

Abbreviated Title: [¹⁸F] FMISO Imaging post TACE

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Title: A Pilot Study of an Integrated Imaging Strategy to Phenotype Progression of Liver Tumors during and after Chemoembolization

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- A. Obtain information by intervening or interacting with living individuals for research purposes*
- B. Obtaining identifiable private information about living individuals*
- C. Obtaining the voluntary informed consent of individuals to be subjects*
- D. Makes decisions about subject eligibility*
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
- G. Some/all research activities performed outside NIH*

Investigational Agents:

Drug Name:	[¹⁸ F] Fluoromisonidazole, 1 H-(3-[¹⁸ F]-fluro-2-hydroxyl-propyl)-2-nitro-imidazole, [¹⁸ F] FMISO
IND Number:	124706
Sponsor:	Dr. Elliot Levy
Manufacturer:	Cardinal Health

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PRÉCIS

Background

- TACE is the standard therapy for inoperable primary liver cancers or tumor control prior to transplantation. The mechanisms for TACE's failure remains poorly understood.
- Although acute hypoxia and significant tumor necrosis occurs following TACE, the tumor adaptive response and localization for such have not been well characterized.
- Imaging tools using a hypoxia-specific tracer [¹⁸F] FMISO may help identify the pattern and distribution of acute post-TACE tumor hypoxia relative to demonstrated tumor progression.
- The primary hypothesis of this study states that tumor progression post-TACE arises from changes in tumor phenotype induced by treatment-related hypoxia superimposed on the dynamic process of underlying tumor hypoxia.

Objectives

To determine the feasibility of hypoxic tumor identification despite relatively high liver background signal, and describe patterns of tumor hypoxia in the immediate post-TACE treatment period using PET imaging [¹⁸F] MISO uptake registered with cross-sectional imaging.

Eligibility

- Patients ≥18 years of age with inoperable primary hepatic malignancy or hepatic-dominant metastatic disease and be otherwise eligible to receive TACE treatment. Patients with hepatocellular carcinoma should have intermediate stage disease according to the BCLC staging system (Stage A4 or B).
- Patients must not have had chemotherapy or radiation therapy to liver for at least 2 weeks prior to starting study treatments.
- Patients must not have an acute, critical illness.
- Patients must not be pregnant
- Able to understand and be willing to sign a written informed consent

Design

- Fifteen patients with primary or metastatic liver malignancy will be enrolled into this pilot, non-randomized, open study of the feasibility of using ¹⁸F-fluoromisonidazole PET scanning to determine hypoxic tumor identification and localization, and to identify the pattern and distribution of acute post-TACE tumor hypoxia relative to demonstrated tumor progression.
- Twenty-four to seventy-two hours after standard of care TACE, patients will undergo PET scanning using 0.1mCi/kg (maximum 10mCi) of ¹⁸F-fluoromisonidazole ([¹⁸F] MISO).

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the feasibility of hypoxic tumor identification despite relatively high liver background signal, and describe patterns of tumor hypoxia in the immediate post-TACE treatment period using PET imaging [¹⁸F] MISO uptake registered with cross-sectional imaging.

1.2 BACKGROUND AND RATIONALE

1.2.1 Hypoxia and the Tumor Microenvironment

Hepatocellular carcinoma (HCC) is the sixth most common cancer across the globe and it represents the third most common cause of cancer related deaths. HCC represents 90% of primary liver cancers. Liver tumor resection or liver transplantation, are first-line treatment options for HCC. Patients who are neither a candidate for surgery or transplantation can undergo minimally invasive procedures such as local ablation or chemoembolization. Often there is tumor progression despite these treatments¹. The implications of tumor hypoxia following chemoembolization are unclear, although an association between hypoxia and more aggressive tumor phenotype is well known. As early as 1955, Thomlinson and Gray hypothesized that the presence of hypoxia may render lung cancers resistant to radiotherapy¹. Tumor hypoxia occurs when oxygen consumption is out of balance with supply, as with reduced perfusion or diffusion-limited oxygen delivery. Clinically relevant hypoxia is detected in approximately 50% of all solid tumors irrespective of their size and histological features².

Durand and Aquino-Parsons³ studied tumor perfusion in a human xenograft tumor model and observed varying degrees of overlap of fluorescent staining or changes in fluorescence intensity corresponding to significant variations in tumor perfusion over relatively short periods of time. More recently more complex mechanisms resulting in significant fluctuations in red cell flux and tumor oxygenation have been implicated as potential determinants of tumor radio-resistance and chemo-resistance^{4,5}. These fluctuations in tumor oxygenation may occur in cycles of extremely variable duration, on the order of minutes to hours, depending upon tumor type; various studies using different models have determined cycle durations of less than 2 cycles/minute⁶, cycles every 20-30minutes⁷ or 12 hours in patients imaged with PET hypoxia agents^{8,9} tumor hypoxia and TACE therapy of liver tumors.

TACE (transarterial chemoembolization) consists of the local transcatheter intrahepatic arterial delivery of chemotherapeutic agents combined with temporary occlusion of the artery(s) supplying the targeted neoplasm(s). The combination of acute ischemia and high concentrations of chemotherapeutic agent results in significant tumor necrosis, although the exact contribution of each mechanism remains poorly understood. Although TACE is considered palliative therapy for hepatic malignancy, TACE has been shown to prolong survival in patients with unresectable hepatocellular carcinoma (HCC) and is considered the standard of care for patients with unresectable intermediate HCC¹⁰. The treatment has also been shown to have a measurable and statistically significant decrease in the size of treated lesions in metastatic liver disease¹¹. The most common adverse effect of TACE is post-embolization syndrome, consisting of transient abdominal pain, nausea, vomiting, fever, and fatigue. Despite worldwide use of TACE for

unresectable HCC as well as chemo-refractory hepatic metastatic disease, TACE treatment failure is poorly understood. Several factors may play a role in tumor progression despite TACE, including tumor resistance to chemotherapeutic drugs, which may be enhanced by hypoxia.

Hepatic arterial embolization has been shown to yield discrete reductions in tumor perfusion in a liver tumor model using TRIP MRI imaging¹². In the same tumor model, embolization with 40-120µm microspheres was found to result in increased HIF-1a (hypoxia-inducible factor 1a) stabilization¹³. These results confirm the degree and effect of acute embolization-related hypoxia, which represents a unique subset in the spectrum of the hypoxic tumor microenvironment; acute severe hypoxia is superimposed upon portions of normoxic and cycling hypoxic tumor by virtue of proximal occlusion of the arterial supply of the tumor(s). Tumor tissue either undergoes ischemic necrosis or adaption to the acute hypoxic environment through hypoxia-induced gene expression and subsequent proliferation.

1.2.2 [¹⁸F]-FMISO

[¹⁸F] Fluoromisonidazole, 1 H-(3-[¹⁸F]-fluoro-2-hydroxyl-propyl)-2-nitro-imidazole, [¹⁸F] FMISO is an investigational PET radiopharmaceutical for injection and intended for use as tumor hypoxia imaging agent. [¹⁸F] FMISO possesses desirable qualities for evaluating hypoxia including an ideal partition coefficient and a relatively low required dose ($\leq 10\text{mCi}$). [¹⁸F] FMISO is reduced only in hypoxic tissues, resulting in hypoxia-specific intracellular accumulation.¹⁴ Imaging studies of head and neck as well as pancreatic tumor hypoxia using [¹⁸F] FMISO have been previously published¹⁵. This agent has shown no toxicity among 600 patients who received at least four administrations.

1.2.3 Rationale

The primary hypothesis of this study states that tumor progression post-TACE results from changes in tumor phenotype induced by sublethal treatment-related hypoxia. The goal of the proposed pilot study is to test the feasibility of hypoxia imaging of the liver post-TACE. Early imaging detection of residual hypoxic tumor acutely following TACE may ultimately correspond to undertreated tumor and could be used to optimize TACE outcomes with targeted combinational therapies.

This pilot study will evaluate fifteen patients who will receive TACE therapy for primary or metastatic hepatic malignancy. They will undergo PET imaging of the liver with [¹⁸F] FMISO to: 1) determine the feasibility of hypoxic tumor identification despite relatively high liver background signal, and 2) identify the pattern and distribution of acute post-TACE tumor hypoxia relative to demonstrated tumor progression despite therapy. Patients will be followed according to standard community practice with conventional cross-sectional imaging (CT and/or MRI) to confirm tumor progression. Image fusion analysis will be performed to determine degree of correlation between focal hypoxia and site(s) of progression.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- 2.1.1.1 Patients must have confirmed inoperable primary hepatic malignancy or hepatic dominant metastatic neoplastic disease evidenced by histology or cytology, or characteristic enhancement pattern on CT or MRI together with an abnormal serum alpha-fetoprotein >200mg/dl in the case of hepatocellular carcinoma.
- 2.1.1.2 Patients with hepatocellular carcinoma should conform to intermediate stage disease according to the BCLC¹⁶ staging system (Stage A4 or B) and be otherwise eligible to receive TACE treatment¹⁷.
- 2.1.1.3 Patients must have had no chemotherapy or radiotherapy to the liver for their malignancy for at least 2 weeks (or until response can be adequately assessed) prior to treatment and must have recovered from all clinically significant side effects of therapeutic and diagnostic interventions.
- 2.1.1.4 Serum creatinine less than or equal to 2.0 mg/dl unless the measured creatinine clearance is greater than 60ml/min
- 2.1.1.5 Age \geq 18 years
- 2.1.1.6 Ability of subject to understand and willingness to sign a written informed consent document
- 2.1.1.7 Patient must be able to lie still for the procedure
- 2.1.1.8 ECOG status \leq 2
- 2.1.1.9 In addition, for patients receiving TACE outside NIH:
 - Patient must have physician willing to collaborate with NIH PI by providing required medical record and digital MR/ CT scan documentation pre and post TACE procedure.
 - Patient must be willing to sign an Authorization for the Release of Medical Information form.
- 2.1.2 Exclusion Criteria
 - 2.1.2.1 Patients who have received prior TACE treatment
 - 2.1.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to misonidazole or other agents used in study.
 - 2.1.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
 - 2.1.2.4 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.5 Patients of childbearing age must not be pregnant. The effects of [¹⁸F] FMISO on the developing human fetus are unknown. Pregnancy is a contraindication for TACE.

2.1.3 Recruitment Strategies

Investigators will work closely to identify patients with colleagues at the NCI and in the local community including tumor board meetings to enlist their assistance in referrals.

2.2 SCREENING EVALUATION

Patients may have TACE either at the NIH or the institution of their choice.

The study procedure on this protocol is the FMISO scan, which will be performed at the NIH ONLY. An eligibility checklist will be completed by the Principal Investigator during initial contact. An eligibility checklist including inclusion/exclusion criteria will be completed by referring physician for patients treated with TACE outside NIH or the Principal Investigator for patients treated with TACE at NIH. Referring physicians will fax or email a completed checklist at least one week prior to TACE. Following the Principal Investigator's review of the returned checklist and confirmation of eligibility, patients will be contacted by a research staff member to 1) discuss the study and answer questions, and 2) to offer enrollment into the protocol and schedule an appointment(s) for [¹⁸F] FMISO PET-CT scanning.

The eligibility checklist will be reviewed with the patient when the patient provides informed consent and undergoes FMISO imaging. The consent process is described in section 9.4 and may occur over the telephone and by mail.

2.3 REGISTRATION PROCEDURES

The Principal Investigator, along with key research personnel, will screen and enroll all eligible patients on the study. The screening and enrollment process will be documented in CRIS. All patients enrolled in the study will receive a unique patient identifier and will be entered in the study's screening and enrollment logs which are kept in our research database. The study research database will be maintained in an electronic folder in a larger central shared drive with a secure password and Clinical Center network back-up, in accordance with NIH CC policy.

2.4 BASELINE EVALUATION

No specific pre-procedure laboratory studies are required prior to FMISO administration. Pre-TACE standard of care evaluation commonly occurs no more than four weeks prior to TACE and includes laboratory and imaging studies. These may include but not limited to:

- Baseline CT and MRI of the abdomen
- Tumor measurements
- Baseline laboratories including an acute care, hepatic, and mineral panel, PT, aPTT, INR, CBC with differential, and AFP at outside institution.
- Baseline history and physical exam
- B-hCG (Urine or Serum) will be performed within 48 hours of FMISO imaging

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

Fifteen patients with metastatic or primary hepatic malignancy will be enrolled to yield a minimum of ten evaluable patients. Prior to TACE, all patients will undergo conventional baseline imaging. The first five patients enrolled will receive a single dose of the study imaging agent (FMISO) post-TACE to determine imaging parameters and feasibility. Subsequent to the feasibility study, the remaining patients (#6-15) will receive the hypoxia imaging agent before and following TACE to determine changes in uptake pattern attributable to arterial embolization. Following TACE patients will be monitored according to standard of care until tumor progression is documented. Registration of functional and/or metabolic imaging demonstrating progression with immediate post-TACE hypoxia imaging will be performed for correlative analysis.

3.1.1 TACE guidelines

TACE will be performed per institution standard of care or separate protocol specifications. Documentation of the TACE procedure will be provided to the PI.

3.1.2 FMISO Hypoxia Imaging

Following screening and eligibility determination, patients will be contacted by a research staff member to offer enrollment into the protocol and schedule an appointment for [¹⁸F] FMISO PET-CT scanning. Consented patients are scheduled for [¹⁸F] FMISO PET-CT scanning. If the patient is not an inpatient at NIH CC, they should arrive approximately 1-2 hours before the appointed time for imaging, to go through outpatient admissions, and then to the PET scanning department to sign informed consent. Once imaging is completed, the patient, based on their clinical condition, will return to the inpatient ward, transferred to a day hospital or clinic, or discharged home for further monitoring or instruction.

3.1.3 Post TACE Cross-sectional Imaging for determination of progression despite TACE

Patients will receive CT and MRI of the abdomen with contrast at 4-6 week intervals following TACE to detect tumor progression despite TACE per standard of care. Scanning interval may be increased to 3 months if stable disease is documented on at least two successive imaging studies. If these studies were done outside NIH CC, digital copies will be provided to PI at each post-TACE interval for progression documentation and analysis (Section 3.3)

3.2 DRUG ADMINISTRATION

[¹⁸F] FMISO imaging technique will be adapted from previously reported imaging studies for head and neck malignancies¹⁷ and pancreatic malignancy¹⁸. The [¹⁸F] FMISO will be administered intravenously at a dose of 0.1mCi/kg for hypoxia imaging. PET-CT imaging of the abdomen will be performed 120 minutes after injection. A repeat scan at 240 minutes after injection may be obtained if tumor-to background uptake is suboptimal and only if the patient's condition permits. Each scan requires up to 30 minutes. Based upon previous reports, it is expected that [¹⁸F] FMISO uptake will peak within target liver tumor two hours following intravenous administration. Considerable background activity is expected in normal liver tissue, and techniques to maximize signal-to-noise activity in target tumors may include 1)

characterization of observed focal uptake relative to serum [¹⁸F] FMISO activity, where a tumor: serum ratio >1.2 has been considered indicative of hypoxia, or 2) delayed imaging up to 4 hours post-injection with subtraction techniques to identify focal tumoral uptake.

3.3 IMAGE ANALYSIS

Feasibility of FMISO PET imaging post-TACE will be assessed by individually characterizing FMISO uptake in treated tumors as absent, background (equivalent to normal liver), or increased relative to liver background. Lesions demonstrating any increased activity compared to background liver will be further characterized as diffusely or focally increased activity.

Changes in FMISO PET activity before and following TACE will be descriptively compared and change in peak SUV will be assessed as response to embolization.

Individual liver tumors which demonstrate progression defined by increased size and/or enhancement will be evaluated for geographic FMISO uptake correlation. CT or MRI images demonstrating progression will be registered with FMISO PET-CT images automatically using OncoNav software (developed at the Center of Interventional Oncology) to determine whether qualitatively increased or decreased FMISO uptake is observed in spatial relation to tumor progression.

Increased FMISO activity which correlates positively with tumor progression will be further quantified using calculated standardized uptake values (SUV) or tumor-to- serum activity ratio in manually selected regions of interest (ROI).

3.4 STUDY CALENDAR

Patients will be scheduled for pre-TACE imaging up to one week before TACE and post-TACE imaging 24 to 72 hours based on their clinical condition. Patients will sign the protocol consent prior to [¹⁸F] FMISO administration and imaging. Per PET scanning protocols, patients will be NPO (≥4-6 hours) before actual scanning. Patients will obtain standard of care post-TACE imaging by their primary oncology team, however, the research team may follow up, typically, but not required with clinic visits or phone calls. Follow up imaging and tumor measurements/s are the only research-related activities to be performed until tumor progression, withdrawal from study or a new, non-TACE, treatment is indicated. If this follow-up occurs outside NIH CC, documentation must be provided to the study PI.

	Pre- ^[18F] FMISO PET Scan	^[18F] FMISO PET Scan ^{4,5}	Standard of Care and Research follow up post TACE ^{3,4,7}
Informed consent ¹	X		
^[18F] FMISO dose approximately 10mCi ⁴		X	
Primary or metastatic malignant hepatic disease ²	X		
CT/ MRI ⁴	X		X

Tumor measurements ^{4,8}	X		X
Demographics ⁴	X		
Medical history ⁴	X		X
Physical exam ⁴	X		X
Vital signs ⁴	X		X
Height ⁴	X		
Weight ⁴	X		
Creatinine ⁴	X		
B-hCG Urine or Serum ^{3,6}	X		
Adverse event evaluation		X ³	X

1. Informed consent must occur prior to any study specific procedure or scan. See also section 9.4
2. In the absence of a pathological diagnosis of hepatocellular carcinoma, the diagnosis shall be made by the combination of serum alpha-fetoprotein ≥ 200 mg/ml and CT or MRI of the liver showing an imaging appearance characteristic of hepatocellular carcinoma
3. AE evaluation will be obtained within 24 hours post TACE FMISO injection.
4. Patient must have physician willing to collaborate with NIH PI by providing required medical record and digital MR/ CT scan documentation pre and post TACE procedure. Imaging done outside NIH must be digitally provided to NIH for tumor measurement/assessment
5. NIH only
6. FMISO imaging will be performed **only** post TACE in **the first five consecutively enrolled patients** and pre and post TACE in the **remaining** patients.
7. Pregnancy test for women of childbearing potential. Test must be within 48 hours of PET scan
8. Standard of care follow up post- TACE q 4-6 weeks. Scanning interval may be increased to 3 months if stable disease is documented on at least two successive imaging studies
9. Imaging done outside NIH digitally provided to NIH for tumor measurement/assessment

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL AND OFF STUDY CRITERIA

3.5.1 Off Treatment

Patient will be considered “off treatment” 24 hours following post-TACE [¹⁸F] FMISO injection. No research-related follow up such as adverse event monitoring, will take place after this time period.

3.5.2 General Off-Study Criteria

- Inability to complete ¹⁸F-MISO imaging
 - Patients will be considered “unevaluable” for the study if [¹⁸F] FMISO imaging is incomplete or deficient and will be replaced (see Section 6.2.1). As an example, an FMISO scan which in the opinion of the Principal Investigator does not demonstrate hepatic uptake relative to background liver activity will be considered deficient and will not be included in the data analysis.
- Patient decides to withdraw from the study

- Toxicity which prevents further imaging (e.g. renal dysfunction defined as serum creatinine >2.0mg/dl which precludes CT or MRI imaging)
- Death
- Progression of disease
- Additional treatment of primary or metastatic hepatic malignancy (i.e., transplantation, resection)

The reason for study removal and the date the patient was removed must be recorded in the study database.

3.6 FOLLOW-UP

Research-related follow up may be obtained outside NIH CC as part of routine pre- and post-TACE care. Patient must have physician willing to collaborate with NIH PI by providing required medical record and digital MR/ CT scan documentation pre and post TACE procedure. Imaging done outside NIH must be digitally provided to NIH for tumor measurement/assessment.

Primarily, after the patient is considered “off treatment”, research-related follow-up consists of standard of care post-TACE imaging which is q 4-6 weeks. Scanning interval may be increased to 3 months if stable disease is documented on at least two successive imaging studies

Other typical, but not required, evaluations may also include clinical visits, phone calls from the research team, and laboratory testing.

3.7 STUDY STOPPING RULES

Enrollment will be halted; IRB will be notified if:

- Any grade 3 adverse event definitely attributed to [¹⁸F] FMISO (occurring within 24 hours of injection)
- Any grade 4 or grade 5 adverse event regardless of attribution
- Patients not receiving TACE at NIH CC will be observed for adverse events according to one or more of the following:
 - Patient must have physician willing to collaborate with NIH PI by providing required medical record and digital MR/ CT scan documentation pre and post TACE procedure
 - patients will be provided with the PI’s contact information to report symptoms which could represent an adverse event,
 - telephone call from the PI’s designee on the day following the FMISO scan to document signs or symptoms
- Patient(s) will be monitored until there is improvement or resolution of toxicity.
- Following review and approval by the IRB study enrollment will resume.

Enrollment will be limited to six patients if fewer than 2 patients demonstrate demonstrable ¹⁸F-FMISO uptake in liver tumors, consistent with diagnostic uptake of radiopharmaceutical in fewer than 30% of patients with liver cancer.

4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Patients will receive the standard of care supportive measures for patients undergoing DEB-TACE and additional care at the discretion of their primary oncology team.

5 BIOSPECIMEN COLLECTION

This protocol does not require bio-specimen collection. If specimens are obtained, they will be done so on another NCI protocol.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data collection for this study will include imaging data used to identify acute post-embolization tumor hypoxia, as well as conventional post-treatment imaging and measurement of tumor markers used to identify tumor progression despite therapy. Other follow up data such as date of death will also be collected. The [¹⁸F] FMISO PET-CT imaging and post-treatment CT and MRI will be stored in PACS prior to image registration and analysis. PET-CT and conventional CT images will be transferred to a workstation for registration analysis. Identifiers will be removed from fused images for characterization of degree of overlap between documented tumor progression and acute post-treatment hypoxia. Imaging data including determination of response by mRECIST criteria as well as tumor marker levels will be collected in an Excel spreadsheet that will be stored in a password-protected PC kept in a secured office.

Grade 2 events and higher will be recorded in the study database. Grade 1 events will not be recorded or reported.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Source data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS and FDA regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 RESPONSE CRITERIA

6.2.1 Definitions

6.2.1.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with [¹⁸F] FMISO up to 24 hours post injection and any adverse events including allergic reactions, FMISO extravasation, or any Grade 3 or greater AE within the 24-hour time frame post injection will be followed until resolution.

6.2.1.2 Evaluable for imaging response and inclusion in cohort of subjects

Only those patients who have measurable disease present at baseline, and who have received baseline imaging (CT or MRI) and post TACE PET imaging with [¹⁸F] FMISO and at least one follow-up visit that includes CT or MRI.

6.2.1.3 Target lesions

Only measurable lesions targeted to undergo TACE will be evaluated. A sum of the diameters (longest for non-nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

6.2.2 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of TACE (cross-sectional imaging within four weeks of TACE treatment).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging will include one or all of the following: CT (triple phase), MRI or PET scan.

6.2.2.1 Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

6.2.3 Response Criteria

All of the patients who met the eligibility criteria (with the possible exception of those who could not undergo ¹⁸F-MISO imaging) should be included in the main analysis of the response to the imaging agent. All conclusions should be based on all eligible patients.

For the purposes of this study, patients with baseline CT or MRI and should be re-evaluated for response per standard of care approximately 4 to 6 weeks following TACE treatment with an abdominal CT and MRI. Scanning interval may be increased to 3 months instead of 4-6 weeks if stable disease is documented on at least two successive imaging studies obtained at the 4-6 week post-TACE interval.

Response and progression of only targeted tumors will be evaluated in this study using the revised modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines.¹⁹

Complete Response (CR)	Disappearance of any intratumoral arterial enhancement
Partial Response (PR)	At least 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking the baseline sum of the diameters of target lesions

Stable Disease (SD)	Any cases that do not qualify for either PR PD
Progressive Disease (PD)	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesion, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

European Association for the Study of Liver, European Organization for Research and Treatment of Cancer. Journal of Hepatology, 2012 56:908-943.

Serum alpha-fetoprotein levels will be assessed and compared pre- and post-TACE per standard of care as a marker for tumor progression despite TACE. Cross-sectional and PET imaging will continue to be obtained at 4-6 week intervals until imaging evidence of disease progression is obtained and compared with FMISO imaging.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA&SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be evaluable for toxicity due to [¹⁸F] MISO for a period of one day after radiopharmaceutical administration (exceeding 10 half-lives of the radiopharmaceutical). An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
 - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB REPORTING

7.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.2.2 NCI Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
 - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
 - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
 - All Grade 5 events regardless of attribution;
 - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

An investigator must **immediately** report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to the IND Sponsor/ Investigator Dr. Elliot Levy at:

National Institutes of Health/Clinical Center

9000 Rockville Pike

Building 10, Rm. 1C367

Bethesda, Maryland 20892

T: 301-402-5368

F: 301-496-9933

levyeb@cc.nih.gov

7.4 FDA REPORTING CRITERIA

7.4.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendar days after receiving the request.

7.4.2 FDA Annual Reports (Refer to [21 CFR 312.33](#))

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet regularly while patients remain in the study. Any adverse event, toxicity, and imaging evaluations will be discussed as a group.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Sponsor Monitoring Plan

Dr. Virginia Guptil, Clinical Center Clinical Research Quality Coordinator from the Office of the Deputy Director for Clinical Care will monitor this study and will not be affiliated in any way with the trial conduct. She is qualified by training and experience to monitor the progress of clinical trials.

All enrolled patients will have follow up evaluations per standard of care until they show disease progression, withdrawal from the study or begin another treatment. All patients will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director of the NIH Clinical Center.

8 STATISTICAL CONSIDERATIONS

The study is a proof of concept protocol. It aims to determine the feasibility of acute hypoxia imaging of the liver following TACE. Power and significance calculations are not applicable to this small sample feasibility study.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

The study will seek to enroll both adult men and women who meet eligibility criteria, including whites, non-whites, and minorities. Transarterial chemoembolization is considered standard of care for unresectable hepatic malignancy where the dominant tumor burden is found in the liver.

Patients with primary or metastatic liver tumors will be eligible for treatment with hepatic chemoembolization and study-defined imaging. Hepatocellular carcinoma is variously ranked as the fourth to sixth most common neoplasm worldwide. Annualized rate among men is 22.1 per 100,000 and 8.5 women per 100,000 population has been described worldwide.

Cholangiocarcinoma most commonly occurs in females over 60 years of age, and the incidence in western countries is 2-6 cases per 100,000 people per year.

Patients who may be unable to comprehend the study requirements and associated risks may not be able to adequately appreciate the relatively small potential benefit which might be derived from participation. These patients will be considered ineligible to enroll.

9.2 PARTICIPATION OF CHILDREN

The most common types of liver cancer in children include hepatoblastoma, hepatocellular carcinoma, undifferentiated embryonal sarcoma of the liver, and infantile choriocarcinoma of the liver. Hepatocellular carcinoma and hepatoblastoma can be cured by surgical resection. Other treatments for childhood liver cancer include chemotherapy, radiation therapy, and percutaneous ethanol injection. HCC and hepatoblastoma can be treated with chemoembolization followed by resection. The aim of the proposed study is to describe an imaging phenotype of liver tumor recurrence in patients undergoing chemoembolization for unresectable liver cancer; chemoembolization treatment in children is intended to downsize or downstage tumors to achieve resectability, and study-related imaging and tissue sampling is not indicated in this clinical scenario.

9.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

9.3.1 Risk of IND agent

Although there has been no reported toxicity for the [¹⁸F] FMISO dose required for hypoxia imaging two potential risks common to radiopharmaceutical imaging agents that are possible include:

- Allergic reaction
- Extravasation of the imaging agent into the skin/subcutaneous tissue from Intravenous infiltration.

9.3.1.1 Risk of Radiation from Research Procedure

This research study involves exposure to radiation from **PET-CT with 10mCi of [¹⁸F] FMISO**. According to the Investigator's Brochure, the calculated total body dose for a 70kg man injected with 3.7 MBq/kg (~10mCi) is 0.013 mGy/MBq. Effective dose ranges from 0.013-0.014 mSv/MBq. The highest organ-specific radiation dose is observed in the bladder wall, likely due to urinary excretion of ~3% of the administered dose. The mean effective CT radiation dose associated with the PET-CT study should be less than 6 mSv. The amount of radiation patients will receive in this study is below the guideline of 5 rem/per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem/per year from natural sources, such as the sun, outer space, and the earth's air and soil.

The NIH Radiation Safety Committee will review this protocol to assure it meets standard safety criteria.

9.3.2 Potential benefits to subjects

There is no direct benefit to patients. Their participation advances our understanding of the disease and the imaging tools.

9.4 CONSENT PROCESS AND DOCUMENTATION

9.4.1 NIH TACE-treated study subjects

The Principal Investigators or associate investigators will explain the rationale of the study, including the study plan, the risks and potential benefits, when the patient is also evaluated for TACE in the outpatient clinic or prior to TACE administration. Patients will be given ample time to process the consent, ask questions and be counseled adequately to satisfy all parties. Patients will have an opportunity to deliberate at home and provide witnessed telephone consent after the initial intake visit.

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.4.2 Referral center TACE-treated study subjects

The treating physician(s) will inform the patient about the study, and the Principal Investigator or associate investigator will explain the study in detail, including the study plan, risks, and potential benefits either by telephone or in person before the TACE procedure is performed or before or at the time of the planned FMISO injection and scan. If consent is to be obtained prior to the TACE procedure, the informed consent document can be sent to the subject. In any case the consent form will be witnessed as described above. A fully executed copy will be provided to the study subject, and the process will be documented in CRIS as a progress note. A copy of the consent document and progress note will be included in the subject's research record.

9.4.3 Informed consent of non-English speaking subjects:

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 PHARMACEUTICAL INFORMATION

10.1 SOURCE

Doses of drug will be obtained from Cardinal Health's manufacturing site located at 7051 Muirkirk Meadows Drive, Suite K Beltsville, MD 20705. Acquired doses will be maintained in

the Clinical Center PET department and dosing will be managed by the PET department research pharmacist, Luke Park (301-496-1090, LPark@cc.nih.gov).

10.2 TOXICITY

10.2.1 Animal Toxicity Studies

Studies done in male Sprague-Dawley rats to evaluate [¹⁸F] FMISO neurotoxicity showed that at high doses of 300 to 400mg/kg the rats after motor testing showed signs of neurotoxicity including ataxia, tremors, vocalizations, circling, head jerking and hyperactivity, all of which resolved.²⁰ No evidence of peripheral nerve toxicity was reported.

10.2.2 Human Toxicity Studies

There are no studies published which report toxicity of [¹⁸F] FMISO in humans. The Investigator's Brochure for [¹⁸F] FMISO provides a list (Table 8) of human imaging studies from 1994 to the present which includes a total of approximately 600 patients who received up to 4 doses of FMISO (3-30mCi) and PET scanning and for which no adverse events are identified.²⁰

Studies of MISO toxicity have shown that side effects may be observed at doses 5 to 6 times greater than needed for PET scanning. Oral MISO in oral doses ranging from 4-10g has been used to enhance cytotoxicity of radiotherapy in patients with advanced cancer. All patients experienced some degree of nausea, vomiting and anorexia for 24 hours. The severity of the nausea and vomiting was correlative to a high MISO dose. Studies where MISO was given in multiple doses reported peripheral neuropathy in doses of 3-5g/m.^{2, 21}

Two fatalities are reported in patients with advanced cancer who died with convulsions. One patient had consumed 51g in 6 doses over 17 days and the other consumed 16g in 2 doses over 3 days.²²

The planned dose of [¹⁸F] FMISO will be approximately 10mCi which includes approximately 15 micrograms of misonidazole which is unlikely to be associated with MISO-related side effects.

10.3 FORMULATION AND PREPARATION

[¹⁸F] fluoromisonidazole, 1 H -1-(3-[¹⁸F]-fluoro-2-hydroxy-propyl)-2-nitroimidazole [¹⁸F] FMISO, cross referencing Cancer Imaging Program IND 76,042

[¹⁸F] FMISO is a radiolabeled imaging agent that has been used for investigating tumor hypoxia with positron emission tomography (PET). [¹⁸F] FMISO is an investigational agent and the Cancer Imaging Program Cardinal Health partnering with the American College of Radiology Imaging Network supplies [¹⁸F] FMISO. The PET scanning department will procure and maintain the [¹⁸F] FMISO. Cardinal Health is the only entity to have a drug master file with the Food and Drug Administration (FDA) to produce this imaging agent.

[¹⁸F] FMISO is the only active ingredient and it is dissolved in a solution of ≤ 10ml of 95% isotonic saline, 5% ethanol (v:v). The drug solution is stored in a gray butyl septum sealed, sterile, pyrogen-free glass vial with a 12 hour expiration. The vials are to be stored at room temperature.

10.4 DOSING

≤10mCi

10.5 STABILITY AND STORAGE

[¹⁸F] FMISO has a 12 hour shelf life and is to be stored at room temperature. The Clinical Center PET department pharmacy will procure, store, dose and prepare for injection.

10.6 ADMINISTRATION PROCEDURES

[¹⁸F] FMISO is given intravenously. The prepared dose is then given by the staff of the CC, PET department per their standard guidelines.

10.7 INCOMPATIBILITIES

[¹⁸F] FMISO is a small water-soluble molecule with a molecular weight of 189.14 Daltons. It has an octanol-water partial coefficient of 0.41, so that it would be expected to reflect plasma flow as an inert freely-difusible tracer immediately after injection, but later images should reflect its tissue partition coefficient in normotoxic tissues.

10.8 MECHANISM OF ACTION

[¹⁸F] FMISO has a nearly ideal partition coefficient and when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentrations, rather than by downstream biochemical reactions. FMISO is not trapped in necrotic tissue because mitochondrial electron transport is absent. The normal route of elimination is renal.

**The rotarod test is widely used to evaluate the motor coordination of rodents, and is especially sensitive in detecting cerebellar dysfunction*

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12 APPENDICES

12.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

12.2 APPENDIX B: ELIGIBILITY CHECKLIST

Eligibility Criteria		Confirmation Checklist
Patient Name		First _____ Last _____
Primary diagnosis		<input type="checkbox"/> Cytology For patients with HCC: <input type="checkbox"/> Tumor enhancement + AFP >200 <input type="checkbox"/> BCLC Stage A4 <input type="checkbox"/> BCLC Stage B
CT + MRI		<input type="checkbox"/>
Age		<input type="checkbox"/> >18 years _____
History & Physical Exam		<input type="checkbox"/> including intercurrent illnesses
Height & Weight		<input type="checkbox"/>
ECOG Status		<input type="checkbox"/> ≤ 2 _____
Serum creatinine		<input type="checkbox"/> <2.0 mg/dl _____ (unless creatinine clearance greater than 60ml/min)
B-hCG Urine or Serum		<input type="checkbox"/> Negative
Eligible for TACE		<input type="checkbox"/>
No prior TACE		<input type="checkbox"/>
No biologic, chemo-, or radiotherapy for at least two weeks prior to enrollment		<input type="checkbox"/>
Able to understand and sign an informed consent document		<input type="checkbox"/>
Able to lie still and cooperate for PET scan		<input type="checkbox"/>
No pregnancy		<input type="checkbox"/>
Prior allergic reaction to misonidazole or iodinated contrast		<input type="checkbox"/>
No concurrent investigational agents		<input type="checkbox"/>
Known brain metastases		<input type="checkbox"/>

Abbreviated Title: [¹⁸F]-FMISO Imaging Post TACE

Version Date: 08/31/2016

Uncontrolled intercurrent illness	<input type="checkbox"/>	(active infection, CHF, angina, cardiac arrhythmia, psychiatric/social)
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A Pilot Study of an Integrated Imaging Strategy to Phenotype Progression of Liver Tumors during and after Chemoembolization

The completed eligibility checklist should be received by the Principal Investigator not less than one week prior to TACE AND at least 48 hours prior to FMISO imaging.

Office: (301) 402-5368 Fax: (301) 496-9933 Email: levyeb@cc.nih.gov

Address: National Institutes of Health
Department of Radiology and Imaging Sciences
10 Center Drive, Rm 1C367
Bethesda, Maryland 20814-9692