Pilot Study of Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging for the assessment of radiation therapy outcome for liver cancer patients

Protocol Number: **18-2874**

Principal Investigator: **Moyed Miften, PhD (Radiation Oncology)**

Version Date: 01/16/2020

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), **Moyed Miften, PhD (Radiation Oncology)** is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
IIT	Investigator-Initiated Trial
RT	Radiation Therapy
DCE-CT	Dynamic Contrast Enhanced Computed Tomography
HCC	Hepatocellular Carcinoma
SBRT	Stereotactic Body Radiation Therapy
RECIST	Response Evaluation Criteria In Solid Tumors
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
K_{Trans}	Volume transfer constant
SOC	Standard of Care

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: *Pilot Study of Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging for the assessment of radiation therapy outcome for liver cancer patients*

Objectives:

- ***Primary Objective:***

Investigate the association between radiation therapy dose distribution and change in perfusion measurement following treatment.

- ***Secondary Objective:***

Explore any demographic differences in perfusion metrics.

Endpoint:

- ***Primary Endpoint:***

Primary endpoints include therapeutic radiation dose delivered and DCE-CT profusion metrics at baseline, following first treatment, and 6 weeks after treatment. Profusion metrics include: KTrans (aka extraction-flow product), blood volume and blood flow.

- ***Secondary Endpoint:***

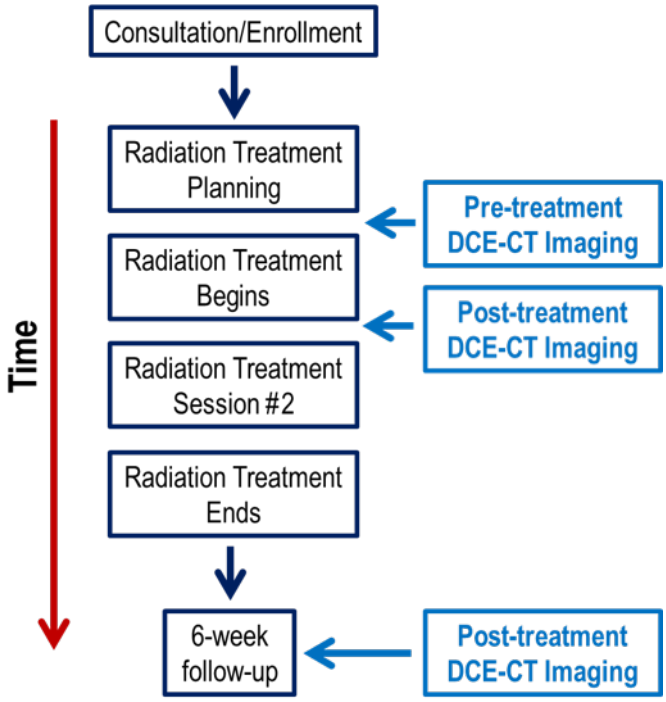
Demographic information (e.g., sex, age, race, etc.) will be combined with primary profusion endpoints.

Population:

- ***Sample size***
  - *Maximum number of participants that can be enrolled is 15 (allow for screen failures)*
  - *Minimum number of participants to be enrolled 10 (number of participants needed to answer scientific question/aims)*
- ***Gender*** *Male and Female*
- ***Age Range*** *18-100*
- ***Demographic group*** We expect patients enrolled on the study to have consistent gender, age, racial, and ethnic distributions to the population living in the state of Colorado.
- ***General health status*** *Liver HCC or Metastases.*
- ***Geographic location*** *Receiving treatment at UC Metro*

Phase:	*Pilot*
Number of Participating Sites enrolling participants:	*1*
Study Duration:	*12 months*

SCHEMATIC OF STUDY DESIGN



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1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The proposed study is in the field of radiation oncology, where functional imaging will be used to assess the outcome of radiation therapy (RT) for liver cancer patients.

Radiation therapy for liver cancer

Liver cancer is a prevalent public health problem. The number of new liver cancer cases was estimated to be 39,000 in 2016. Furthermore, liver cancer was estimated to represent approximately 5% of all cancer deaths in 2016. The five-year survival rate of all liver cancers is estimated to be 18% [1]. Liver cancer is comprised of intrahepatic bile duct cancers (25%) and hepatic cell carcinomas (75%). Since less than 25% of hepatic cell carcinomas are eligible for surgical resection, radiation therapy is a treatment option for many liver cancer patients [2,3]. However, therapy success is suboptimal. Optimization of cancer therapy based on a patient's unique biological characteristics, called "personalized cancer therapy", is becoming achievable [4]. One aspect of the patient's unique tumor microenvironment is the characteristics of blood perfusion. Though there are several imaging modalities that can quantify perfusion, DCE-CT is one accessible option. In addition, this study focuses on using SBRT as the radiation therapy treatment modality. SBRT delivers radiation therapy over a short time interval (typically, 3-8 sessions). This differs from conventional external beam radiation therapy, where a typical treatment course can last anywhere from 10 to 30 sessions, or more (this is dependent on the total radiation dose to the tumor). Historical experiences using large-field liver RT have had limited success, because tolerable doses of whole-liver RT (approximately 30 Gy) are insufficient to control most lesions [5-7]. Higher doses of whole-liver RT are associated with a significant risk of radiation-induced liver damage. Recent data have demonstrated that high-dose partial liver RT and SBRT may be safer and more effective than whole-liver RT for patients with liver tumors [8-12].

The smaller number of treatment session associated with SBRT helps to reduce patient burden, and may have unique biological effect on the tumor vasculature not found in the conventional form of radiation therapy [13]. McCammon et al [14] demonstrated a dose-effect for liver tumors. They showed increased dose and smaller gross tumor volume were significant predictors of higher local control. Lesions treated to a nominal dose of 54 Gy or greater had a 3-year actuarial local control rate of 89.3% compared with 59.0% and 8.1% for those treated to 36–53.9 Gy and less than 36 Gy. On multivariate analysis, only increased dose retained statistical significance.

DCE-CT for radiation therapy

Blood flow is a vital characteristic of the tumor microenvironment. Before treatment, perfusion may help to predict whether patients will respond to therapy. Measuring change in perfusion after therapy may be used to assess the success of therapy. Assessment of SBRT is traditionally accomplished using change in tumor morphology, using the RECIST criteria [15]. However, this is problematic because tumor volume change does not necessarily describe change in tumor physiology. In addition, large necrotic regions of tissue may be included in the morphological quantification [16].

Quantification of tumor perfusion has been accomplished in several modalities including MRI and CT [17,18]. Recent advances in scanner and image quality has made CT a viable modality for the quantification of perfusion in Oncology. Some of the advantages of measuring perfusion with CT instead of MRI include, but are not limited to: increased spatial resolution, decreased scan time, and study and scanner cost.

Perfusion is the transport of blood to a unit volume of tissue per unit of time and usually refers to the blood transport at the capillary level. CT perfusion is based on the increase and subsequent decrease of contrast agent concentrations in tissues as a function of time. The typical CT perfusion protocol consists of a pre-contrast image acquisition followed by dynamic image acquisitions performed sequentially after intravenous injection of an iodinated CT contrast agent. This allows the temporal changes in CT attenuation in the tissue volume of interest to be measured. Modern CT scanners (>16slices) allow scanning of large volumes of liver tumors, including the portal vein. The tissue enhancement measured after contrast material injection can be divided into two temporal phases. In the first phase, the enhancement is mainly due to the contrast material within the intravascular space, and thus the enhancement is determined by the blood flow. In the second phase, tissue enhancement results as contrast material passes from the intravascular to the extravascular-extracellular space, and thus the enhancement depends on the blood volume and the permeability of capillaries to the contrast agent.

After CT data acquisition, various CT perfusion parameters can be calculated. Image processing is performed to correct for motion during the scan, and manual selection of arterial (and/or portal) input functions and ROI definition allows model-based voxel wise computation of perfusion parameters. The effective time-intensity curve obtained from liver tissue is a result of an overlay of both the arterial and the portal venous components of perfusion. The normal liver is predominantly supplied by the low-pressure portal vein (75%) and supplemented by high-pressure hepatic artery (25%), but HCC or metastatic liver tumors can lead to global or regional perfusion changes. For example, patients with HCC may display increased hepatic arterial flow from the appearance of unpaired arteries. In the case of hepatic metastasis, proliferation of endothelial cells may result in increased hepatic arterial flow.

CT Perfusion Parameters

To obtain CT perfusion parameters, several kinetic model-based approaches have been developed. Single-compartment models allow for estimates of blood flow, blood volume, and MTT. Blood flow refers to the volume flow rate of blood through the vasculature (mL/min/100 mL). Blood volume is the volume of blood within the vasculature that is actually flowing (mL/100 mL). MTT is average time it takes for blood to traverse between the arterial inflow and the venous outflow, measured in seconds. Dual-compartment models are necessary to extract parameters that describe the interstitial space. Permeability surface area product is the product of permeability and the total surface area of capillary endothelium in a unit mass of tissue or tumor (measured as mL/min/100 mL). Flow extraction product is the product of blood flow and the extraction fraction, which is the fraction of contrast agent arriving at the tissue that leaks into the extravascular space in a single passage through the vasculature (measured as mL/min/100 mL).

CT perfusion parameters can thus be related to the pathologic features of tumor angiogenesis, although the relationship is complex. Blood volume and blood flow are known to correlate with microvessel density within the tumor. Blood volume reflects the density of tumor microvessels, and is not affected by cardiac output. Permeability-related values such as permeability surface area product and flow extraction product are surrogates for vascular leakiness directly related to poorly formed vascular basement membrane. Decreased MTT usually reflects the presence of arteriovenous shunts, which are frequently demonstrated in the tumor.

The utility of perfusion falls under two categories: prediction of toxicity following radiation therapy, and outcome assessment as measured by dose response from radiation therapy treatment. Perfusion will characterized for a number of different parameters from a pharmacokinetic model. Multiple pharmacokinetic models can describe perfusion. For completeness, we will examine several models including: tissue homogeneity, Tofts, extended Tofts, and Patlak. Model goodness of fit will be assessed with root mean square error. The following perfusion parameters, derived

from previously mentioned pharmacokinetic models, will be quantified for each DCE-CT session: blood flow, blood volume of vascular space, blood volume of extracellular space, and intra-compartment plasma flow. For each model, these perfusion parameters will have the mean, extremums, and standard deviation of each parameter value calculated.

The utilization of DCE-CT for outcome assessment in RT has been previously studied in several cancer sites, including the liver. However, no study, to the best of our knowledge, has attempted to use DCE-CT as an outcome assessment tool for SBRT treatment of liver cancer. This study aims to gather preliminary data to assess the feasibility of using change in perfusion measurements following SBRT of liver cancer for outcome assessment. In this study, outcome assessment will be done using therapeutic radiation dose delivered as a surrogate measurement for treatment response. With the assumption that there is a positive relationship between treatment response and therapeutic radiation dose delivered, should this prove feasible, data captured in this study will be used to power a larger study aimed at developing a model that uses perfusion measurements for outcome assessment and prediction of prognosis following SBRT treatment.

2.2 RATIONALE

We are proposing a pilot study to evaluate the feasibility of Dynamic Contrast Enhanced Computed Tomography (DCE-CT) imaging for outcome assessment of radiation therapy (RT) for the treatment of liver HCC and metastases. DCE-CT, also known as perfusion CT, is a functional imaging modality that uses repeated computed tomography imaging after injection of an iodine-based contrast agent. DCE-CT allows for a quantitative assessment of blood flow in malignant solid tumors and healthy surrounding tissue. This data provides for patient-specific information about the blood-flow characteristics of the tumor, as well as surrounding healthy tissue. The goal of this study is to use each patient's tumor perfusion information for outcome assessment of radiation therapy for the treatment of liver HCC and metastases.

In this study, we propose to focus on Stereotactic Body Radiation Therapy (SBRT) as the radiation therapy treatment modality. SBRT delivers radiation therapy over a short time interval (3-8 sessions). This differs from conventional external beam radiation therapy, where a typical treatment course can last anywhere from 10 to 30 sessions. The smaller number of treatment session associated with SBRT may have unique biological effect on the tumor vasculature not found in the conventional form of radiation therapy.

Measuring change in perfusion after therapy may be used to assess the success of therapy. Assessment of RT is traditionally accomplished using change in tumor morphology, using the RECIST criteria [16]. However, this tumor volume change does not necessarily describe change in tumor physiology. In addition, large necrotic regions of tissue may be included in the morphological quantification[18]. The utilization of DCE-CT for outcome assessment in RT has

been previously studied in several cancer sites, including the liver [1,3-5]. However, no study, to the best of our knowledge, has attempted to use DCE-CT as an outcome assessment tool for SBRT treatment of liver cancer. This study aims to determine if perfusion changes from SBRT of liver cancer may be used for outcome assessment and prediction of prognosis.

Quantification of tumor perfusion has been accomplished in several modalities including MRI and CT [6,7]. Recent advances in scanner and image quality has made CT a viable modality for the quantification of perfusion in Oncology. Some of the advantages of measuring perfusion with CT instead of MRI include, but are not limited to: increased spatial resolution, decreased scan time, and study and scanner cost.

Summary:

Previous studies in other cancer sites have shown DCE-CT is suitable for use in human subjects. In addition, these studies have shown DCE-CT provides useful information for outcome assessment of radiation therapy. No work has studied DCE-CT for outcome assessment of SBRT treatment of liver malignancies. The preliminary results of our work shows that the DCE-CT imaging protocol has been optimized, and is suitable for patient use.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Study participants will receive contrast enhanced CT scans. Adverse reactions following the use of CT contrast are usually mild to moderate, self-limited, and transient. In clinical studies, CT contrast was associated with the following adverse reactions at a frequency greater than 1%: pain (2.8%), burning sensation (1.4%), nausea (1.2 %), hot flashes (1.5%), and warmth (1.1%). Less well defined but perhaps more important is the risk of contrast-induced nephropathy, which has incidence of 2% in general population but can have high (~30%) incidence in patients with chronic renal impairment.

Patients who participate in this study will also receive slightly higher doses of ionizing radiation than those who do not, due to the extra imaging scans; on the order of 5 mGy to tissues of the abdomen. Patients will go on to receive SBRT for liver malignancies, which forms the primary component of the normal ionizing radiation dose in this population. This treatment delivers an average of roughly 10 Gy to normal tissue; the additional imaging represents a 0.05% increase in overall ionizing radiation dose from radiotherapy related procedures. We expect the additional DCE-CT scans will result in no additional adverse events (AEs).

2.3.2 KNOWN POTENTIAL BENEFITS

The goal of this study is to determine if perfusion, as measured from DCE-CT, can be imaged in the liver to assess treatment response from radiation therapy. This may provide unique physiological information that will improve outcome assessment, as well as predict treatment efficacy, for patients treated with SBRT for liver cancer. Specifically, this study investigates if perfusion characteristics, as well as their respective changes from pre-treatment to post-treatment DCE-CT imaging, may have a relationship with prognosis. This will potentially provide a strong measure of treatment prognosis that will provide the physician with crucial information that may guide follow-up treatments if prognosis is predicted to be poor.

Additionally, this study will provide preliminary data that will help design a future investigation into the predictive performance of perfusion at pre-treatment and intra-treatment. The ability of pre-treatment perfusion characteristics to predict response will be examined. This is potentially a powerful tool to predict patient-specific response before treatment begins. It may be possible to customize treatment planning based on pre-treatment perfusion characteristics.

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- Justify the importance of the knowledge gained: This study protocol proposes a prospective, rigorous, and safe study to provide preliminary data to assess the utility of DCE-CT liver imaging in radiation oncology.

3 OBJECTIVES AND PURPOSE

Primary Objective: Investigate the association between the delivered radiation therapy dose distribution and the change in perfusion measurement following treatment.

The goal of this study is to determine if perfusion, as measured from DCE-CT, can be imaged in the liver to assess treatment response from radiation therapy. Total therapeutic radiation dose delivered during SBRT will be used as a surrogate measurement for treatment response. This may provide unique physiological information that will improve outcome assessment, as well as predict treatment efficacy, for patients treated with SBRT for liver cancer.

Specifically, this study investigates if perfusion characteristics, as well as their respective changes from pre-treatment to post-treatment DCE-CT imaging, may have a relationship with therapeutic radiation dose. This will potentially provide a strong measure of treatment prognosis that will

provide the physician with crucial information that may guide follow-up treatments if prognosis is predicted to be poor. Additionally, we will be able to assess if DCE-CT imaging parameters changes after liver SBRT treatment are reproducible and relative to normal liver function.

Secondary Objective: Explore any demographic differences in perfusion metrics.

The secondary objective will be used to provide descriptive information on demographic differences in perfusion metrics. Should a larger study be warranted this information will be crucial in study design and analysis to control for demographic differences.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a pilot study designed to evaluate the feasibility of DCE-CT imaging for outcome assessment of radiation therapy for the treatment of liver cancer. Because this is a pilot study, no clinical decisions or interventions will deviate from standard of care.

Pre-treatment perfusion assessment will be performed before the start of SBRT. The first Post-treatment perfusion assessment will be within six hours after the end of the first fraction of SBRT. The final Post-treatment perfusion assessment will be six weeks after the end of SBRT (with an allowed time window of 4-8 weeks).

Step 1 (Enrollment & Screening):

Patients with liver cancer receiving stereotactic body radiation (SBRT) as part of their standard of care will be eligible for study enrollment. SBRT is similar to conventional, photon-based radiation therapy. SBRT differs from conventional radiation therapy by utilizing less treatment sessions, also call ‘a fraction’, and a higher radiation dose per treatment session. Typically, SBRT is 5 fractions, whereas conventional radiation therapy may have 10 to 30 fractions, depending on the total prescribed radiation dose. DCE-CT imaging will be added at three specific time points of the clinical workflow for the quantification of perfusion.

Step 2 (Pre-treatment perfusion assessment):

Subjects will have DCE-CT imaging before the initiation of radiation therapy. Under SOC, all patients receiving radiation therapy undergo a planning CT simulation session. This session of CT imaging produces the CT study that will be used to create the radiation treatment plan. Under this

study, an additional DCE-CT scan will be acquired to quantify a patient's baseline perfusion characteristics.

Step 3 (Initiation of Radiation Therapy and Post-treatment perfusion assessment):

Subjects will begin radiation therapy for treatment of liver cancer or metastases. Each individual treatment session, also known as a "fraction", will utilize on-board imaging to ensure localization of treatment to the patient's unique anatomy for each session. This is the SOC with no modifications to the radiation treatment characteristics. Subjects will have DCE-CT imaging within six hours of receiving the first fraction of radiation therapy to assess the SBRT related changed to baseline perfusion characteristics.

Step 4 (Completion of Radiation Therapy):

Subjects will complete radiation therapy in 1 to 2 weeks, depending on prescribed radiation dose. This is the SOC with no modifications to the radiation treatment characteristics.

Step 5 (Six-week follow-up/Post-treatment perfusion assessment):

Subjects will have a follow-up visit with the radiation oncologist approximately 6 weeks after the completion of radiation therapy. DCE-CT imaging will be performed at this time to assess perfusion. This perfusion measure will be for outcome assessment of radiation effects. This DCE-CT imaging will be for research purposes.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

Primary endpoints include total therapeutic radiation dose delivered and DCE-CT profusion metrics at baseline, following first treatment, and 6 weeks after treatment. Profusion metrics include: KTrans (aka extraction-flow product), blood volume, and blood flow.

4.2.2 SECONDARY ENDPOINT

Patient demographic data will be combined with the primary endpoints to assess whether perfusion metrics differ depending on baseline demographics.

Demographic information (e.g., sex, age, race, etc.) will be combined with primary profusion endpoints.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form
2. Stated willingness to comply with all study procedures and be available for the duration of the study
3. Be a Male or Female aged 18-100
4. Diagnosed with Liver HCC or metastases
5. Must be receiving or will plan to receive SBRT for Liver HCC or metastases

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Allergy to iodine contrast
2. CT with contrast not offered as a Standard of Care
3. Pregnant women

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be open to all patients meeting eligibility criteria seen at the University of Colorado Cancer Center main campus in Aurora, CO.

Target sample size is 10 patients. In total, the Department of Radiation Oncology treats approximately 50 liver cancer patients with SBRT per year. Assuming an enrollment rate of 40% and a dropout rate of 25%, a conservative estimate is enrolling 10 patients in 12 months.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. Study subjects may be prematurely terminated from the study for the following reasons:

- Physician, PI, and/or patient decides to discontinue radiation treatment
- Noncompliance with the study protocol

- Development of unrelated illness which compromises study participation
- The subject withdraws consent (no further data collection or submission will be expected)

Subjects may stop study participation for any reason without jeopardizing their relationship with the healthcare providers.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Because this is a pilot study, where no clinical decisions will be made based on the DCE-CT, no effort will be made to follow withdrawn study participants or study participants that have completed the study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY (STUDY STOPPING RULES)

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Lead PI (Moyed Miften). If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/ or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB and DSMC.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

As described above, DCE-CT will be utilized to correlate perfusion imaging tumor changes with local control and normal tissue perfusion changes with normal tissue toxicities. All patients will undergo DCE-CT performed at the time of CT simulation, after the first fraction of SBRT, and 6 weeks after completion of SBRT (see schema). The DCE-CT scan performed at the time of CT simulation and subsequent scans will be performed in treatment position (which will be defined on an individual patient basis by the treating radiation oncologist). DCE-CT will be performed on

the Siemens AS open scanner within the University of Colorado Department of Radiation Oncology. Iodine contrast agent (50-100 mL) will be injected, per standard of care, at 3 mL per second and axial images centered at the tumor will be acquired.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

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 this visit, the study team will explain the study to the patient and obtain informed consent. After consent has been obtained, the study team will assess if the subject meets study criteria and can be enrolled into the study.

2. *Pre-treatment DCE-CT Imaging*

During the initial CT simulation process, the pre-treatment perfusion imaging will be obtained using DCE-CT. The initial CT simulation process is used to create the radiation therapy treatment plan and is a part of SOC. At the end of the CT simulation session, additional DCE-CT imaging will be acquired.

3. *Delivery of Radiation Therapy*

Treatment will be performed on a linear accelerator with on-board imaging capabilities to align the subject to the same treatment position for every treatment session. Throughout treatment, the subject will have a weekly evaluation with the radiation oncologist to help manage any health problems that may arise.

Subjects will have DCE-CT imaging within six hours of receiving the first fraction of radiation therapy to assess the SBRT related changed to baseline perfusion characteristics.

4. *Six week follow-up visit/Post-treatment DCE-CT Imaging*

The subject will have a SOC six week follow-up visit with the radiation oncologist. During the consult, the radiation oncologist will assess any issues arising from radiation treatment. At this

consult, the subject will also undergo their final session of DCE-CT imaging to assess perfusion changes after completion of radiation therapy.

7.2 STUDY SCHEDULE

7.2.1 SCREENING

The screening process will be begin once a patient is referred to radiation oncology for radiation therapy for the treatment of liver cancer. The patient will undergo a standard consultation with a radiation oncologist. The patient will be explained the risks and benefits of participation in the study. The patient will also be explained the study is completely voluntary. Patients will be informed of the study, explained the study purpose and asked to provide informed consent.

7.2.2 ENROLLMENT/BASELINE

- Verify inclusion/ exclusion criteria.
- Obtain Demographic information.
- Baseline clinical information (drinking status, medications, medical treatments including cancer treatments, cancer history)
- Obtain urine pregnancy test in women of childbearing potential.
- CT simulation for radiotherapy planning
- DCE-CT (performed at the time of CT simulation)

7.2.3 FOLLOW-UP

- Subjects will have DCE-CT imaging within six hours of receiving the first fraction of radiation therapy to assess the SBRT related changed to baseline perfusion characteristics
- DCE-CT imaging will be made at 6 weeks (+/- 1 week) after completion of SBRT.
- Record adverse events as reported by participant or observed by investigator if related to DCE-CT.
- Record participant's adherence to treatment program.

7.2.4 FINAL STUDY VISIT

- Record adverse events as reported by participant or observed by investigator if related to DCE-CT.

- Record participant's adherence to treatment program.

7.2.5 EARLY TERMINATION VISIT

No procedures will be performed.

7.2.6 UNSCHEDULED VISIT

No procedures will be performed.

7.2.7 SCHEDULE OF EVENTS TABLE

Study Visits					
	Screening	**Baseline Visit**	**Mid-Treatment**		**6 weeks Follow-up**
Visit Window	-28 Days to Day 0	Day 0- Prior to Treatment	Between 1st and last treatment fractions		4-6 weeks post-treatment
Procedures					
Visit with Radiation Oncologist	X	X	X		X
Informed Consent	X				
DCE-CT imaging		X (R)	X (R)		X (R)
Adverse Events		X	X		X

Study Event	Suggested timeline	Procedure	SOC or Research
Screening	At time of initial consult with Radiation Oncology	Consultation with Radiation Oncologist	SOC
		Patient signs consent form	Research
Pre-Treatment DCE-CT imaging	Within 3 weeks prior to the initiation of radiation therapy	CT imaging for treatment planning	SOC
		DCE-CT imaging	Research
Delivery of Radiation Therapy	1-2 Weeks	Delivery of Radiation treatment of liver cancer	SOC
6 week follow-up visit	4-6 weeks after completion of radiation therapy	Appointment with radiation oncologist	SOC
		DCE-CT imaging	Research

7.4 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

There are no restrictions on concomitant medications, treatments (i.e. chemotherapy, hormonal, immunotherapy) and procedures while on study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans.

Because this is an imaging study, where no clinical decision will be altered, we will only record AEs that have to do with the research procedures. The three research procedures are the pre-treatment, post-first fraction, and post-treatment DCE-CT imaging.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or **serious suspected adverse reaction**. An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in

any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Because this is an imaging study, where no clinical decision will be altered, we will only record SAEs that have to do with the research procedures. The three research procedures are the pre-treatment, post-first fraction and post-treatment DCE-CT imaging.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY INTERVENTION

Because this is an imaging study, where no clinical decision will be altered, we will only record AEs that have to do with the research procedures. The three research procedures are the pre-treatment, post-first fraction and post-treatment DCE-CT imaging.

8.2.3 EXPECTED ADVERSE EVENTS

The Investigator will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately. All AEs will be followed to adequate resolution.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until the last study visit. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Reporting of UAPs, SAEs, and reportable AEs will be performed pursuant to the UCCC DSMC and IRB institutional policy.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the adherence to be stable.

SAEs will be reported pursuant to section 8.6.

8.4.3 UNANTICIPATED PROBLEM REPORTING

This study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed in section 8.6). AEs, noncompliance and protocol violations will be recorded and reported as required either promptly (within 5 days of Sponsor-Investigator's knowledge) or at the time of the study's continuing review.

It is the responsibility of the PI to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The PI is responsible for reporting the UAP to the UCCC DSMC, if applicable.

8.5 STUDY HALTING RULES

Administration of a study intervention will be halted when three grade 3 AEs related to DCE-CT that are determined to be at least "probably related" are reported to the clinician. The clinician will notify the study sponsor and PIs immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the UCCC DSMC members within 24 hours of this occurrence and will provide the UCCC DSMC with AE listing reports. The UCCC DSMC will convene an *ad hoc* meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor. The study sponsor will inform the FDA of the temporary halt and the disposition of the study, if applicable.

8.6 SAFETY OVERSIGHT

Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, 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 study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. 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, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Study audits conducted by the DSMC will consist of review of the regulatory records, consent forms and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The utility of perfusion falls under two categories: predictive performance from DCE-CT imaging changes, and outcome assessment of radiation therapy treatment. Perfusion will characterized for a number of different parameters from a pharmacokinetic model. Multiple pharmacokinetic models can describe perfusion. For completeness, we will examine several models including: tissue homogeneity, Tofts, extended Tofts, and Patlak. Model goodness of fit will be assessed with root mean square error. The following perfusion parameters, derived from previously mentioned

pharmacokinetic models, will be quantified for each DCE-CT session: blood flow, blood volume of vascular space, blood volume of extracellular space, and intra-compartment plasma flow. For each model, these perfusion parameters will have the mean, extremums, and standard deviation of each parameter value calculated.

Treatment response will be assessed using the DCE-CT imaging changes from the baseline to the 6-week follow-up. Changes in perfusion parameters will be compared to the delivered dose with correlation coefficients, logistic regression analysis, and receiver operating characteristic analysis.

10.2 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  No formal hypothesis testing will be conducted for the primary analysis

10.3 ANALYSIS DATASETS

All participants who completed their baseline DCE-CT scan, had at least one radiation therapy treatment and one follow-up DCE-CT scan will be included in the analysis dataset to assess change in perfusion measurements from baseline to first follow-up. The analysis dataset for change in perfusion metrics at 6 weeks will include participants who completed their radiation treatment and have both baseline and 6-week DCE-CT scans.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

How profusion metrics change following SBRT treatment is unknown. Therefore, this is a prospective, pilot study is primarily aimed at gathering preliminary data on profusion metrics and assessing the relationship between change in profusion and radiation dose delivered from SBRT. Due to the limited knowledge on how radiation therapy will affect profusion metrics, change in profusion metrics following therapy will be assessed both after a patient's first treatment and at 6-weeks following their end of the SBRT treatment. Descriptive statistics will be provided for all measured variables.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint of this study is change in profusion metrics from baseline to end of first radiation treatment and 6-weeks after treatment has ended. Additionally, total radiation dose delivered from SBRT will be captured and used as a surrogate measurement for treatment response.

Individual profusion metrics will be plotted as well as means with corresponding standard errors for the three time points. Change in profusion metrics from baseline versus radiation dose received will be plotted separately for the two follow-up DCE-CT scans. Correlation between change in profusion and total radiation dose received will be evaluated using Spearman's correlation coefficient.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

To assess descriptively whether there are signs that profusion metrics differ based on patient demographics the following demographic information will be captured; age , sex, race, clinical stage at diagnosis. Change in profusion metrics from baseline to each of the two follow-up DCE-CT scans will be stratified by demographic information and descriptive statistics will be presented, e.g., sample size, mean, median, standard deviation, and range.

10.4.4 SAFETY ANALYSES

Should an AE related to the study intervention (i.e., additional DCE-CT scans) occur, the study will be terminated. Definition and monitoring of AEs are detailed in section 8.

10.4.5 ADHERENCE AND RETENTION ANALYSES

There are no pre-planned adherence and retention analyses.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics for patient demographics will be collected and reported.

10.4.7 PLANNED INTERIM ANALYSES

There are no planned interim analyses.

10.5 SAMPLE SIZE

The study will enroll a minimum of 10 patients with a maximum enrollment of 15 patients to allow for screen failures and dropouts. This sample size was based the number of patients that would be reasonable for the Department of Radiation Oncology to recruit within a year. The Department of Radiation Oncology treats approximately 50 liver cancer patients with SBRT per year. Assuming an enrollment rate of 40% and a dropout rate of 25%, a conservative estimate is enrolling a maximum of 15 patients in 12 months.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

To protect confidentiality of participants, medical and research records for this trial will be maintained in compliance with regulatory and institutional requirements.

The following data will be collected on electronic-based Case Report Forms (eCRFs):

- Demographic information (age, sex, race)
- Baseline clinical information (drinking status, medications, medical treatments including cancer treatments, cancer history)
- Results of study procedures as detailed in protocol

Only the following people will have access to data and documents collected on CRFs:

- Study investigators and research staff participating in this study

Our site will permit authorized representatives of the UCCC and regulatory agencies to examine clinical records for quality assurance reviews, audits, and valuation of study safety, progress, and data validity. In additional to study monitors, study personnel on the study roster will have access to the study data.

Should study participants withdraw their consent from the study, no further data will be collected on them for this study.

Source data and documents will be kept according to HIPAA guidelines.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. The name of the investigator(s) responsible for the protocol.
4. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information and participants will sign an Informed Consent Form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap™. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 7 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to CUCC DSMC. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the -SOP and/or study procedures manual.

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

17 LITERATURE REFERENCES

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18 APPENDICES

Version	Date	Significant Revisions

Principal Investigator: Moyed Miften, PhD
COMIRB No: 18-2874
Version Date: 01/16/2020
Study Title: Pilot Study of Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging for the assessment of radiation therapy outcome for liver cancer patients

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Key Information

Please read all the information below and ask questions about anything you don't understand before deciding of you want to take part.

You are being asked to be in a research study. Participation is voluntary.

Purpose of the study: We are doing this study to learn more about how Dynamic Contrast Enhanced Computed Tomography (DCE-CT) can be used to assess how an individual's liver cancer responds to standard radiation treatment.

Procedures: If you agree to participate, the following will happen:

- You will have a screening visit to make sure you are eligible to be in the study.
- If you are eligible, you will have a DCE-CT Scan of your liver before, during, and after standard radiation treatment (total of 3 scans).
- You will be in the study for approximately 3 months.

Risks: Participation in research involves risks, including the following:

- The risk of CT scans includes exposure to radiation. A special dye (contrast material) will be given to you before the scan. Although rare, the contrast material may cause an allergic reaction. The contrast material may cause kidney damage.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: You can receive standard radiation treatment without participating in this study. Please discuss standard treatment and care options with your doctor.

Detailed Consent

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about if an imaging method known as Dynamic Contrast Enhanced Computed Tomography (DCE-CT) can help doctors assess liver cancer and metastases.

You are being asked to be in this research study because you have been diagnosed with liver cancer or metastases and are currently (or will be) on the standard of care radiation treatment known as Stereotactic Body Radiation Therapy (SBRT).

Other people in this study

Up to *15* people from your area will participate in the study.

Up to *15* people around the country will be in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you will receive.

You will undergo standard computed tomography (CT) imaging for radiation therapy planning. This is often called "CT simulation." The CT image will be used to determine

which portion of your liver may be functioning well and which portions are not. This will help your radiation oncology team better understand how radiation effects liver function.

In addition to receiving the standard of care radiation treatment for your liver cancer or metastases, three DCE-CT imaging sessions will be performed.

The next section is an overview of the procedures that will be done and what will be expected of you if you participate in this study.

Study Procedures
Below are the study procedures that will take place.

- **Informed Consent (*Research*)**
  This informed consent form will be discussed with you and you will given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging (*Research*)**
  This form of computed tomography imaging allows doctors to inject a contrast agent and collect images in the area of interest. This information may be able to assess your liver cancer or metastases by looking at the tumor as well as the surrounding tissue and obtaining information that is unique to you.

Study Visits
Below is a list of when the study procedures will take place.

1. **Screening**
   You will learn about the study and provide your consent if you wish to participate **(*Research*)**.

2. **Baseline Visit (Prior to Treatment) at Day 0**
   Within three weeks prior to your radiation therapy beginning, you will have the following procedures performed:
   - Obtain demographic and clinical information **(*Research*)**
   - Dynamic Contrast Enhanced Computed Tomography (DCE-CT) imaging performed to further assess your liver cancer or metastases **(*Research*)**

3. **First Fraction of Radiation Therapy at 1-2 weeks after Baseline Visit**
   You will have the following procedures performed when you come for you radiation therapy visit:
   - Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging performed to assess any possible changes to your liver cancer or metastases **(*Research*)**

4. **Follow-up Visit after ~6 weeks following Radiation Therapy**
   Four to six weeks after your radiation therapy, you will have the following performed:
   - Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging performed to assess any possible changes to your liver cancer or metastases **(*Research*)**

How long will I be on the study?

The total length of the time you will participating in this study is about 3 months.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include the same discomforts and risk which may be encountered during standard radiation treatment for liver cancer. These side effects are listed below and your physician will discuss the chances of these toxicities and their treatments in the specific context of your cancer and radiation plan.

In addition to the below risks, this study may include risks that are unknown at this time.

- **Risk of Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging**

  There is a risk of slightly higher doses of radiation because of the extra imaging scans. The additional exposure from this type of imaging is about 0.05% increase from the radiation you would otherwise be receiving from your radiation therapy.

  In addition to the small increase of radiation, Dynamic Contrast Enhanced Computed Tomography (DCE-CT) scans have the following risks:

Dynamic Contrast Enhanced Computed Tomography (DCE-CT) Imaging Known Risks
RARE, SOME MAY BE SERIOUS In 100 people receiving contrast, 3 or fewer may have:
• Contrast-induced nephropathy (damage to kidneys) – this risk low in patients without chronic renal impairment (2%) but is high (30%) in patients with chronic renal impairment • Pain • Burning Sensation • Nausea • Hot Flashes • Warmth

- **Risk of Loss of Confidentiality**

  There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

- **Risk of Pregnancy**

  If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear. You should notify your physician immediately if there is a chance that you could be or become pregnant during radiation therapy. Discuss appropriate birth control methods with your doctor.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about Dynamic Contrast Enhanced Computed Tomography (DCE-CT) and how it could be used to make an improved diagnosis of patients with liver cancer. Physicians are hoping this information could provide information that may allow for a customizable treatment plan.

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

Are there alternative treatments?

You could proceed with Stereotactic Body Radiation Therapy without participating in this study.
You could also receive alternative treatments for your liver cancer or metastasis, or choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being sponsored by the University of Colorado Cancer Center.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

There are some medical treatments that you would have to get for your condition whether you were in this study or not. You will have to pay for these. There are other medical treatments that you will get because you are in this research study. The research study will pay for those. Those medical treatments are listed above in the “Study Procedures” section of the form under “Research.”

You and/or your health plan/ insurance company will need to pay for the standard of care items of treating your cancer.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Moyed Miften, PhD immediately. His phone number is (720) 848-0135.

If you are hurt by this research, we will give you medical care. However, medical treatment will have to be provided by your insurance company for a research related injury. The term “research-related injury” means physical injury caused by drugs or procedures required by the study which are different from the medical treatment you would have received if you had not participated in the trial.

Who do I call if I have questions?

The researcher carrying out this study is Moyed Miften, PhD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Moyed Miften, PhD at (720) 848-0135. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Moyed Miften, PhD with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospitals have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Moyed Miften, PhD
Department of Radiation Oncology
1665 Aurora Ct., Suite 1032
Mail Stop F706

Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals, but we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed for these procedures:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Billing or financial information

What happens to the Data that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data collected from you during this study are important to this study and to future research. If you join this study:

- The data given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data collected from you.

- If data are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to participate in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study. I will get a signed and dated copy of this consent form.

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name: _____

A signature line for a witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Signature

Witness of consent process