Assessment of Treatment-induced Tissue Hypoxia after Transcatheter Arterial Embolization of Hepatocellular Carcinoma: a Feasibility Study with [^{18}F]FMISO PET/CT

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1.0 ..... PROTOCOL ABSTRACT/OVERVIEW

Overview:

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world, the third leading cause of cancer deaths, and has more than tripled in incidence since 1975[1]. Over 33,190 new cases of liver cancer were anticipated to occur in the U.S. in 2014 with 80% of these being HCC[2]. The overall 5-year survival is poor at 16%, but increases to 29% when diagnosed early[2]. With the dismal prognosis, better evaluation of existing treatments is needed to prolong the overall survival. Current treatment options include transcatheter arterial chemoembolization (TACE) with a Lipiodol emulsion, drug-eluting bead transcatheter arterial chemoembolization (DEB-TACE), and bland small particle transcatheter arterial embolization (TAE). Evaluation of the effect of these treatments typically does not occur until 2-3 months after the procedure is performed. However, new hypoxia imaging agents could be utilized in the 24 hours after the procedure to determine treatment effect. In particular ^{18}F-fluoromisonidazole (other names are ^{18}F-FMISO, [F-18]FMISO or [^{18}F]FMISO) has been shown to accumulate in hypoxic areas of the liver after arterial ligation[3]. This agent could be used to determine where areas of hypoxia exist after TAE to determine if there is adequate embolization, and to evaluate the standardized uptake values to see if a correlation exists with recurrence. If there is evidence for uptake after embolization, and if uptake correlates with recurrence, earlier intervention could be performed to reduce the risk of recurrence. We would like to perform a prospective, single-arm, feasibility study to determine if [^{18}F]FMISO shows increased uptake in tumors after TAE.

Objectives:

Our primary objective is to determine the variability of [^{18}F]FMISO uptake in HCC tumors compared to normal liver after transcatheter arterial embolization by determining the difference in the mean of the maximum standardized uptake value (SUVmax) and tumor-to-liver ratio (TLR) of a region of normal liver and of up to 5 index tumors per subject.
Our secondary objectives are to determine if areas of tumor recurrence as determined by CT or MRI within a 6 month period after transcatheter arterial embolization show evidence of increased [^{18}F]FMISO on initial post-treatment [^{18}F]FMISO PET/CT, to determine the variability in SUVmax and TLR of untreated HCC compared to normal liver, and to determine any toxicities related to [^{18}F]FMISO use for PET/CT.

Eligibility:

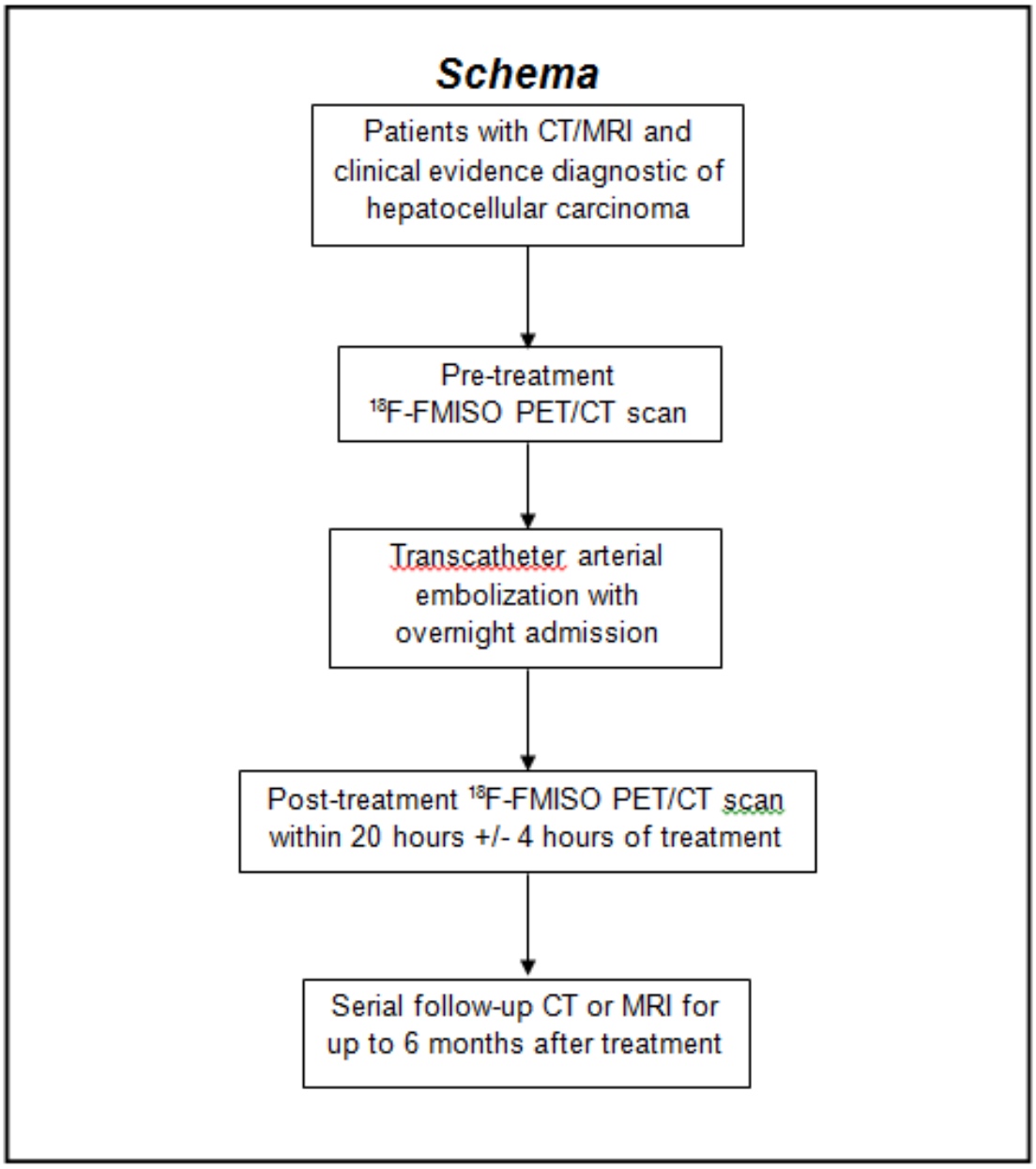
Eligible subjects will be over 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and imaging and clinical features of tumor(s) diagnostic for hepatocellular carcinoma. The total bilirubin should be less than 3.0, and they must be either a Child-Pugh A or B. The tumor(s) must be amenable to transcatheter arterial embolization and the subjects should be able to provide informed consent.

Study Design:

This will be a single-arm, prospective observational study to test the feasibility of using [^{18}F]FMISO in subjects with hepatocellular carcinoma. Subjects will undergo [^{18}F]FMISO PET/CT before and after transcatheter arterial embolization and will be followed for 6 months after initial treatment for evidence of recurrence. We anticipate it will take approximately 6 months to enroll the desired number of subjects.

Required Sample Size:

As this is a feasibility study, we will be enrolling 5 subjects in the study.



2.0 Background and Rationale

Burden of Disease

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world, the third leading cause of cancer deaths, and has more than tripled in incidence since 1975[1]. Over 33,190 new cases of liver cancer were anticipated to occur in the U.S. in 2014 with 80% of these being HCC[2]. The overall 5-year survival is poor at 16%, but increases to 29% when diagnosed early[2]. With the dismal prognosis, better evaluation of existing treatments is needed to prolong the overall survival.

Embolization is a treatment for intermediate HCC that relies on creating anoxic environments to kill tumor

Treatment for patients with intermediate stage HCC (Barcelona Clinic Liver Cancer BCLC stage B), defined as Child-Pugh class A or B liver disease with an ECOG performance status of 0 and multinodular disease, is conventional transcatheter arterial chemoembolization (TACE) with ethiodized oil, TACE with drug eluting beads (DEB-TACE) or small particle transcatheter arterial embolization (TAE) without a chemotherapeutic agent[4]. No clear advantage has been found for TACE versus DEB-TACE or for DEB-TACE versus TAE in retrospective or prospective trials, with recent prospective randomized controlled studies showing no statistically significant difference in response (TACE vs DEB-TACE) or overall survival (DEB-TACE vs TAE)[5–7]. The mechanism of TACE and DEB-TACE relies on both hypoxia and cytotoxic chemotherapeutic action, whereas the mechanism for TAE relies on anoxia alone. In addition, there has been no chemotherapeutic agent that has been shown to be superior, with practitioners using doxorubicin, epirubicin, mitomycin C, cisplatin, and other agents either singly or in combination[8,9]. For small particle TAE, anoxia is necessary to ensure cell death, as hypoxia has an insignificant effect on cell death[10] (Figure 1).

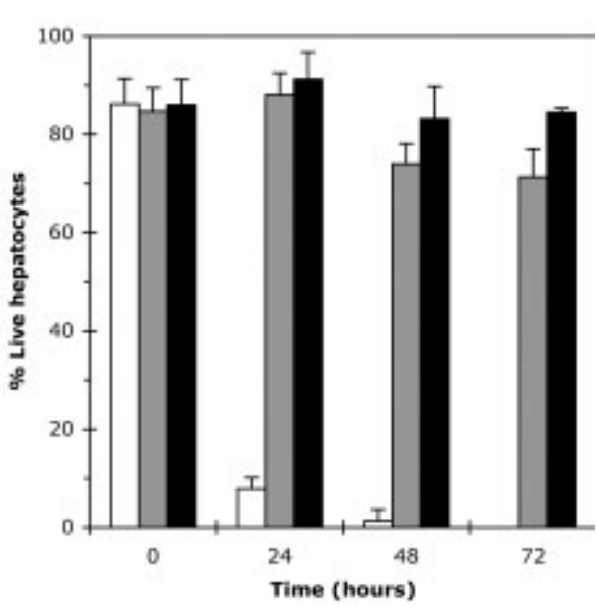


Figure 1. Hepatocytes cultured in an anoxic 0% oxygen environment (white) resulted in marked cell death, while hepatocytes cultured in 2% oxygen (gray) and normoxia (black) did not have significant cell death[10].

It has been shown that hypoxia generates a series of changes in tumors that promote tumor progression

Hypoxia has been a recent topic of interest due to the realization of its deleterious effects and its role in promoting tumor progression. These include upregulation of VEGF to promote angiogenesis and upregulation of glycolysis, which is associated with activation of oncogenes[11]. Hypoxia also improves the survival ability of cells by inhibiting apoptosis[12].

Embolization causes upregulation of factors that increase tumor cell survival

Embolization of tumors creates an increase in hypoxia inducible factor (HIF-1α), particularly at the border of necrosis and viable tumor, which in turn upregulates other pro-angiogenic factors[13,14]. HCC cells have been found to proliferate more efficiently when exposed to a hypoxic environment[13]. In addition, tumors that lie in “watershed” zones, or areas with blood supply from

different segments of the liver, have shown increased tumor viability when only one arterial segment is treated[15]. Based on these findings, it is possible that identifying areas of incompletely treated tumor where hypoxia is present could lead to earlier treatment than is currently possible.

Hypoxia imaging agents can allow for earlier determination of these borderline regions between necrosis and viable tumor

Determining where areas of hypoxia exist is difficult with current MRI and CT imaging techniques. The molecular imaging agent [^{18}F]FMISO (^{18}F-fluoromisonidazole) has been widely investigated for its use in imaging areas of hypoxia[16,17]. The radiotracer accumulates in cells via passive diffusion and cannot undergo re-oxidation in hypoxic conditions thereby remaining trapped within the cell. It does not accumulate within necrotic cells. Given that embolization creates hypoxic and anoxic environments, evaluation of these areas pre-treatment and post-treatment to identify changes could provide early imaging evidence for areas at increased risk of recurrence. Tumors in the liver have a markedly greater proportion of their blood flow from the arterial supply, in contrast to normal liver, which has a greater blood supply from the portal venous supply (Figure 2)[18]. This suggests that [^{18}F]FMISO should be able to accumulate within areas of hypoxia as it can still flow via the portal venous circulation within the liver.

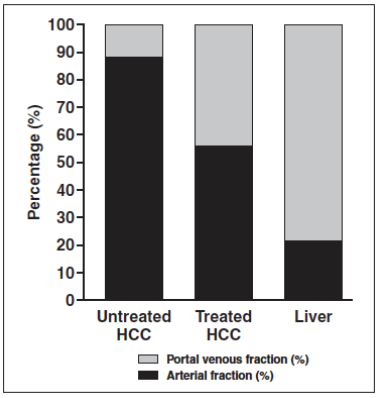


Figure 2. Arterial fraction of blood flow is significantly greater in HCC compared to normal liver[18]. Treated HCC has a greater proportion of blood flow from the portal venous supply which theoretically would allow for increasing [^{18}F]FMISO accumulation.

[^{18}F]FMISO has been shown to be able to detect areas of hypoxia in liver

Hypoxia imaging using [^{18}F]FMISO in liver was demonstrated in a pig model by ligating the arterial supply with continued portal venous supply to one lobe of the liver and allowing continued portal venous and arterial supply to the contralateral lobe[3]. In this study, the partial pressure of oxygen in liver was directly measured with an Eppendorf electrode and found to correlate with SUV values of [^{18}F]FMISO uptake (Figure 3). In addition, the geometric mean of the SUV for normal and hypoxic liver was found to be 1.31 (95% CI 1.09-1.57) and 5.7 (95% CI 4.71-6.9), respectively, for pigs breathing room air. This indicates a significant difference in [^{18}F]FMISO uptake for hypoxic liver compared to normoxic liver. This study demonstrated the utility of using [^{18}F]FMISO in the liver despite ligation of the arterial supply, particularly because of the continued delivery of the radiotracer to the liver via portal venous blood supply.

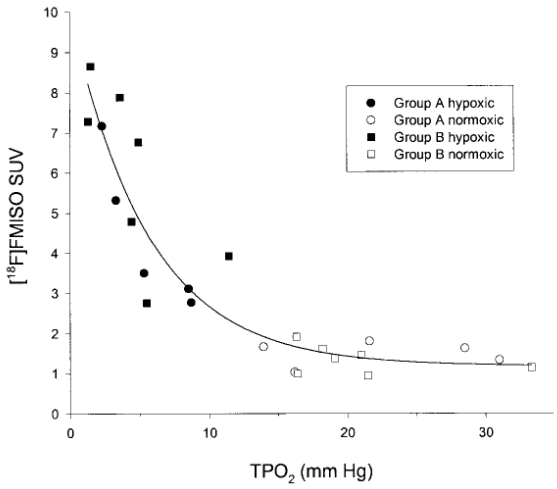


Figure 3. Correlation of SUV uptake in hypoxic liver compared with direct partial pressure oxygen measurement with an Eppendorf electrode. There is a high correlation between low oxygen levels and increased [^{18}F]FMISO uptake[3]. SUV = Standardized uptake value, TPO_2 = Tissue partial pressure oxygen

Earlier detection of residual tumor after treatment may be possible with hypoxia-specific imaging agents like [^{18}F]FMISO

After TAE, portions of the tumor and surrounding tissue may become hypoxic, but not severe enough to result in necrosis. Sub-lethal hypoxia increases levels of vascular endothelial growth factors (VEGF) and hypoxia-inducible factor-1 alpha (HIF-1 alpha), which then selects and promotes a more aggressive disease that is often increasingly resistant to subsequent treatments[12,13,19]. Normal liver tissue is supplied by portal venous blood and has been shown to have normal levels of HIF-1 alpha, an indicator of hypoxia, after embolization in animal models in contrast to tumor which relies on arterial blood supply and has markedly increased levels of HIF-1 alpha[13]. Early detection of this hypoxic tumor tissue could enable earlier intervention with the objectives of preventing disease progression and improving overall survival. Hypoxia specific imaging agents have been developed and used in the evaluation of cancers of the head and neck, lung, kidneys and brain[16,17]. Among them, [^{18}F]FMISO has been used and validated most extensively. [^{18}F]FMISO is lipophilic and enters cells through passive diffusion. It is reduced by nitroreductase inside the cell. In hypoxic conditions, the metabolites cannot undergo re-oxidation to diffuse out of the cell. Instead, they become trapped and accumulate within the cell. [^{18}F]FMISO is not retained in necrotic cells because they lack functional nitroreductase enzymes. [^{18}F]FMISO has also shown superior imaging characteristics for liver tumors compared to other hypoxia imaging agents (Figure 4)[20]. Many clinical studies have been performed with [^{18}F]FMISO, several of which have shown that [^{18}F]FMISO is capable of providing prognostic information either prior or after treatment[21]. Several studies have shown the potential of [^{18}F]FMISO in determining treatment response with radiation and chemoradiation therapies in both head and neck cancers (HNC) and non-small cell lung cancers (NSCLC)[22–24]. These studies show that tumors with areas of hypoxia as demonstrated by [^{18}F]FMISO uptake correspond with worse outcome or disease recurrence. Given the similar hypervascular nature of HNC and NSCLC as compared to hepatocellular carcinoma, we anticipate hepatocellular carcinoma will show a similar prognostic correlation with [^{18}F]FMISO uptake.

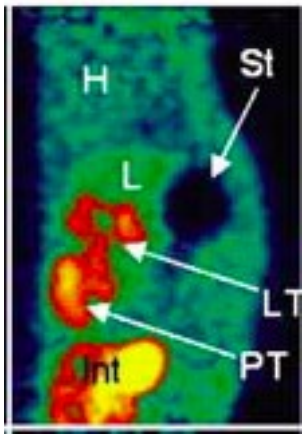


Figure 4. [^{18}F]FMISO imaging in a rat liver. H = Heart, St = Stomach, L = Liver, LT = Liver Tumor, PT = Peritoneal Tumor, Int = Intestine. Liver tumor can be distinguished from normal liver[20].

If detected early, tumor recurrence is amenable to repeat embolization sooner than is currently done

Currently, treatment response is assessed using a combination of CT and MR to evaluate tumor size and enhancement 1-3 months after treatment with the optimal imaging time at approximately 2 months[25]. This approach has several limitations. Tumor size is not a reliable indicator of treatment response because TAE reduces the viability of the tumor, but does not reduce the overall tumor volume. Persistent enhancement at the treatment site is not specific for viable tumor because post-treatment granulation tissue or inflammation can also enhance, particularly at the periphery at 1 month follow-up CT scans[26]. Finally, post-treatment changes detected on current imaging modalities take time to manifest. Successful identification of hypoxic areas after embolization could lead to earlier re-intervention and arrest of expected tumor progression. If identified immediately after treatment, this could lead to earlier intervention within days to weeks of demonstration of residual tumor. Currently, patients typically wait months prior to retreatment to ensure the areas of concern represent residual tumor.

Significance

If [^{18}F]FMISO is shown to be effective in determining post-embolization hypoxia which correlates with tumor recurrence, then re-treatment of incompletely treated tumors could be performed in days or weeks rather than the current practice of several months. This, in turn, could result in improved tumor control and possibly in improved cancer-free survival.

3.0 Study Objectives

3.1 Primary Objective

Determine the variability of ^{18}F-FMISO uptake in HCC tumors compared to normal liver after transcatheter arterial embolization by determining the difference in the mean of the maximum standardized uptake value (SUV_{max}) and tumor-to-liver ratio (TLR) of a region of normal liver and of up to 5 index tumors.

Endpoint: Measurement of SUV_{max} and TLR of tumors 20 hours +/- 4 hours after embolization.

3.2 Secondary Objectives

1. Determine if areas of tumor recurrence as determined by CT or MRI within a 6-month period after transcatheter arterial embolization show evidence of increased ^{18}F-FMISO **labeling** on the initial post-treatment ^{18}F-FMISO PET/CT.

   The endpoint will be assessed by comparison of SUV_{max} and TLR of tumors with recurrence to tumors without recurrence.

2. Determine the variability in SUV_{max} and TLR of untreated (non-embolized) HCC lesions compared to normal liver by determining the difference in the mean of the SUV_{max} and TLR of normal liver and tumor.

   The endpoint will be assessed by measuring SUV_{max} and TLR of untreated HCC tumor compared to normal liver. Untreated tumor will be defined as any tumor that has not undergone any locoregional or systemic treatment within 3 months.

3. Determine any toxicities related to [^{18}F]FMISO use for PET/CT.

   The endpoint will be assessed by documenting unanticipated toxicities related to [^{18}F]FMISO use over a 10 half-life period beginning from injection. Only grade 3 or greater toxicities according to the Common Terminology Criteria for Adverse Events version 4 will be considered significant[27].

4.0 Eligibility Criteria

4.1 Inclusion Criteria

Potential subjects will be enrolled if they meet the following criteria:

1. Over 18 years of age
2. ECOG performance status of 0, 1, or 2
3. Histopathologic or imaging and clinical features of tumor(s) diagnostic for hepatocellular carcinoma with at least one tumor ≥ 1.5 cm. Imaging features diagnostic for hepatocellular carcinoma will be defined as Liver Imaging Reporting and Data System (LI-RADS) 4 or greater.
4. Total bilirubin < 3.0
5. Child-Pugh A or B
6. Tumor amenable to transcatheter arterial embolization
7. Able to provide informed consent

4.2 Exclusion Criteria

Potential subjects will be excluded if they meet any of the following criteria:

1. Uncontrolled large ascites
2. Main or segmental portal vein thrombosis
3. Locoregional treatment of hepatocellular carcinoma within the prior 3 months or chemotherapy within the previous 3 months
4. Inability or contraindication to undergo transcatheter arterial embolization
5. Inability to lay flat for at least 2 consecutive hours
6. Severe acute illness
7. Uncontrolled chronic illness such as hypertension, diabetes, or heart failure
8. Contraindication to CT or MRI contrast
9. Pregnancy

5.0 Research Design and Methods

5.1 Study Design

This is a prospective, observational single-arm feasibility study to evaluate the variability of [^{18}F]FMISO in determining areas of hypoxia in hepatocellular carcinoma after treatment with transcatheter arterial embolization.

The study will begin with a screening period during which subjects will be evaluated for possible enrollment in the study. Subjects will be screened by an interventional radiologist or clinical coordinator in the Interventional Radiology (IR) clinic at the Veterans Affairs Palo Alto Health Care System. Subjects do not require a histologic confirmation of HCC, but will require an imaging scan be diagnostic for HCC in subjects with risk factors for primary liver cancer. Subjects that meet the entry criteria and do not have any exclusion criteria will be eligible for the trial. If not already completed within 8 weeks of treatment, subjects who are potential candidates will need to undergo a triphasic MRI or CT scan. The type of scan performed (CT or MRI) will be the same as the prior scans the subject underwent for surveillance or diagnosis. This must occur within 8 weeks prior to treatment. Subjects enrolled in the trial will then undergo an [^{18}F]FMISO PET/CT scan within 4 weeks prior to treatment. The [^{18}F]FMISO PET/CT study will be interpreted by a board certified nuclear medicine physician where the largest lesions, up to five, will be index lesions that will be chosen for follow-up. The SUV_{max} and tumor-to-liver ratio (TLR) will be documented. Most studies have used tumor-to-blood ratio (TBR) or tumor-to-muscle ratio (TMR) with a cut-off of 1.2 as an indicator of hypoxia[21]. However, the liver has increased radiotracer uptake and so will require normalization to non-tumor liver, similar to a method described for patients with renal cell cancer[28].

Subjects will next undergo transcatheter arterial embolization, then have repeat [^{18}F]FMISO PET/CT scanning between 20 hours +/- 4 hours after completion of treatment. The [^{18}F]FMISO study will be interpreted by a board certified nuclear medicine physician where the index lesions will be evaluated for the SUVmax and TLR.

The subject will then undergo routine follow-up CT or MRI 2 months +/- 2 weeks after treatment. The follow-up study (CT or MRI) will be the same as the prior study that the subject had. The index lesions will be reviewed by an interventional or diagnostic radiologist for evidence of recurrence. If there is new or recurrent disease, the subject can undergo any treatment deemed suitable by the liver tumor board for the residual tumor including, but not limited to, chemotherapy, surgery, or locoregional ablative or intra-arterial treatment. If there is no evidence for recurrent disease, the subject will undergo repeat CT or MRI after 3 months +/- 2 weeks. The index lesions will be reviewed by an interventional or diagnostic radiologist for evidence of recurrence. Again, if there is recurrent disease, the subject can undergo any treatment deemed suitable by the liver tumor board for the residual tumor including chemotherapy, surgery, or locoregional ablative or intra-arterial treatment. Subjects will be followed for a total of 6 months from completion of initial transcatheter arterial embolization. Subjects will continue to attend all routine medical appointments during the study including clinic visits.

The primary endpoint will be determination of the difference in the mean in SUV_{max} and TLR between tumor and unaffected liver after treatment.

The secondary endpoints will be correlation of tumors with recurrence with areas of increased TLR, determination of the variability in SUV_{max} and TLR in untreated HCC compared to normal liver, and toxicity. Initial ^{18}F-FMISO scans will be used to document the index lesions and determine the TLR. Post-treatment triphasic CT or MRI scans will be used to evaluate for tumors with recurrence. All adverse events will be recorded and categorized according to the Common Terminology Criteria for Adverse Events v4[27].

5.2 Research Facility

The clinical study will be conducted at the Veteran's Administration (VA) Palo Alto Health Care System (VAPAHCS). This is a major research-oriented VA facility with $52 million in annual research expenditures, more than 65 active research projects, and nearly 250 Principal Investigators pursuing laboratory, clinical, and health services research. All Stanford University facilities and resources are open and available to the investigators, including core computing, microscopy, library, biostores, and analytical facilities. The VAPAHCS has invested significant resources into the Nuclear Medicine and Radiology programs. The Nuclear Medicine program currently has a General Electric (GE) Discovery VCT PET/CT scanner. In addition, they have 3 GE Infinia Hawkeye SPECT/CT systems. The radiology department has 2 HD750 64-slice GE CT scanners, one of which has a dual-energy package, one 3.0 Tesla GE Discovery MR750 and a 1.5 Tesla GE MRI. The interventional radiology section has 2 angiography suites, one of which is equipped with a 16-slice GE CT scanner combined with a GE Innova 4100 fluoroscopic suite. In addition, the 2nd room has a GE Innova 3131 biplane system. Participant testing rooms, physical exam rooms, and a reception area are located within an outpatient clinic area and are immediately available for the project.

5.3 Study Calendar / Schedule

	Visit 1: Screening	Visit 2	Visit 3: Treatment	Visit 4	Visit 5
Informed Consent	X				
Eligibility Criteria Assessment	X				
Demographics	X				
Medical History	X				
Physical Examination	X				
Vital Signs	X				
Serum Pregnancy Test (if applicable)	X		X		
Hematology Serum Chemistry	X		X		
[^{18}F]FMISO PET/CT Scan		X	X		
Transcatheter Arterial Embolization			X		
Adverse Events		X	X		
Triphasic CT or MRI	X[a]			X	X

[a]If not already completed within 8 weeks of treatment

5.4 Pre-Registration Procedures

We will recruit subjects who are referred to the interventional radiology clinic for intra-arterial treatment of their HCC. Because the patient gender distribution at the Veterans Affairs Palo Alto Health Care System (VAPAHCS) has a significantly greater male proportion, we anticipate most or all of the subjects will be male. However, we will attempt to recruit female subjects as much as possible. Efforts will be made to recruit ethnic minorities in proportion to their representation in the local veterans community. Because no children are seen in Interventional Radiology at VAPAHCS, pediatric subjects will be excluded from the study.

5.5 Registration Visit and Procedures

Subjects will be screened at their clinic visit to determine if they are eligible to participate. Subjects must have clinical history and imaging characteristics diagnostic of HCC or histologic confirmation of HCC. Subjects referred to the clinic will undergo detailed discussion of the proposed study by the clinical coordinator or PI. With the subject's verbal permission, the eligibility criteria will be reviewed both directly from the subject and through the subject's electronic medical record. If the subject meets the eligibility criteria, the subject will be asked to sign an informed consent and the subject will be enrolled in the trial. If a scan within 8 weeks of the anticipated treatment is not available, the subject will be scheduled for a triphasic CT or MRI scan. Serum hematology and chemistry tests must be available within 4 weeks prior to the initial visit. If they are not available, the subject will be scheduled for blood tests. The subject will also be scheduled for all lab tests, the initial [^{18}F]FMISO PET/CT scan, transcatheter arterial embolization, post-treatment [^{18}F]FMISO PET/CT scan, and post-treatment follow-up triphasic CT or MRI. The transcatheter arterial embolization treatment will be scheduled with the subject within 8 weeks of the [^{18}F]FMISO PET/CT scan. If the subject is a female, a serum pregnancy test will be obtained unless the subject is post-menopausal.

5.6 Imaging and Intervention Visit(s)

5.6.1 [^{18}F]FMISO PET/CT Visit

[^{18}F]FMISO will be prepared by experienced radiopharmaceutical chemists from the MIPS cyclotron and radiochemistry facility in the Department of Radiology at Stanford University under the supervision of Dr. Frederick T. Chin. The [^{18}F]FMISO will be delivered to the Veterans Affairs Palo Alto Health Care System (VAPAHCS) section of Nuclear Medicine. 3.7 MBq/kg (0.1 mCi/kg, up to 10 mCi) will be injected intravenously into each subject and a PET/CT will be performed 120 minutes +/- 30 minutes after injection. Prior to the injection, the patient's heart rate, blood pressure, oxygen saturation, temperature, and respiratory rate will be measured and documented. Between 120 and 360 minutes after injection, a repeat measurement of the vital signs detailed above will be performed and documented. Patients will be monitored for a minimum of 3 hours after the injection. Any change from the patient's baseline status producing symptoms or change in vital signs causing symptoms will be managed immediately with care to be determined based on symptom severity. If any irregularity is detected on pre-injection or post-injection vital sign measurements, appropriate action will be performed for further evaluation including, but not limited to, electrocardiogram; administration of a fluid bolus; evaluation in the emergency department; or admission to the hospital.

5.6.2 Transcatheter Arterial Embolization Visit

The subject will undergo transcatheter arterial embolization prior to the second PET/CT scan. The transcatheter arterial embolization procedure must be at least 10 half-lives, or 18 hours, after the initial [^{18}F]FMISO PET/CT scan. The subject will have the right or left common femoral artery accessed percutaneously, and a catheter will be placed into the arterial branches feeding the hepatic tumors using fluoroscopic guidance. Embolization will be performed with small particles until stasis is achieved. Particle size can range from 40 microns to 300 microns. Larger particles may be used if deemed clinically necessary. Fluoroscopic imaging will be performed with a GE Innova fluoroscopic unit during the procedure. Upon completion of the procedure, the subject will be admitted for overnight observation. Within 20 hours +/- 4 hours after the procedure, the subject will undergo repeat [^{18}F]FMISO under the same protocol as above.

5.7 General Concomitant Medication and Supportive Care Guidelines

Subjects should remain on all home medications prior to the PET/CT scan. Subjects will remain on all home medications except anticoagulants prior to the transcatheter arterial embolization procedure. Subjects cannot have been on any chemotherapeutic treatment for 3 months prior to PET/CT scan or transcatheter arterial embolization.

5.8 Post-Therapy Visits

Subjects will undergo triphasic CT or MRI of the liver with contrast at 2 months (+/- 2 weeks), and 3 months (+/- 2 weeks) after the first post-therapy scan. A triphasic CT scan will be performed if the initial pre-therapy scan was a triphasic CT scan or if the subject has developed a contraindication to MRI. The triphasic CT scan will be performed in arterial, portal venous, and delayed venous (i.e. equilibrium) phase according to the standard VAPAHCS protocol. Other phases may be obtained as clinically indicated. A 1.5 Tesla or 3 Tesla triphasic MRI will be performed if the initial pre-therapy scan was an MRI. The MRI will be performed in pre-contrast, arterial phase, and several venous phase T1 or gradient echo sequences as well as axial T2 and diffusion-weighted images (DWI). Additional sequences may be performed as deemed clinically necessary for interpretation of the study.

5.9 Criteria for Removal from Study

The Protocol Director may withdraw participants from the study for one or more of the following reasons:

1. Subjects' failure to follow the instructions of the PI and/or study staff.
2. Determination that continuing participation could be harmful to the participants.
3. The study is cancelled.
4. The subject withdraws consent.
5. The transcatheter arterial embolization is not performed.
6. Exclusion criteria are discovered after enrollment but prior to treatment.
7. Other administrative reasons.
8. Unanticipated circumstances.

5.10 Image Acquisition, Archiving, and Interpretation

5.10.1 [^{18}F]FMISO PET/CT scan

[^{18}F]FMISO will be prepared by experienced radiopharmaceutical chemists from the MIPS cyclotron and radiochemistry facility in the Department of Radiology at Stanford University under the supervision of Dr Frederick Chin. The ^{18}F-FMISO

will be delivered to the VAPAHCS section of Nuclear Medicine. The distance between the 2 institutions is < 5 miles and will not affect the dose administered to the subject. 3.7 MBq/kg (0.1 mCi/kg, up to 10 mCi) will be injected intravenously into each subject and a PET/CT will be performed 150 minutes +/- 60 minutes after injection. This dosage was chosen as the historical radiation dosimetry was performed at that value[29]. All scans will be performed on a GE Discovery PET/CT system. Per prior studies, no special subject preparation is required, except that subjects will empty their bladders prior to scanning[30]. A longer acquisition focusing on the liver will be performed to decrease statistical noise. Upon image acquisition, the PET/CT scan will be evaluated on a workstation allowing for fusion of the images. A region-of-interest (ROI) 3 cm +/- 1 cm in diameter will be drawn over a region of normal liver. The average SUV of this operator-defined ROI will be calculated. This will be repeated in 2 additional areas of normal liver. The mean of these 3 values will be obtained and used as the SUV_{mean} of the normal liver. A 2nd ROI encompassing the index tumor(s) will be drawn. Each index tumor must be ≥ 1.5 cm in size. The SUV_{max} will be calculated from this region with the threshold set at 10% of peak standardized uptake value of all voxels in the tumor volume. The TLR will be calculated as the (SUV_{max} tumor/SUV_{mean} liver). The same nuclear medicine physician will perform all [^{18}F]FMISO analyses. All PET/CT scans will be performed on the same GE Discovery scanner with the following parameters: kV = 120; mA = auto mA with min = 30 and max = 100; noise index = 25; and rotation time = 0.5 sec. The CT scan portion of the PET/CT is for attenuation.

For the purposes of this study, ^{18}F-fluoromisonidazole will be manufactured in the Cyclotron & Radiochemistry Facility of the Molecular Imaging Program at Stanford (MIPS) at Stanford University, and is also identified as ^{18}F-FMISO; [F-18]FMISO; and/or [^{18}F]FMISO.

5.10.2 Triphasic CT scan and MRI

Triphasic CT scan will be performed on a minimum 64-detector GE CT scanner. The kVP will be between 80 to 140 and will be determined based on subject body characteristics. The auto mA setting will be used to minimize radiation dose. Contrast will be injected intravenously at a dose to be determined by standard CT protocol. The required series are arterial; portal venous; and delayed venous phase. Each phase will include the entire liver. Additional scans can be obtained as deemed clinically necessary. Multiplanar reformats may be performed but are not required.

Triphasic MRI will be performed on a 1.5 or 3 Tesla GE scanner and include T2; diffusion weighted (DWI); pre-contrast T1 or gradient echo, post-contrast T1 or gradient echo arterial phase; portal venous phase; and delayed venous (ie, equilibrium) phase sequences. Additional sequences may be obtained as clinically necessary. Gadolinium contrast will be administered intravenously according to standard protocol.

Triphasic CT or MRI will undergo official interpretation. The interventional radiologist or diagnostic radiologist will review the index lesions for evidence of recurrence. LI-RADS criteria will be used to define active tumor in the liver. Recurrence will be defined as nodular areas of continued contrast enhancement with delayed venous phase contrast washout in regions previously occupied by

HCC. Ring-like enhancement is often seen normally and will not be considered recurrent tumor[26]. Recurrence will also include tumors that grow more than 20% in any dimension with or without arterial enhancement as long as they demonstrate washout on delayed phase imaging.

5.10.3 Archiving

All imaging studies will be stored on the VAPAHCS PACS servers. Storage on backup servers will be done according to standard VAPAHCS protocol.

6.0 Statistical Considerations

6.1 Study Design and Endpoints

This is a prospective, observational single-arm feasibility study to evaluate the variability of [^{18}F]FMISO in determining areas of hypoxia in hepatocellular carcinoma after treatment with transcatheter arterial embolization.

The primary endpoint will be to determine variability of [^{18}F]FMISO uptake in HCC tumors compared to normal liver after transcatheter arterial embolization by determining the difference in the mean of the maximum standardized uptake value (SUV_{max}) and tumor-to-liver ratio (TLR) of a region of normal liver and of up to 5 index tumors, each greater than or equal to 1.5 cm in diameter. The 5 largest tumors which are LI-RADS 4 or greater will be selected as the index tumors.

The secondary endpoints will be to compare the SUV_{max} and TLR in areas of tumor recurrence to areas without tumor recurrence as determined by CT or MRI within a 6 month period after transcatheter arterial embolization, to determine the variability in the SUV_{max} and TLR of untreated HCC compared to normal liver, and to determine any toxicities related to [^{18}F]FMISO use for PET/CT.

6.2 Objectives and Analysis Plans

Primary objective: Determine the variability of [^{18}F]FMISO uptake in HCC tumors compared to normal liver after transcatheter arterial embolization by determining the difference in the mean of the maximum standardized uptake value (SUV_{max}) and tumor-to-liver ratio (TLR) of a region of normal liver and of up to 5 index tumors, each greater than or equal to 1.5 cm in diameter.
Endpoint: Measurement of SUV_{max} and TLR of tumors 20 hours +/- 4 hours after embolization.
Analysis Plan: Tumor-to-liver ratios (TLR) of SUV_{max} will be calculated for all imaged tumors and analyzed on the logarithmic scale. A variance components model (linear mixed effects with a random intercept for subject effect) will be fitted to the TLR; in such a model the antilog of the overall intercept can be interpreted as an overall TLR averaged across tumors and subjects. We expect up to 5 tumors per subject will be obtained. The 5 largest tumors which are LI-RADS 4 or greater will be selected. The between subject and within-subject variance components will be used to plan further studies. While we do not expect to be powered to obtain statistical significance, the overall TLR will be reported with a P value obtained from the variance components model. A P-value less than 0.05 will be considered significant.

Secondary objective: Determine if areas of tumor recurrence as determined by CT or MRI within a 6 month period after transcatheter arterial embolization show evidence of increased [^{18}F]FMISO on initial post-treatment [^{18}F]FMISO PET/CT.
Endpoint: Comparison of SUV_{max} and TLR of tumors with recurrence to tumors without recurrence.
Analysis Plan: Logistic regression analysis will be performed on the independent variables, SUV_{max} and TLR, and the dependent variable, recurrence of tumor. An odds ratio and 95% confidence interval will be obtained.

Secondary objective: Determine the variability in SUV_{max} and TLR of untreated HCC compared to normal liver by determining the difference in the mean of the maximum

standardized uptake value (SUV_{max}) and tumor-to-liver ratio (TLR) of a region of normal liver and of up to 5 index tumors, each greater than or equal to 1.5 cm in diameter.
Endpoint: Measurement of SUV_{max} and TLR of untreated HCC tumor compared to normal liver.
Analysis: The analysis will be the same as that for the primary objective with analysis performed on a logarithmic scale. A variance component model will be fitted to the TLR. The overall TLR will be reported with a P value obtained from the variance components model. A P value less than 0.05 will be considered significant.

Secondary objective: Determine any toxicities related to [^{18}F]FMISO use for PET/CT.
Endpoint: Unanticipated toxicities related to [^{18}F]FMISO use over a 10 half-life period beginning from injection.
Analysis: Toxicity rates will be calculated and reported as a proportion of number of complications/number of total treatments with a corresponding 95% confidence interval.

6.3 Sample Size Considerations

No prior human studies exist to evaluate liver tumors using [^{18}F]FMISO. Given that this is an observational feasibility study, we will be studying a small population for which we have funding. We therefore will enroll 5 subjects in this study. With 5 subjects, for an 80% power and an $\alpha = 0.05$, and assuming a standard deviation of 1 for the mean of each value, the smallest difference between the means we will be able to detect will be 1.77.

6.4 Study monitoring, interim analyses, and early stopping rules

Study monitoring, including subject accrual and adverse events, will be performed by the study PI. No interim analyses are planned.

7.0 Adverse Events; Safety Issues

7.1 Definition of Adverse Events and Potential Risks

The definition of Adverse Event (AE), from VHA Handbook 1058.01, is “any untoward physical or psychological occurrence in a human subject participating in research. An AE can be an unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have a causal relationship with the research.” According to VAPAHCS HCSM 151-11-03, a local AE is “an AE experienced by a participant enrolled in a VAPAHCS approved research project or that is experienced by a participant at a non-VAPAHCS participating site of a multi-site study where the VAPAHCS is the lead or coordinating site.”

Anticipated adverse events and potential risks are those which typically occur due to embolization and include pain, fever, fatigue, nausea, elevated liver enzymes, infection, abscess, cholecystitis, gallbladder infarction, hemorrhage, thromboembolism, arterial dissection, post-embolization syndrome, splenic infarction, and liver infarction. Anticipated adverse events also includes progression of cirrhotic or cancerous liver disease manifested by jaundice, biliary obstruction, progression of tumors, metastatic disease, liver failure, worsening liver enzymes, worsening cirrhosis, increased portal hypertension, and death. Anticipated adverse events related to use of [^{18}F]FMISO at the doses indicated in the protocol include nausea, vomiting, anorexia, and allergic reaction (rash, fever, etc).

7.2 Definition of Serious Adverse Events (Serious Adverse Events List)

A Serious Adverse Event (SAE) according to VHA Handbook 1058.01 is an injury or illness that:

- Results in death
- Results in a life-threatening experience
- Results in inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Requires additional medical, surgical, behavioral, social, or other intervention needed to prevent any of the above outcomes

Events meeting the criteria for an SAE require notification of the reviewing IRB and the FDA within the specified timeframe identified in section 8.4.

7.3 Adverse Events Characteristics

7.3.1 Grading of Adverse Events

Adverse events for the use of ^{18}F-FMISO will be graded according to the Common Terminology Criteria for Adverse Events version 4[27]. Grading will be as follows:

- Mild – Grade 1
- Moderate – Grade 2
- Severe – Grade 3
- Life threatening or disabling – Grade 4
- Fatal – Grade 5

Adverse events related to the TAE will be graded according to the Society of Interventional Radiology Clinical Practice Guidelines and will be classified as follows[31]:

Minor Complications:

A. No therapy, no consequence
B. Nominal therapy, no consequence; includes overnight admission for observation only

Major Complications:

C. Require therapy, minor hospitalization (< 48 hours)
D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours)
E. Permanent adverse sequelae
F. Death

7.3.2 Definitions of Serious Problem, Unanticipated Problem, and Unanticipated Adverse Events, and Unanticipated Adverse Device Effect

Terms are defined in VAPAHCS HCSM 151-11-03 and are as follows:

A Serious Problem (SP) is a problem that may reasonably be regarded as:

- Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others
- Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs

An Unanticipated and Unexpected refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

Unanticipated Problems (UPs) are events that are:

- Unforeseen (or unanticipated) in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other study materials AND
- Are harmful (or serious) AND
- Are related to the study (or study procedures)

Unanticipated Adverse Device Effect are any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or FDA application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3.3 Attribution of Adverse Events

Attribution of the AE:

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

7.4 Adverse Event Reporting

7.4.1 When and How to Report Adverse Events

It is the responsibility of the investigator to document all Adverse Events (AEs) that occur during the course of the study.

Events Requiring Prompt Reporting to the IRB:

PIs and investigators must report the following events to the IRB as soon as possible, but no later than 5 business days after becoming aware of them:

- Local Unanticipated SAEs, except those occurring on observational studies. Local unanticipated SAEs that the PI determines are not related to the study and/or are anticipated (and therefore are not UPs) should be submitted to the IRB as "Other events or information" (item 7 on the eProtocol Report Form) with a statement in section 8a of the eProtocol Report Form that the PI has

determined the event is not related to the study and/or was not unanticipated. Details on the event should be provided in section 8a or the eProtocol Report Form or the PI can attach documentation detailing the event to the Report Form.

- Local unexpected deaths or life-threatening experiences related to the research and involving participants enrolled at VAPAHCS or on studies where the VAPAHCS is the coordinating institution of a multi-site study. (Item 1 on the eProtocol Report Form).
- Unanticipated problems (events that are unanticipated, harmful and related to the study). (Item 1 on the eProtocol Report Form).
- Unanticipated adverse device effect. (Item 6 on the eProtocol Report Form).
- Serious Unanticipated Problems involving risks to subjects or others, including:
    - Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others. (Item 2 on the eProtocol Report Form).
    - Any Data Monitoring Committee (DMC) report describing a safety problem. (Item 2 on the eProtocol Report Form);
    - Any sponsor analysis describing a safety problem. Interruptions of subject enrollments due to concerns about the safety, rights, welfare of human subjects, research staff, or others. (Item 2 on the eProtocol Report Form).
    - Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others.
    - Any problems reflecting a deficiency that substantively compromised the effectiveness of a facility's human research protection or human research oversight programs.

Events that must be submitted to the IRB within 10 working days from when the PI learns of the event or new information:

- New Information that indicates change to risks or potential benefits of the research, in terms of specificity, severity, or frequency. (Item 2 on the eProtocol Report Form).
- Protocol Deviation or Violation (Item 3 on the eProtocol Report Form), only if:
    - Intended to eliminate apparent immediate hazard to a research participant, or
    - Harmful (caused harm to participants or others, or placed them at increased risk of harm – including physical, psychological, economic or social harm).
- Complaint that is unresolved by the research team, or that indicates increased or unexpected risks. (Item 4 on the eProtocol Report Form).
- Incarceration of the research participant and in the opinion of the PI, it is in the best interest of the participants to remain on the study. (Item 5 on the eProtocol Report Form).
- Other events or information.

Adverse events are serious and unexpected suspected adverse reactions, ie, are possibly, probably, or definitely related to the study drug [^{18}F]FMISO, will be

reported to the FDA via IND Safety Report [21CFR§312.32] within 14 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction.

8.0 Ethical Considerations (Including Informed Consent)

8.1 Protection of Subject Rights

Each participant will receive an oral and written explanation of the purpose of the study, potential risks and benefits of participation in this protocol. The Principal Investigator or a co-investigator will obtain consent. Specifically, participants will be told that:

a) The information derived may eventually lead to better understanding of hypoxia in relation to hepatocellular carcinoma;

b) PET imaging as used in our protocol are research tools, and that consequently, no diagnostic interpretations will be provided;

c) A confidential participant identification number will be used to ensure that information cannot be linked or traced to any person or family; and

d) Data will be evaluated to yield group statistical analyses only. In addition, participants will be given ample opportunity to ask questions of the investigators.

8.2 Confidentiality

All data will be maintained by the Principal Investigator at the VAPAHCS. Data maintained include clinical and demographic forms, adverse event forms, PET data, and CT/MRI data forms. Records will be stored in a locked, secure location within the Department of Radiology. Data will only be accessed by members of the research team assigned to data collection or analysis.

8.3 Inclusion of Women and Minorities

We will make every effort to ensure that gender and race are equally represented in the total sample of participants in proportion with demographic data available for the patient population at the VAPAHCS.

8.4 Audit and Monitoring

Study data and case report forms will be monitored in accordance with VA standard operating procedures, and with national government regulations. The PI will be responsible for monitoring the safety of subjects who have enrolled in the study.

8.5 IND

This study has been submitted to FDA as IND 126878.

9.0 Data Management; Administrative Issues

All electronic data will be stored on a restricted access folder in a protected network drives on password protected VA computers in the Palo Alto VA. Access will be limited to the Principal Investigator, Co-investigators, and any clinical coordinators. Subject data will be maintained in a HIPAA compliant manner with minimization of PHI in a database within the restricted access folder.

All paper forms will be kept in a locked cabinet in a locked office within the VAPAHCS. All data will be maintained for the period of time as required in the Record Control Schedule (RCS).

10.0 Regulatory Considerations

10.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Paper CRFs will be kept in a locked office, only accessible to the research team

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11.0 APPENDICES

11.1 Glossary of Terms

^{18}F-FMISO	^{18}F-Fluoromisonidazole
CT	Computed tomography
DEB-TACE	Drug-eluting bead transcatheter chemoembolization
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
HIF	Hypoxia inducible factor
HNC	Head and neck cancer
kVP	KiloVolt peak
mA	milliAmperes
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
SUV	Standardized uptake values
TACE	Transcatheter arterial chemoembolization
TAE	Transcatheter arterial embolization
TLR	Tumor-to-liver ratio
TMR	Tumor-to-muscle ratio
VAPAHCS	Veterans Affairs Palo Alto Health Care System
VEGF	Vascular endothelial growth factor