloud-based secure file sharing, *e.g.*, Box (https://ucdavis.app.box.com).

15. Potential Benefits to Subjects

Potential benefits from this study include a potentially lower risk to experience pulmonary toxicity by 4D CT ventilation image-guided personalized radiotherapy compared to standard anatomic image-guided radiotherapy. However, there is no guarantee that the patient will benefit directly from participating in this study.

16. Economic Burden to Subjects

There will be no additional costs to subjects because of participation in this study.

17. Sharing of Results with Subjects

The results of this study will not be shared with subjects or subjects' primary care physicians.

18. Devices

In vivo EPID dosimetry with the PerFRACTION software calculates the dose of the day reconstructed from EPID measurements in patient anatomy using the treatment plan CT image data. The calculated dose of the day will be compared with the plan dose to estimate changes in patient anatomy. The performance of in vivo EPID dosimetry will be evaluated by comparing the PerFRACTION analysis results with the dose of the day calculated with the mid-treatment CT image data as reference. This device poses no additional risk to subjects.

REFERENCES

Abratt R P, Willcox P A and Smith J A 1990 Lung cancer in patients with borderline lung functions--zonal lung perfusion scans at presentation and lung function after high dose irradiation *Radiother Oncol* **19** 317-22

Barriger R B, Forquer J A, Brabham J G, Andolino D L, Shapiro R H, Henderson M A, Johnstone P A and Fakiris A J 2012 A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy *Int J Radiat Oncol Biol Phys* **82** 457-62

Bradley J, Graham M V, Winter K, Purdy J A, Komaki R, Roa W H, Ryu J K, Bosch W and Emami B 2005a Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma *Int J Radiat Oncol Biol Phys* **61** 318-28

Bradley J, Paulus R, Komaki R, Masters G A, Forster K, Schild S E, Bogart J, Garces Y I, Narayan S, Kavadi V, Nedzi L A, Michalski J M, Johnson D, MacRae R M, Curran W J, Choy H and RTOG 2013 A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617 *J Clin Oncol* **31** 7501 (Abstract)

Bradley J D, Graham M, Suzanne S, Byhardt R, Govindan R, Fowler J, Purdy J, Michalski J, Gore E and Choy H 2005b Phase I results of RTOG L-0117; a phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with Inoperable NSCLC *J Clin Oncol* **23** 7063 (Abstract)

Bradley J D, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces Y I, Narayan S, Iyengar P, Robinson C, Wynn R B, Koprowski C, Meng J, Beitler J, Gaur R, Curran W, Jr. and Choy H 2015 Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study *Lancet Oncol* **16** 187-99

Carey Sampson M, Katz A and Constine L S 2006 Stereotactic body radiation therapy for extracranial oligometastases: does the sword have a double edge? *Semin Radiat Oncol* **16** 67-76

Castillo R, Castillo E, Martinez J and Guerrero T 2010 Ventilation from four-dimensional computed tomography: density versus Jacobian methods *Phys Med Biol* **55** 4661-85

Castillo R, Castillo E, McCurdy M, Gomez D R, Block A M, Bergsma D, Joy S and Guerrero T 2012 Spatial correspondence of 4D CT ventilation and SPECT pulmonary perfusion defects in patients with malignant airway stenosis *Phys Med Biol* **57** 1855-71

Ding K, Bayouth J E, Buatti J M, Christensen G E and Reinhardt J M 2010 4DCT-based measurement of changes in pulmonary function following a course of radiation therapy *Med Phys* **37** 1261-72

Ding K, Cao K, Fuld M K, Du K, Christensen G E, Hoffman E A and Reinhardt J M 2012 Comparison of image registration based measures of regional lung ventilation from dynamic spiral CT with Xe-CT *Med Phys* **39** 5084-98

Du K, Bayouth J E, Cao K, Christensen G E, Ding K and Reinhardt J M 2012 Reproducibility of registration-based measures of lung tissue expansion *Med Phys* **39** 1595-608

Fu X L, Huang H, Bentel G, Clough R, Jirtle R L, Kong F M, Marks L B and Anscher M S 2001 Predicting the risk of symptomatic radiation-induced lung injury using both the physical and biologic parameters V(30) and transforming growth factor beta *Int J Radiat Oncol Biol Phys* **50** 899-908

Fuld M K, Easley R B, Saba O I, Chon D, Reinhardt J M, Hoffman E A and Simon B A 2008 CT-measured regional specific volume change reflects regional ventilation in supine sheep *J Appl Physiol* **104** 1177-84

Guerrero T, Sanders K, Noyola-Martinez J, Castillo E, Zhang Y, Tapia R, Guerra R, Borghero Y and Komaki R 2005 Quantification of regional ventilation from treatment planning CT *Int J Radiat Oncol Biol Phys* **62** 630-4

Hayman J A, Martel M K, Ten Haken R K, Normolle D P, Todd R F, 3rd, Littles J F, Sullivan M A, Possert P W, Turrisi A T and Lichter A S 2001 Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial *J Clin Oncol* **19** 127-36

Hope A J, Naqa E I, Bradley J D, Vivic M, Lindsay P E, Bosch W R, Purdy J A and Deasy J O 2004 Radiation pneumonitis/fibrosis risk based on dosiemtric, clinical, and location-related factors *Int J Radiat Oncol Biol Phys* **60** S204 (Abstract)

Ireland R H, Bragg C M, McJury M, Woodhouse N, Fichele S, van Beek E J, Wild J M and Hatton M Q 2007 Feasibility of image registration and intensity-modulated radiotherapy planning with hyperpolarized helium-3 magnetic resonance imaging for non-small-cell lung cancer *Int J Radiat Oncol Biol Phys* **68** 273-81

Jenkins P, D'Amico K, Benstead K and Elyan S 2003 Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART) *Int J Radiat Oncol Biol Phys* **56** 360-6

Jiang Z Q, Yang K, Komaki R, Wei X, Tucker S L, Zhuang Y, Martel M K, Vedam S, Balter P, Zhu G, Gomez D, Lu C, Mohan R, Cox J D and Liao Z 2012 Long-term clinical outcome of intensity-modulated radiotherapy for inoperable non-small cell lung cancer: the MD Anderson experience *Int J Radiat Oncol Biol Phys* **83** 332-9

Komaki R, Lee J S, Milas L, Lee H K, Fossella F V, Herbst R S, Allen P K, Liao Z, Stevens C W, Lu C, Zinner R G, Papadimitrakopoulou V A, Kies M S, Blumenschein G R, Jr., Pisters K M, Glisson B S, Kurie J, Kaplan B, Garza V P, Mooring D, Tucker S L and Cox J D 2004 Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer: report of a randomized comparative trial *Int J Radiat Oncol Biol Phys* **58** 1369-77

Machtay M, Bae K, Movsas B, Paulus R, Gore E M, Komaki R, Albain K, Sause W T and Curran W J 2012 Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the radiation therapy oncology group *Int J Radiat Oncol Biol Phys* **82** 425-34

Maguire P D, Sibley G S, Zhou S M, Jamieson T A, Light K L, Antoine P A, Herndon J E, 2nd, Anscher M S and Marks L B 1999 Clinical and dosimetric predictors of radiation-induced esophageal toxicity *Int J Radiat Oncol Biol Phys* **45** 97-103

Marks L B, Bentzen S M, Deasy J O, Kong F M, Bradley J D, Vogelius I S, El Naqa I, Hubbs J L, Lebesque J V, Timmerman R D, Martel M K and Jackson A 2010 Radiation dose-volume effects in the lung *Int J Radiat Oncol Biol Phys* **76** S70-6

Marks L B, Spencer D P, Sherouse G W, Bentel G, Clough R, Vann K, Jaszczak R, Coleman R E and Prosnitz L R 1995 The role of three dimensional functional lung imaging in radiation treatment planning: the functional dose-volume histogram *Int J Radiat Oncol Biol Phys* **33** 65-75

Mathew L, Wheatley A, Castillo R, Castillo E, Rodrigues G, Guerrero T and Parraga G 2012 Hyperpolarized (3)He magnetic resonance imaging: comparison with four-dimensional x-ray computed tomography imaging in lung cancer *Acad Radiol* **19** 1546-53

Palma D A, Senan S, Tsujino K, Barriger R B, Rengan R, Moreno M, Bradley J D, Kim T H, Ramella S, Marks L B, De Petris L, Stitt L and Rodrigues G 2013 Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis *Int J Radiat Oncol Biol Phys* **85** 444-50

Reinhardt J M, Ding K, Cao K, Christensen G E, Hoffman E A and Bodas S V 2008 Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation *Med Image Anal* **12** 752-63

Rosenman J G, Halle J S, Socinski M A, Deschesne K, Moore D T, Johnson H, Fraser R and Morris D E 2002 High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial *Int J Radiat Oncol Biol Phys* **54** 348-56

Seppenwoolde Y, De Jaeger K, Boersma L J, Belderbos J S and Lebesque J V 2004 Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer *Int J Radiat Oncol Biol Phys* **60** 748-58

Siegel R, Ward E, Brawley O and Jemal A 2011 Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths *CA Cancer J Clin* **61** 212-36

Simon B A 2000 Non-invasive imaging of regional lung function using x-ray computed tomography *J Clin Monit Comput* **16** 433-42

Singh A K, Lockett M A and Bradley J D 2003 Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal radiotherapy *Int J Radiat Oncol Biol Phys* **55** 337-41

Staring M, Klein S, Reiber J H C, Niessen W J and Stoel B C 2010 Pulmonary Image Registration with elastix using a Standard Intensity-Based Algorithm. In: *Proc. of the Medical Image Analysis For The Clinic - A Grand Challenge, MICCAI,*

Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E and Choy H 2010 Stereotactic body radiation therapy for inoperable early stage lung cancer *JAMA* **303** 1070-6

Tyldesley S, Boyd C, Schulze K, Walker H and Mackillop W J 2001 Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach *Int J Radiat Oncol Biol Phys* **49** 973-85

Vinogradskiy Y, Castillo R, Castillo E, Tucker S L, Liao Z, Guerrero T and Martel M K 2013 Use of 4-dimensional computed tomography-based ventilation imaging to correlate lung dose and function with clinical outcomes *Int J Radiat Oncol Biol Phys* **86** 366-71

Vinogradskiy Y Y, Castillo R, Castillo E, Chandler A, Martel M K and Guerrero T 2012 Use of weekly 4DCT-based ventilation maps to quantify changes in lung function for patients undergoing radiation therapy *Med Phys* **39** 289-98

Wei X, Liu H H, Tucker S L, Liao Z, Hu C, Mohan R, Cox J D and Komaki R 2006 Risk factors for acute esophagitis in non-small-cell lung cancer patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy *Int J Radiat Oncol Biol Phys* **66** 100-7

Werner-Wasik M, Pequignot E, Leeper D, Hauck W and Curran W 2000 Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated

esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy *Int J Radiat Oncol Biol Phys* **48** 689-96

Werner-Wasik M, Yorke E, Deasy J, Nam J and Marks L B 2010 Radiation dose-volume effects in the esophagus *Int J Radiat Oncol Biol Phys* **76** S86-93

Yamamoto T, Kabus S, Lorenz C, Mittra E, Hong J C, Chung M, Eclov N, To J, Diehn M, Loo B W and Keall P J 2014 Pulmonary ventilation imaging based on four-dimensional CT: Comparison with pulmonary function tests and SPECT ventilation images *Int J Radiat Oncol Biol Phys* **In press**

Yamamoto T, Kabus S, von Berg J, Lorenz C, Chung M P, Hong J C, Loo B W, Jr. and Keall P J 2012 Reproducibility of four-dimensional computed tomography-based lung ventilation imaging *Acad Radiol* **19** 1554-65

Yamamoto T, Kabus S, von Berg J, Lorenz C and Keall P J 2011 Impact of four-dimensional computed tomography pulmonary ventilation imaging-based functional avoidance for lung cancer radiotherapy *Int J Radiat Oncol Biol Phys* **79** 279-88

Yaremko B P, Guerrero T M, Noyola-Martinez J, Guerra R, Lege D G, Nguyen L T, Balter P A, Cox J D and Komaki R 2007 Reduction of normal lung irradiation in locally advanced non-small-cell lung cancer patients, using ventilation images for functional avoidance *Int J Radiat Oncol Biol Phys* **68** 562-71

Yorke E D, Jackson A, Rosenzweig K E, Braban L, Leibel S A and Ling C C 2005 Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study *Int J Radiat Oncol Biol Phys* **63** 672-82

APPENDIX I:

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5 Death (Karnofsky 0).

APPENDIX II:

Eligibility Checklist

_____ (Y) 1. Does the patient have histologically documented primary lung cancer (NSCLC or SCLC)? or histologically documentation of a solid tumor with clear radiographic evidence of spread to the lungs amenable to SBRT (for SBRT patients only; if CT-guided lung biopsy is deemed unsafe by interventional radiology, documented multidisciplinary review confirming radiographic diagnosis of early stage lung cancer or lung metastasis may be used)

_____ (Y) 2. Is definitive thoracic radiotherapy planned?

- Conventionally-fractionated radiotherapy (CFRT) (with or without concurrent chemotherapy)
- Stereotactic ablative radiotherapy (SABR)

_____ (Y) 3. Is the patient ≥18 years of age?

_____ (Y) 4. Is the life expectancy with treatment ≥6 months?

_____ (Y) 5. Is the Zubrod performance status 0-2?

_____ (Y) 6. Does the patient have adequate marrow reserve defined as an ANC ≥1500, plt ≥100,000, Hgb ≥8 g/d?

_____ (Y) 7. Does the patient have adequate end organ function defined as LFTs ≤2x upper limit of normal and creatinine ≤2.0 or creatinine clearance ≥40?

_____ (Y) 8. Is the patient able to provide study specific informed consent?

_____ (N) 9. Has the patient had prior radiotherapy or other malignancy leading to any overlap of planned radiotherapy fields?

_____ (Y/N) 10. Is concurrent chemotherapy planned?

_____ (Y/N) 11. Was a CT with contrast of lung and upper abdomen performed within 8 weeks of registration? (Recommended)

_____ (Y) 12. Was an FDG-PET performed for staging within 8 weeks of registration?

_____ (Y) 13. Does the patient have locally advanced disease?

_____ (Y) 14. If yes on #13, was an MRI or CT of the brain performed for staging within 8 weeks of registration?

_____ (N) 15. Does the patient have any evidence of malignant pleural or pericardial effusion?

_____ (N) 16. Does the patient have radiographic evidence of distant metastases?

_____ (Y/NA) 17. Has the patient agreed to use an effective method of contraception?

_____ (N) 18. If female, is the patient pregnant or lactating?

APPENDIX III:

Patient Assessments

Assessments	Pre-study entry	At time of simulation	Mid-RT (8-10 fx)	Mid-RT (15-17 fx)	Weekly during RT	Q3 months for 2 years post-RT
Evaluations						
History/Physical	≤21 days				X	X
Zubrod, weight	≤21 days				X	X
Histologic or cytologic tumor evaluation****	No Time Limit					
Protocol-specific AE evaluation	≤21 days				X	X
Pulmonary function test	≤3 months					X*
6-min walk test	≤42 days					X†
BODE index	≤42 days					X‡
Imaging (staging)						
CT w/ contrast of lung/upper abdomen	≤56 days †††					X
MRI brain***	≤56 days					As clinically indicated
PET/CT	≤56 days					As clinically indicated
Imaging (RT planning and study)						
Free-breathing CT		X	X§	X**		
4D CT		X	X††	X‡‡		
Labs						
CBC with differential	≤14 days				X	X
Comprehensive metabolic panel including LFTs and creatinine	≤14 days					X

* At 6-month post-RT follow-up only.
† At 6-month post-RT follow-up only.
‡ At 6-month post-RT follow-up only.
§ CFRT only.
** CFRT only.
†† CFRT only.
‡‡ CFRT only.
***Required for locally advanced patients only
††† Recommended
****Biopsy mandatory for CFRT only
CT w/ contrast for SBRT Q3 months for 1 year, then as clinically indicated