# PROTOCOL 13-464

**Title: FDG** PET/CT-Guided Liver Tumor Ablation: Intraprocedural Assessment of Results Using Perfusion PET


**Principal Investigator:**
Paul B. Shyn, M.D. (Abdominal Imaging and Interventional Radiologist)
Brigham and Women's Hospital



NCT02018107

Date Posted: 3/1/2019

Date Posted: 3/1/2019

# ON HOLD

## STATUS PAGE

## PROTOCOL 13-464

## ALL RESEARCH ACTIVITIES MUST STOP DUE TO EXPIRED STUDY APPROVAL

Research activities include, but are not limited to, recruitment and enrollment of subjects, collection of specimens, research on previously collected specimens, review of medical records or other health information, data analysis, and performance of research tests/procedures, treatment, or follow-up on previously enrolled subjects.

- If you wish to reinstate IRB approval of your project, please submit a continuing review form immediately via OHRS submit. If the continuing review form has been submitted and the continuing review is in process, you must await IRB approval before resuming any research activities.

- If any research activities are necessary for subject safety and welfare, a Request to Continue Research Interventions may be submitted for IRB consideration. This form can be found on the OHRS website and be submitted via OHRS submit.

- If a request to continue research interventions has already been approved, please refer to that email notice for information about research that may continue during this lapse in IRB approval. The study team is responsible for notifying the relevant departments of this approval.

- If you do not wish to continue this project, you must submit a final report using the study completion form.

Any questions regarding this hold should be directed to the study's Principal Investigator.

Status Page

PROTOCOL 13-464

**Closed to New Accrual**

Closure Effective Date: 03/09/2018
No new subjects may be enrolled in the study as described above.
Any questions regarding this closure should be directed to the study's Principal Investigator

DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Office for Human Research Studies

# Protocol Front Sheet

**DFCI Protocol No.: 13-464**

## 1. PROTOCOL INFORMATION

**Title:** PET/CT-Guided Liver Tumor Ablation: Intraprocedural Assessment of Results Using Perfusion PET
**Phase:** [pull down] **Sponsor Study Number:**

## 2. DF/HCC STUDY CONTACT INFORMATION

**Primary Study Contact:** Paul B. Shyn, M.D. **Email:** pshyn@partners.org **Phone:** 617-732-6304

**INVESTIGATORS:** (List only those under DFCI IRB, *i.e.*, from institutions listed in Section 6 below)

| | | | | | |
|---|---|---|---|---|---|
| **Overall PI:** | Paul B. Shyn, M.D. | **Phone:** | 617-732-6304 | **Institution(s):** | BWH |
| **Site Responsible PI:** | Paul B. Shyn, M.D. | **Phone:** | 617-732-6304 | **Institution(s):** | BWH |

## 3. DRUG / DEVICE INFORMATION N/A:

☒ **Drug(s), Biologic(s)**: N13-ammonia, Arm #1; (Arm #2: F18-fluorodeoxyglucose, FDA approved for indication - no IND or IND exemption required)
**Provided by:** BICOR BWH
**IND Exempt:** ☒ -or-
**IND#:** **Holder Type:** [pull down]
**IND Holder Name:**

☐ **Device(s) Name**:
**Provided by:**
**IDE Exempt:** ☐ -or-
**IDE #:** **Holder Type:** [pull down]
**IDE Holder Name:**

## 4. PROTOCOL COORDINATION, FUNDING, MODE

**Regulatory Sponsor:**
DF/HCC Investigator Cancer Imaging

**CTEP Study**: No

**Funding/Support** (check all that apply):
☒ Industry: Siemens
☐ Federal Organization:
Grant #:
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

**Primary Disease Group:** Cancer Imaging

**Protocol Involves** (check all that apply as listed in the protocol document, even if not part of the research but is mandated by the protocol document):

☐ Chemotherapy
☐ Immunotherapy
☐ Surgery
☐ Bone Marrow/Stem Cell Transplant
☐ Cell Based Therapy
☐ Gene Transfer (use of recombinant DNA)
☐ Radiation Therapy
☐ Hormone Therapy
☐ Vaccine
☐ Data Repository
☐ Exercise/Physical Therapy
☐ Genetic Studies
☐ Human Material Banking
☐ Human Material Collection
☒ Medical Record Review
☐ Questionnaires/Surveys/Interviews
☒ Radiological Exams
☐ Required Biopsy Study
☐ Human Embryonic Stem Cell
☐ Quality of Life
☒ Other: Radiotracer administration for PET scans during routine Interventional Radiology Tumor Ablation procedure

## 5. SUBJECT POPULATION (also applies to medical record review and specimen collection studies)

**Total Study-Wide Enrollment Goal:** 75 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No
**Total DF/HCC Estimated Enrollment Goal:** 75 **Adult Age Range:** 18+ **Pediatric Age Range:** N/A
**Will all subjects be recruited from pediatric clinics?** ☐ Yes ☒ No
**If enrolling both adults and pediatric subjects, anticipated percent of pediatric subjects:** N/A
**Retrospective Medical Record Reviews only (Please provide date range):** from to

## 6. DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Beth Israel Deaconess Medical Center (BIDMC)
☐ Boston Children's Hospital (BCH)
☒ Brigham and Women's Hospital (BWH)
☒ Dana-Farber Cancer Institute (DFCI)
☐ Massachusetts General Hospital (MGH)
☐ Beth Israel Deaconess Medical Center – Needham (BIDMC-Needham)
☐ Dana-Farber/New Hampshire Oncology-Hematology (DFCI @ NHOH)
☐ Dana-Farber at Steward St. Elizabeth's Medical Center (DFCI @ SEMC)
☐ Dana-Farber at Milford Regional Cancer Center (DFCI @ MRCC)
☐ Mass General/North Shore Cancer Center (MGH @ NSCC)
☐ Mass General at Emerson Hospital – Bethke (MGH @ EH)
☐ DF/BWCC in Clinical Affiliation with South Shore Hospital (DFCI @ SSH)

## 7. NON-DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Cape Cod Healthcare (CCH)
☐ Lowell General Hospital (LGH)
☐ New Hampshire Oncology-Hematology-P.A. (NHOH)
☐ Newton-Wellesley Hospital (NWH)
☐ Dana-Farber/Faulkner Hospital (FH)
☐ New England Cancer Specialists (NECS)
☐ Broad Institute

## 8. DF/HCC INITIATED STUDIES ONLY - INSTITUTIONAL PARTICIPANTS UNDER OTHER IRB (N/A: )

**DF/HCC Multi-Center Protocols:** (list institution/location)

**DF/PCC Network Affiliates:** (list institution/location)

## Protocol Number: 13-464

**Approval Date:** 11/26/13 (IRB meeting date when protocol/consent approved or conditionally approved)

**Activation Date:** 01/22/14 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

| Date Posted | Revised Sections | IRB Approval Date | OHRS Version Date |
|---|---|---|---|
| 02/04/14 | Consent Form replaced due to Amendment #1 | 02/03/14 | 02/04/14 |
| 02/25/14 | Correction: Consent Form replaced due to incorrect version previously provided (missing signature box) | 02/03/14 | 02/04/14 |
| 06/17/14 | Protocol replaced due to Amendment #2 | 06/11/14 | N/A |
| 11/26/14 | ON HOLD: All research must stop due to lapsed Continuing Review. Study expired 11/26/14 | N/A | N/A |
| 04/27/15 | Protocol, Consent Form and Front Sheet replaced due to Amendment #3 | 03/31/15 | 04/27/15 |
| 04/27/15 | On HOLD removed; Study renewal/ Consent Form footer replaced due to Continuing Review #1 | 04/02/15 | N/A |
| 04/28/15 | Temporary closed to new accrual: administrative hold by DMSC as of 4/28/2015. Questions regarding the temporary hold can be directed to the DSMC (via Nareg Grigorian in QACT) | n/a | n/a |
| 05/29/15 | Re-open to accrual – due to Amendment #4 | 05/18/15 | N/A |
| 06/18/15 | Temporary closed to new accrual: administrative hold per the IRB on 06/04/15 (OE #4). | n/a | n/a |
| **Date Posted** | **Revised Sections** | **IRB Approval Date** | **OnCore Version Date** |
| 09/29/15 | Study Re-Opened due to Amendment #5 | 08/28/15 | N/A |
| 11/17/15 | Consent Form replaced due to Amendment #6 | 11/09/15 | 11/13/15 |
| 03/24/16 | Consent Form replaced due to Amendment #7 | 02/29/16 | 03/07/16 |
| 03/31/16 | Study renewal / Consent Form footer replaced due to Continuing Review #2 | 03/24/16 | 03/31/16 |
| **Date Posted** | **Revised Sections** | **Approved Date** | **Version Date (OnCore)** |
| 12/12/16 | Arm 2 of study opened; Arm 1 now closed to accrual: Protocol, Eligibility Checklist and Front Sheet replaced; Arm 2 Consent Form added due to Amendment #8 | 10/04/16 | 12/12/16 |
| **Date Posted** | **Revised Sections** | **Approved Date** | **Version Date (OnCore)** |
| 03/22/2017 | Study renewal/ Consent Form footers replaced due to Continuing Review #3 | 03/16/2017 | 03/22/2017 |
| 03/15/2018 | Study renewal/Consent Form footers replaced per Continuing Review #4 | 03/01/2018 | 03/15/2018 |
| 03/26/2018 | Permanent Closure to New Accrual: due to Funding (effective date: 03/09/2018; Amendment #9) | n/a | n/a |
| 03/01/2019 | ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired 13-464 | N/A | N/A |
| | | | |
| | | | |
| | | | |

**ProtocolVersion Date:** Version 4; 9/6/2016

**NCI Protocol**#*: N/A*

**Local Protocol** #:

**Title: FDG** PET/CT-Guided Liver Tumor Ablation: Intraprocedural Assessment of Results Using Perfusion PET

## Principal Investigator:

Paul B. Shyn, M.D. (Abdominal Imaging and Interventional Radiologist)
Brigham and Women's Hospital

**Coordinating Center:** *N/A*

## Co-Investigators:

Kemal Tuncali, M.D. (Abdominal Imaging and Interventional Radiologist)
Victor H Gerbaudo, PhD, MSHCA: (Clinical Nuclear Oncology Scientist, Associate Scientific Director, AMIGO)
Stuart G. Silverman, M.D. (Abdominal Imaging and Interventional Radiologist)
Vincent Levesque, M.S. (Medical Physicist)
Tina Kapur, PhD (Executive Director, AMIGO)

All investigators: Brigham and Women's Hospital

**Statistician:** Paul J. Catalano, ScD (DFCI)

**Study Coordinator:** Danielle Chamberlain

**Responsible Research Nurse: N/A**

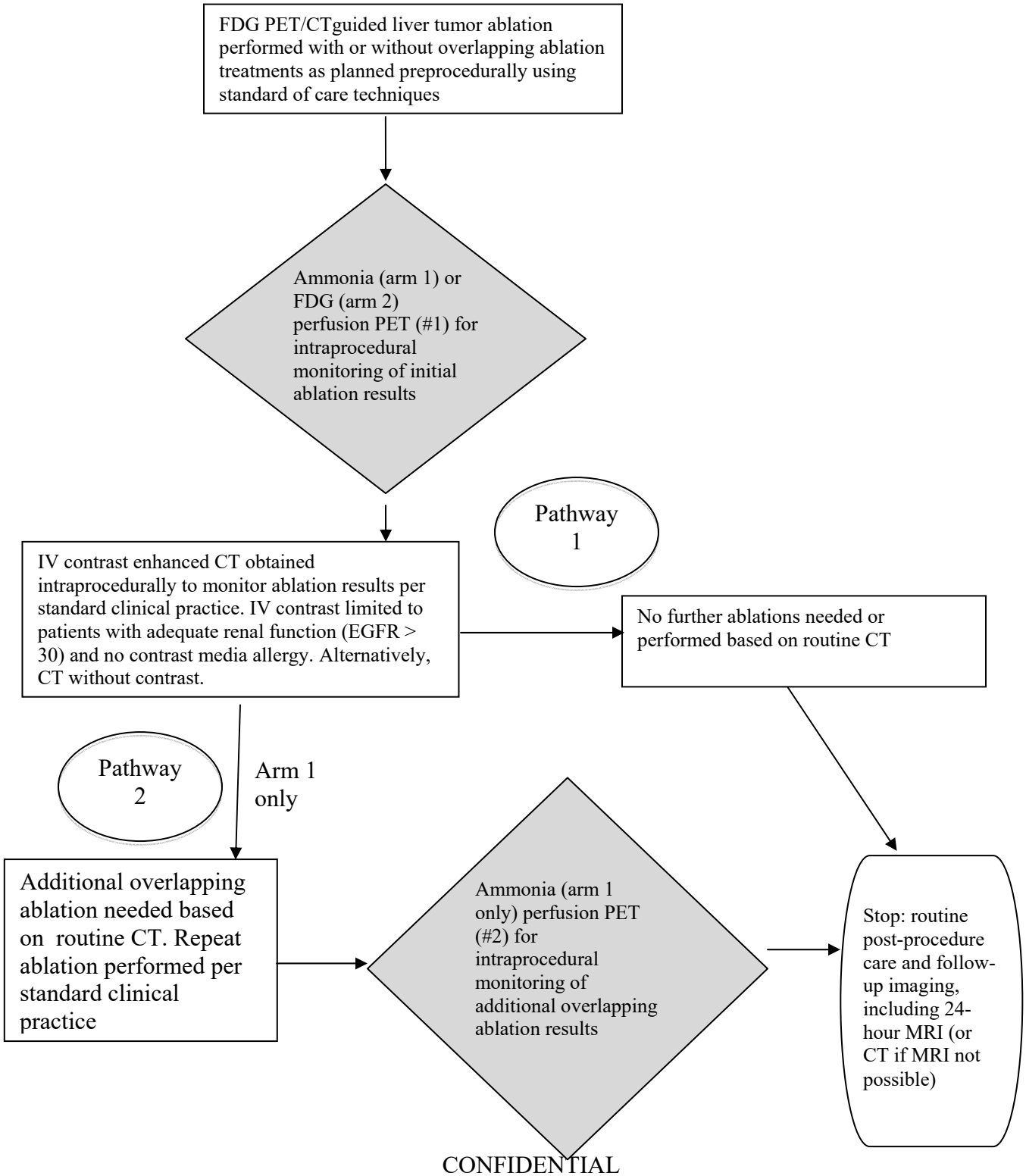
**Responsible Data Manager:** Paul B. Shyn, M.D.

**Agent(s):** *Arm 1: N13-Ammonia (IND # 119482, exempt, 8/27/13) , BWH cyclotron (BICOR)*
*Arm 2: F18-fluorodeoxyglucose (FDG), BWH cyclotron (BICOR)*

## SCHEMA

### Perfusion PET Assessment of Liver Tumor Ablations

(Gray diamonds contain research activities; Arm 1 is as shown; Arm 2 substitutes FDG for Ammonia and only uses pathway 1)



**Perfusion PET Assessment of Liver Tumor Ablations**
**Protocol Version Date 9/6/2016**

## TABLE OF CONTENTS

# 1. OBJECTIVES

## *1.1 Study Design - Abstract*

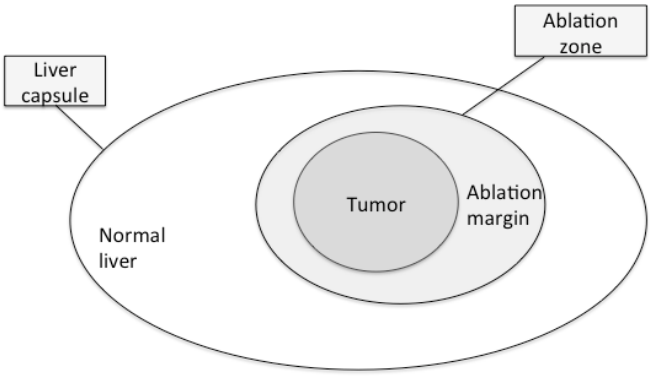
**Arm 2:** This study has two arms. Arm 1 is the protocol as written below using Ammonia perfusion PET to assess ablation results of standard FDG PET/CT-guided liver tumor ablations. Arm 2 is the identical protocol, but substitutes the radiopharmaceutical FDG for Ammonia to assess ablation results of standard FDG PET/CT-guided liver tumor ablations. Arm 2 will not include the option of performing a second intraprocedural perfusion PET scan. FDG is FDA-approved for oncologic imaging as in this study. No IND or IND exemption is required. The protocol is identical in all other respects. All protocol comments pertaining to Arm 2 will be placed in new paragraphs beginning with "Arm 2:" in bold letters. Throughout the protocol, Arm 2 simply substitutes FDG for N-13 ammonia. In Arm 2, All AP-PET scans (which are the only research intervention of the study) are performed using FDG instead of N-13 ammonia.

Arm 1 and Arm 2 are independent and no randomization or enrollment criteria for one arm or the other are defined.

The purpose of this study is to evaluate a novel imaging technique for intra-procedural assessment, also known as monitoring, of image-guided percutaneous liver tumor microwave or cryoablation (thermal ablation) procedures. Monitoring assures that the tumor is being ablated completely (and nearby critical structures left unharmed) by allowing the interventionalist to view ablative changes and make intra-procedural adjustments to the location of the ablation applicators, the number of overlapping ablation treatments, or the duration of ablation applications. As a result, improved monitoring has the potential to improve patient outcomes. We will assess a novel method for monitoring $^{18}$F-fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT)-guided liver tumor ablations: intra-procedural $^{13}$N-ammonia perfusion PET (AP-PET). N-13 ammonia is FDA-approved for cardiac perfusion imaging, but will be used in this study for the off-label indication of imaging perfusion of the liver. The standard dose and IV route of administration will be employed. We will compare this method of assessing immediate technical success of ablation procedures to standard assessments using intra-procedural contrast-enhanced CT (CECT). We will also compare final intra-procedural ammonia perfusion PET to gold standard 24-hour magnetic resonance imaging (MRI) or CT for predicting longer term technique effectiveness as demonstrated on routine MRI (or if MRI is not possible, on CT) obtained at a minimum of three to 12 months after the procedure.

This study will evaluate if AP-PET can be used intra-procedurally during FDG PET/CT-guided ablation procedures to identify regions of the ablation zone that do not adequately treat the tumor. The ablation zone is the volume of tissue destroyed by the ablation treatment. Adequate ablation treatment of tumor is generally defined by a minimum ablation margin of 5-10 mm. The ablation margin refers to the rim of normal tissue beyond the tumor included within the ablation zone in order to assure that even microscopic tumor

extensions beyond the visible tumor are fully destroyed.




The ablation zone includes the ablated tumor and a cuff of ablated surrounding normal liver (ablation margin).

The ability to directly visualize and assess the ablation margin requires visibility of both the tumor and the boundaries of the ablation zone. Unfortunately, tumor visibility using CT or US is often lost or diminished immediately following thermal ablation. On the other hand, the entire ablation zone is generally visible as a region of decreased or absent enhancement on CECT scans obtained following the ablation. The ablation zone is usually poorly defined on US imaging obtained after ablation. Because of these limitations of CT and US, the ablation margin is usually estimated using side-by-side comparisons of the size and shape of the ablation zone as depicted on intra-procedural post-ablation CECT with the pre-procedural MRI or CT appearance and location of the tumor. Alternatively, retrospective software fusion of the post-ablation CECT with pre-procedural MRI or CT can be used. Unfortunately, these standard approaches often do not allow for confident point-by-point assessment of the entire circumference of the ablation margin. These limitations of our standard imaging techniques for the intra-procedural assessment or monitoring of thermal ablation procedures in the liver underscore the need for identifying more robust techniques. This study explores a novel imaging technique with the potential to improve our intra-procedural assessment of ablation results and, in turn, patient outcomes.

Adult patients referred to our Tumor Ablation Clinic for image-guided percutaneous ablation of liver tumors will be considered for enrollment. Patients who meet our standard clinical criteria for image-guided liver tumor ablations will be offered the opportunity to enroll in this prospective study. Standard clinical criteria include a known primary or metastatic malignancy of the liver for which local therapies are being considered. These may include tumors that are unresectable for any reason or tumors in patients who have co-morbidities precluding surgery. Liver tumor ablations are also performed to reduce the

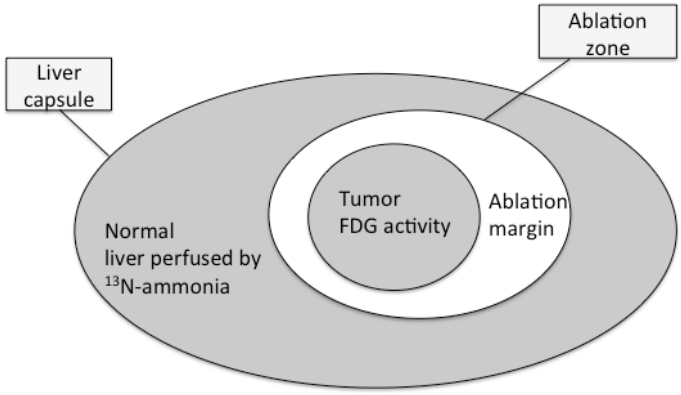
tumor burden in patients with advanced disease or to palliate symptoms such as pain. Liver tumor ablation may serve as a bridge to liver transplantation in patients with hepatocellular carcinoma. Ablation may be an option for patients who do not wish to undergo open surgical procedures. It is expected that approximately 2/3 of the tumors will prove to be FDG-avid and 1/3 non-FDG-avid. It is anticipated that we will ablate a single liver tumor per procedure in approximately 70% of patients, two liver tumors in 15% of patients, three liver tumors in 10% of patients, and more than three tumors in 5% of patients, based on our recent practice experience. Patients will be excluded for uncorrectable coagulopathy or severe inter-current illness. Tumor ablation procedures will be performed as they are routinely performed by our team in clinical practice using FDG PET/CT and possible supplemental US guidance. Targeting can be accomplished based on tumor visibility on any one or more of these imaging modalities (US, PET, or CT). FDG-avidity is not essential for the targeting of tumors. Patients enrolled in this study will receive ablation treatments that will not be compromised by the research portions of the procedures.

The ablation will be planned and the ablation applicators inserted percutaneously using routine FDG PET/CT and possible supplemental US guidance. The ablation will then be performed using current protocols with either microwave ablation or cryoablation devices. Microwave ablation and cryoablation devices offer complimentary advantages that enable us to safely and effectively treat many liver tumors. Cryoablation may be better tolerated and less painful when ablating liver tumors close to the liver capsule or diaphragm. The iceball created during cryoablation is usually well visualized during the ablation, which can offer safety advantages when ablating near critical structures. Microwave ablation has fewer tendencies to induce thrombocytopenia or myoglobinemia than cryoablation, which can be an advantage in patients with baseline thrombocytopenia or renal insufficiency. Microwave ablation is better able to overcome vascular heat-sink phenomena that can limit the ablation of tumor cells abutting large blood vessels. Our standard practice is to choose the most appropriate ablation technology based on the individual patient's specific circumstances. Radiofrequency ablation is not included in this protocol, as microwave ablation has almost completely replaced the use of radiofrequency ablation in our practice.

When the initial ablation is completed, intra-procedural AP-PET-1(research scan #1) will be performed and the findings recorded. Specifically, the ablation margin separating the FDG-avid tumor from the normal ammonia-perfused liver will be assessed for visibility and thickness along the entire circumference. Patients with adequate renal function (EGFR >60) will then undergo intra-procedural contrast-enhanced CT, as is now performed in routine clinical practice to monitor initial results. Non-contrast CT will be used in cases of inadequate renal function or contrast allergy. If no additional overlapping ablation applications are deemed necessary or appropriate based on routine CT (Pathway 1), the procedure will be concluded at this point. AP-PET information may be used to aid the margin assessment if CT is inconclusive. Note that routine CT will always be used to determine the safety of additional overlapping ablation, per routine clinical practice. This is because proximity of ablation devices to critical structures can only be imaged with CT and not with PET. The patient will then undergo routine 24-hour post-procedure liver MRI

or CT. If the CT scan suggests an inadequate ablation margin of less than 5-10 mm at any portion of the tumor surface, additional ablations will be applied to the under-treated areas (Pathway 2), if deemed safe and appropriate based on standard clinical practice. Then, AP-PET-2 will be repeated (research scan #2). Not more than two AP-PET scans will be performed during the entire procedure. The AP-PET scan(s), illustrated schematically below, constitute the only research component of the protocol.

**Arm 2:** Arm 2 will not include the option of AP-PET 2 (research scan #2) due to the longer half-life of FDG.




The devascularized ablation zone contains trapped high tumor FDG activity and low ablation margin FDG activity, whereas normal liver is perfused with high activity $^{13}$N-ammonia. The relatively photopenic ring around the tumor confirms the presence of an adequate ablation margin.

For patients with FDG-avid tumors, visibility rates of the entire ablation margin using AP-PET-1will be compared to the visibility rates of the entire ablation margin using the intra-procedural CECT scan. Visibility rates using AP-PET-1 will also be compared to the visibility rates using the intra-procedural CECT scan fused to FDG PET (FDG PET/CECT). The concordance rates of the final intra-procedural AP-PET (research scan #1 or #2) with gold standard 24-hour post-procedure MRI or CT will be determined.

For those patients with non-FDG-avid tumors, retrospective software fusion of AP-PET-1 with pre-procedural MRI or CT will be used to assess visibility rates of the ablation margin and will be compared with visibility rates of the ablation margin using retrospective fusion of the intra-procedural CECT and pre-procedural MRI or CT. Similarly, in patients with non-FDG-avid tumors the concordance rate of final intra-procedural AP-PET (research scan #1 or #2) fused to pre-procedural MRI or CT, with gold standard 24-hour post-procedure MRI or CT will be determined. The analysis of AP-PET utility in patients with non-FDG-avid tumors is a secondary objective of this study, but is nevertheless of interest, as AP-PET may prove valuable in these patients who cannot receive IV contrast or

potentially as a superior assessment for patients who can receive IV contrast. Prediction of longer term technique effectiveness rates (local recurrence rates) based on blinded retrospective reads will be compared for the final intra-procedural AP-PET scan and 24-hour MRI or CT, using local tumor progression as assessed on routine follow-up MRI or CT scans performed at least 3 to 12 months after the ablation procedure as the gold standard. Liver contrast-enhanced MRI is preferred for routine 24-hour follow-up imaging, however, contrast-enhanced CT may be substituted if the patient cannot undergo MRI due to contraindications such as incompatible implanted devices.

The results of this study are expected to show that AP-PET can be used to reveal areas of ablation under-treatment or areas of optimal treatment that are not consistently identified with contrast-enhanced CT alone. Better intra-procedural assessment of tumor ablation results has the potential to improve image-guided tumor ablation technical success and effectiveness rates.

## *1.2 Primary Objectives*

**Arm 2:** The primary and secondary objectives are identical for Arms 1 & 2 of the study (except that in Arm 2, no research scan #2 will be performed).

- 1. For FDG-avid tumors, compare the rates of complete, circumferential ablation margin visibility during FDG PET/CT-guided liver ablations using two imaging techniques: intra-procedural AP-PET-1(research scan #1) and intra-procedural CECT. Discordance rates for complete ablation margin visibility between the two imaging techniques will be calculated.
- 2. For FDG-avid tumors, compare the rates of complete, circumferential ablation margin visibility during FDG PET/CT-guided liver ablations using two imaging techniques: intra-procedural AP-PET-1 and intra-procedural CECT fused with FDG PET (FDG PET/CECT). Discordance rates for complete ablation margin visibility between the two imaging techniques will be calculated.
- 3. In assessing adequacy of the ablation margin for FDG-avid tumors, the concordance rates of final intra-procedural AP-PET(research scan #1 or #2) with gold standard 24-hour post-procedure MRI or CT will be determined. (Includes patients with renal insufficiency who cannot receive intra-procedural iodinated IV contrast.)
- 4. For non-FDG-avid tumors, compare the rates of complete, circumferential ablation margin visibility during FDG PET/CT-guided liver ablations using two imaging techniques: 1) intra-procedural AP-PET-1 fused to pre-procedural MRI or CT and 2) intra-procedural CECT fused to pre-procedural MRI or CT. Discordance rates for complete ablation margin visibility between the two imaging techniques will be calculated.
- 5. In assessing adequacy of the ablation margin for non-FDG-avid tumors, the concordance rate of final intra-procedural AP-PET (research scan #1 or #2) fused to pre-procedural MRI or CT with gold standard 24-hour post-procedure MRI or CT will be determined. (Includes patients with renal insufficiency who cannot receive intra-

procedural iodinated IV contrast.)

### *1.3 Secondary Objectives*

- 1. For FDG-avid tumors, rates of local tumor progression based on a minimum of 3-12 month imaging follow-up will be compared for ablation margin adequacy assessed by blinded retrospective reads of final intraprocedural AP-PET (research scan #1 or #2) and 24-hour post-procedure MRI or CT. (Includes patients with renal insufficiency who cannot receive intra-procedural iodinated IV contrast.)

## 2. BACKGROUND

### *2.1 Study Agent(s)*

- No therapeutic drugs are involved in this study. The nuclear imaging radiopharmaceutical N-13 ammonia is an FDA-approved radiotracer that will be used for an off-label diagnostic imaging indication. The tracer will be administered by the standard IV route and using the standard 10 mCi dose. Instead of imaging perfusion of the heart (FDA-approved indication), the tracer will be used in this study to image perfusion of the liver (off-label indication).
- **Arm (2):** FDG will be used not only for the routine targeting phase of the procedure but also as the perfusion agent instead of N-13 ammonia. FDG is FDA-approved for oncologic imaging as in this study. The total FDG dose including the targeting dose (8-10 mCi) and the research perfusion dose (2-4 mCi) will together fall within the standard dose for routine diagnostic or interventional FDG PET/CT scans (< 15 mCi). This "split-dose" technique allows the research PET perfusion scan to be performed without adding to the routine FDG dose received by patients not undergoing the research PET perfusion scan.

### *2.2 Study Disease*

- Liver tumors, including primary or metastatic malignancies.

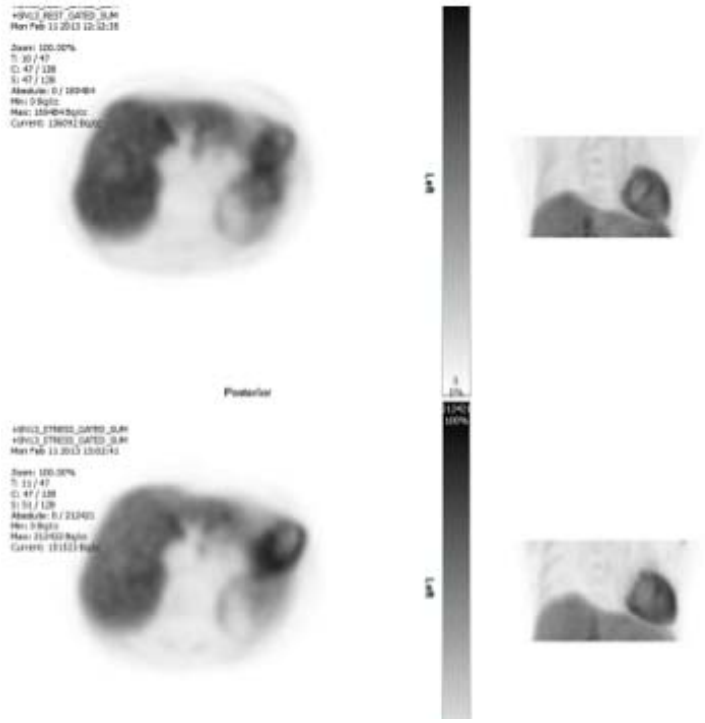
### *2.3 Rationale and Correlative Studies Background*

- **Percutaneous image-guided thermal ablation procedures are increasingly used to treat liver tumors (1). These procedures are most commonly performed using US or CT guidance. Not all tumors are well-visualized using CT and/or US guidance, which has prompted the increasing use of PET/CT for guidance of percutaneous interventional procedures. PET/CT-**

**guided tumor ablations are becoming more common due the advantage of targeting tumors not visible using other imaging techniques and targeting tumors based on metabolic characteristics (2-4). This allows for targeting of specific regions of tumors based on viability, glucose metabolic activity, and other biologic characteristics (e.g. hypoxia, DNA synthetic activity).**

- **Regardless of the imaging guidance modality used, monitoring the ablation is important to assure that the tumor and a sufficient margin of surrounding normal liver are ablated. An adequate ablation margin minimizes the risk of local tumor recurrence. It is an accepted, important goal of all liver tumor ablations that the ablation zone extends least 5-10 mm beyond the tumor at all points of the tumor surface (1). This assures that microscopic disease just outside the visible tumor is treated. The ablation margin surrounding the tumor is analogous to a surgical margin that provides confidence the entire tumor has been removed including microscopic extensions into adjacent normal tissues.**
- Current techniques for intra-procedural assessment of tumor ablation margins have limitations. For example, when performing CT-guided ablations, it is standard practice to obtain an intra-procedural contrast-enhanced CT (CECT) to monitor whether the tumor is being treated fully and an adequate ablation margin is being obtained following thermal ablation. CECT is usually performed only once near the end of the procedure since one dose of IV contrast material is usually the limit for a 24-hour period. If a reduced dose of IV contrast is used, this may allow for two intra-procedural CECT scans, however, this may limit the effectiveness of the method. For example, the degree of liver enhancement is reduced making it difficult to distinguish tumor from liver. Patients with a contrast material allergy or severe renal insufficiency (EGFR < 30) are often not considered candidates for CECT. An additional limitation of CECT in the assessment of liver tumor ablations is that once ablated, the tumor is usually difficult to distinguish from the surrounding ablated normal liver tissue. Consequently, direct visualization of the ablation margin is often not possible using CECT. US is even less effective in assessing ablation results in that tumor visibility is rapidly obscured by the developing ablation zone and the ablation zone margins are usually indistinct. For liver tumors, MRI performs better in depicting not only the exact borders of the ablation zone, but also in showing the residual tumor. As a result, 24-hour follow-up MRI with contrast can be an effective method for confirming the thickness or size of the ablation margin. Follow-up MRI, however, does not allow for intra-procedural assessment of ablation results during US, CT, or PET/CT-guided ablations that might prompt immediate further treatment while the patient is still on the scanner table.
- An effective imaging technique for monitoring ablations that can be safely performed repeatedly during ablation procedures is needed.
- We have previously shown that, during PET/CT-guided tumor ablation procedures, tumor FDG activity is not dissipated by thermal ablation, whether through heating or freezing (2). Tumor FDG activity remains unperturbed following ablation allowing for continued excellent PET visibility of the tumor for hours after the procedure. This unique feature of PET imaging can potentially be used to help monitor the thickness of the ablation zone

margin. One option is to incorporate CECT into the PET/CT protocol for assessing ablation results. In this scenario, the ablated tumor is depicted by FDG avidity on PET, whereas the ablation zone is defined using CECT, all obtained as a combined PET/CT protocol. The drawback of this approach is the potential for PET/CT image misregistration, for example, misalignment of anatomical structures as depicted on the PET acquisition when compared to the CT acquisition of the PET/CT scan, resulting from respiratory motion. PET offers an alternative to CECT in defining the ablation zone. Perfusion PET using a very short half-life radiopharmaceutical, N-13 ammonia, can also demonstrate the ablation zone due to its utility as a perfusion imaging agent. N-13 ammonia is primarily used for myocardial perfusion imaging, but is also known to demonstrate liver perfusion well (5-8). Below are images from a cardiac ammonia perfusion PET study (note excellent liver perfusion activity).



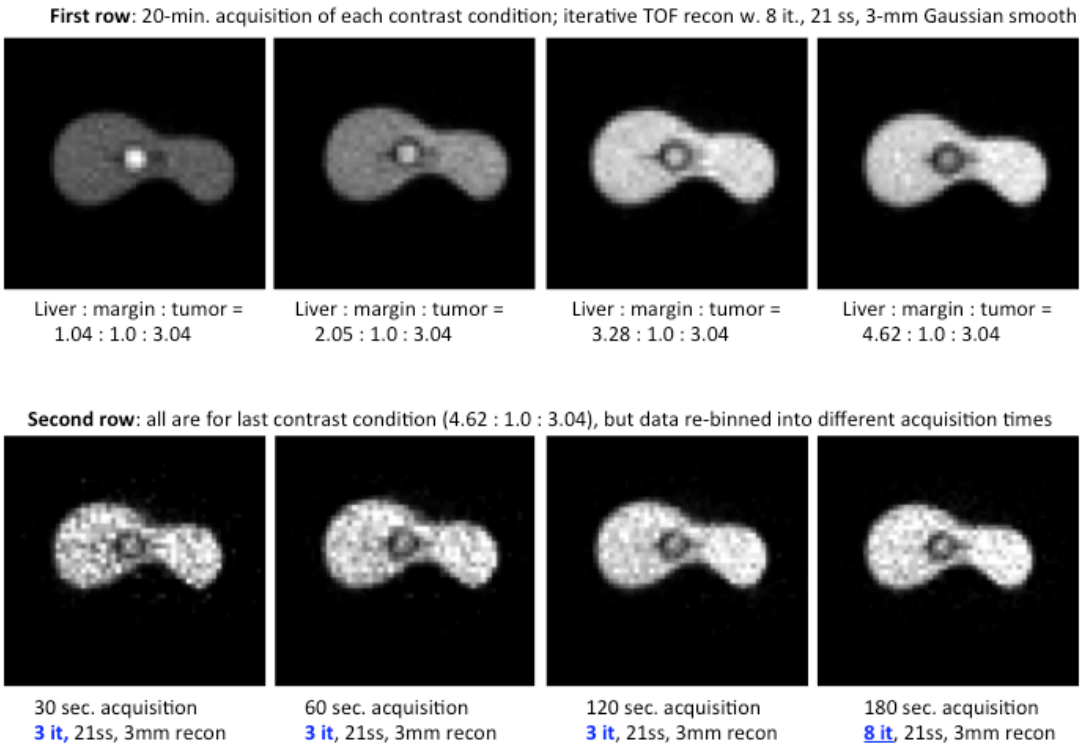
- Since all ablations, including microwave ablation or cryoablation, reduce or eliminate blood perfusion throughout the ablation zone, PET/CT can be used to define the ablation zone as a hypo-perfused region using the FDA-approved PET perfusion agent $^{13}$N-ammonia. Unablated liver remains perfused whereas the ablation zone does not. The ablation zone then appears as a photopenic region surrounded by radiopharmaceutical uptake in the unablated, perfused parenchyma. In the scenario of a successful FDG PET/CT-guided thermal ablation of a liver tumor, the expected appearance during AP-PET would be a target pattern. The ablated tumor retains FDG activity and would form the center "hot spot" of the target. The ablation zone margin would appear as a "cold" ring due to minimal FDG activity and absence of perfusion by N-13 ammonia. The outer surrounding unablated liver would appear "hot" due to perfusion by N-13 ammonia. In the scenario of an unsuccessful FDG PET/CT-guided ablation, the ablation margin

depicted as a "cold" rim would either be absent or incomplete, indicating an inadequate ablation margin. AP-PET would be obtained using a radiopharmaceutical administration protocol identical to our standard cardiac practice. PET image acquisition will be obtained dynamically, as the N-13 ammonia is injected intravenously, using 15 second frames over 5 minutes.

- The advantages of using AP-PET to define the adequacy of the ablation zone margin include a very low radiation dose to the patient, substantially less than a diagnostic CT scan and approximately one-tenth the dose from FDG PET, using equal administered activity (9). AP-PET is thus an ideal intraprocedural monitoring method that can be used repeatedly. Incorporating CECT into the PET/CT protocol could be used to assess the ablation zone margin relative to the FDG-avid tumor, but is subject to the problem of misregistration of the PET and CT images (3). In other words, the PET and CT components of a PET/CT scan are acquired at different time points and may not line up perfectly with each other, for example, due to respiratory motion between the PET and CT scans. Using FDG PET to visualize the ablated tumor and AP-PET to visualize the perfused tissue eliminates the issue of misregistration, since both are imaged at the same time and in the same position using a single PET scan.

- **Arm 2:** The advantages of using FDG as the perfusion agent for the AP-PET scan include that it does not require an on-site cyclotron – thus the technique has the potential for wide applicability. FDG is used in clinical practice during tumor ablation procedures in a split-dose fashion, dividing a standard dose into two parts: one for the targeting phase of the procedure and one for the final assessment phase of the procedure. This keeps the total radiation dose within that of a standard diagnostic PET/CT scan.

- Our Nuclear Medicine physicists at BWH have performed a PET/CT phantom study (see images below) that created compartments simulating the expected radioactivity concentrations in normal liver, the ablation margin, and the tumor that support the potential of AP-PET to demonstrate the ablation margin of FDG-avid tumors even with acquisitions as short as 30 seconds. The ablation margin appears as a dark ring around the FDG-avid tumor. Surrounding normal liver remains perfused by activity.




- **This study will assess the rates of complete ablation margin visibility using AP-PET alone in comparison to CECT alone or fused PET/CECT. This study will assess the concordance of final intraprocedural assessment of tumor ablation results using AP-PET with results observed on gold standard 24-hour contrast-enhanced MRI or CT.**
- **Patients may benefit from participation in this study if AP-PET can be used to identify an inadequate ablation margin not evident on CECT or in patients who cannot undergo CECT and are scanned without contrast. In such cases, additional overlapping ablations may be performed during the same procedure and thus increase the chance of technical success (complete tumor ablation rate) and technique effectiveness (low local recurrence rate). The safety of any additional ablation applications would be based on routine intraprocedural CT scans per standard practice.**

# 3. PARTICIPANT SELECTION

## *3.1 Eligibility Criteria*

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- Adults, 18 years or older

- Referral from an internist, oncologist, or surgeon for liver tumor ablation consultation
- ECOG Performance Status < 3
- Liver tumor ablation judged to be appropriate based on clinical assessment in the BWH Tumor Ablation Clinic by the tumor ablation interventional radiologist, per standard clinical practice
- Ability to understand and the willingness to sign a written informed consent document.

## *3.2 Exclusion Criteria*

*Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study. (Each are relative contraindications to ablation in current clinical practice.)*

- Uncorrectable coagulopathy (due to bleeding risk)
- Pulmonary disease precluding monitored anesthesia care or general anesthesia
- Severe renal insufficiency, EGFR < 30
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Childs-Pugh Class C cirrhosis
- Occlusive main portal vein thrombosis
- Presence of biliary-enteric anastomosis (due to risk of biliary infection)
- Pregnant women are excluded (because both CT and PET/CT scans involve the use of ionizing radiation which may pose a potential teratogenic effect on the fetus.)

## *3.3 Inclusion of Women, Minorities and Other Underrepresented Populations*

- This study will enroll patients with primary or secondary liver tumors based on referral for image-guided tumor ablation. Patient enrollment will not be based on sex, ethnicity, or race. Patients from underrepresented populations with a potentially higher incidence of cirrhosis and HCC will be enrolled using the same criteria as for all other patients. The study design is not expected to impose limitations on any particular subpopulation.

- The patient will be referred by a treating internist, oncologist, or surgeon, at DFCI or BWH involved in managing the patient's liver tumor(s), for image-guided thermal

ablation. The patient must be evaluated by one of the interventional radiologists, investigator or co-investigator on this protocol, who perform liver tumor ablation procedures at BWH, and must be deemed a suitable candidate for the procedure(s) and based on our standard clinical practice.

# 4. REGISTRATION PROCEDURES

## *4.1 General Guidelines for DF/HCC and DF/PCC Institutions*

- Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the day of the procedure. Any participant not registered to the protocol before the procedure will be considered ineligible and registration will be denied.

- *A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.*

- Following registration, participants may undergo the ablation procedure protocol. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not meet protocol requirements, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

## *4.2 Registration Process for DF/HCC and DF/PCC Institutions*

- The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   **Reminder:** Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

**Exception:** DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

### *4.3 General Guidelines for Other Participating Institutions - N/A*

### *4.4 Registration Process for Other Participating Institutions - N/A*

## 5. TREATMENT PLAN

The treatment plan for this study involves the non-therapeutic administration of a radiopharmaceutical, N-13 ammonia, one to two doses, during the tumor ablation procedure. The N-13 ammonia perfusion PET scan is a diagnostic imaging test. The tumor ablation procedure is performed according to our standard clinical practice and is not itself a research activity. The use of N-13 ammonia to image liver perfusion with a PET scanner is the research portion of the procedure. The patient will receive one or two doses of N-13 ammonia (10 mCi/dose) for intraprocedural assessment of ablation results. Not more than two doses will be administered and one or both doses will be administered on the day of the tumor ablation procedure only.

**Arm 2:** FDG is used instead of N-13 ammonia for the research PET scan. Only one Perfusion PET scan with FDG will be performed. The FDG dose will be divided, using 8-12 mCi for targeting and 2-5 mCi for the perfusion scan. The total FDG dose will not exceed a standard FDG dose (≤ 15 mCi) used for routine diagnostic PET/CT scans or interventional PET/CT procedures.

## 6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

There are no expected toxicities related to the IV administration of the N-13 ammonia radiopharmaceutical, however, the radiopharmaceutical is associated with a small radiation dose to the patient. Each 10 mCi dose of N-13 ammonia delivers an effective dose to the patient of approximately 0.74 mSv. The accompanying CT dose is 0.6 mSv for each ammonia PET/CT scan. Accordingly, the patient will receive an effective dose of 1.34 mSv if a single N-13 ammonia scan is performed and 2.68 mSv if two scans are performed. This is compared with an annual estimated background radiation dose associated with living in the U.S. of 3.5 mSv. No dosing delays or modifications are anticipated, however, if a dose cannot be obtained due to technical issues, the patient's procedure would be completed per standard clinical practice and would not be adversely impacted by the inability to perform the ammonia PET scan. If the patient did not receive the N-13 ammonia dose during the procedure, they would no longer be eligible to participate in the study.

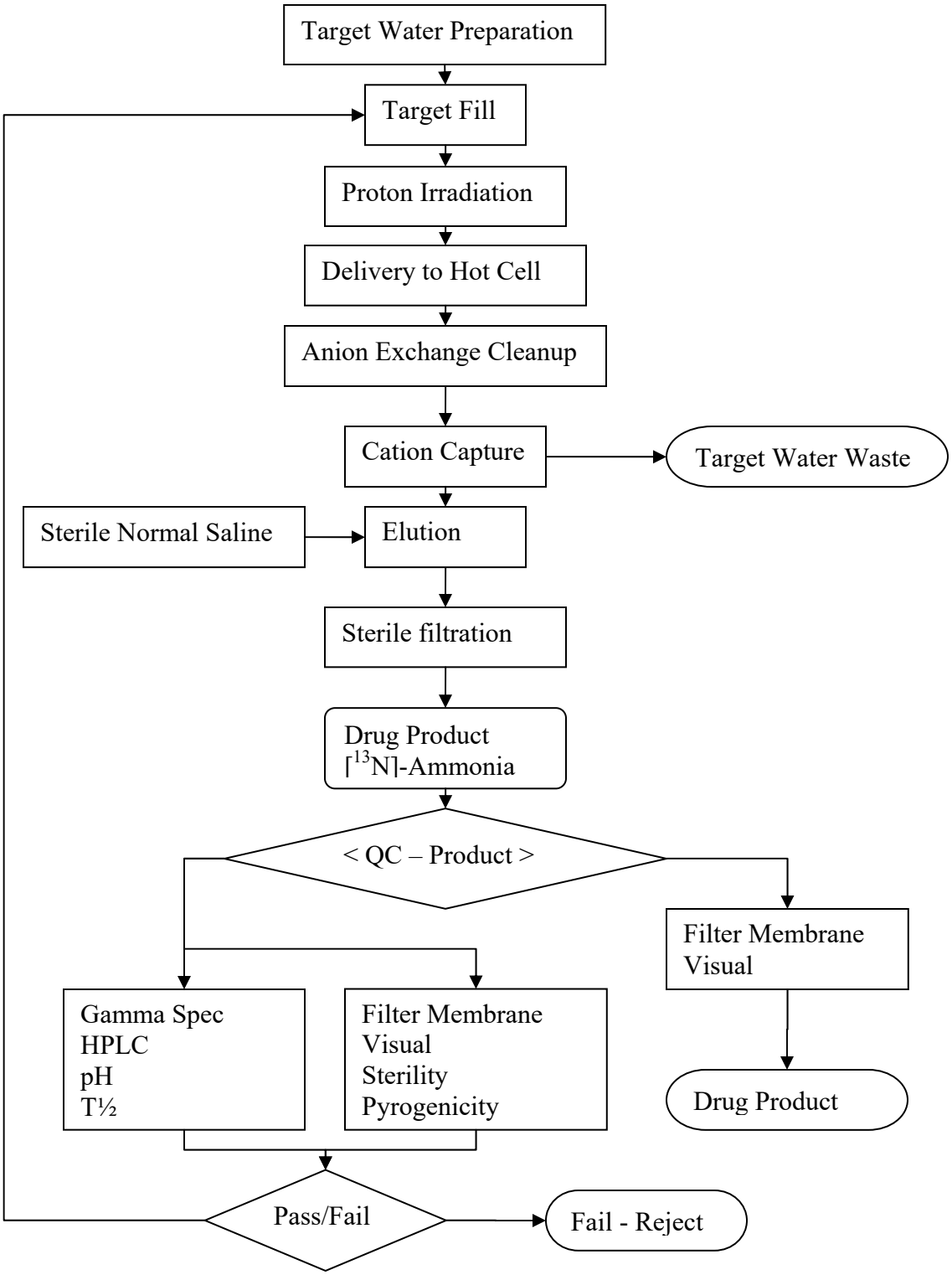
**Arm 2:** In Arm 2 of the study, FDG is used instead of N-13 ammonia for the perfusion scan. The FDG will be administered using our standard clinical practice of splitting the FDG dose into a targeting dose (8-12 mCi) and a perfusion dose (2-5 mCi), so that the total dose does not exceed a routine FDG dose used for diagnostic PET/CT scans (≤ 15 mCi). Accordingly, the patient will not receive more radiation dose than they would if not participating in this research protocol; the radiation dose will be identical to a routine FDG PET/CT-guided ablation procedure.

## 7. DRUG FORMULATION AND ADMINISTRATION

**N-13 ammonia production overview (not required for FDG production, as this is FDA-approved for the study indication)**

The radiopharmaceutical, N-13 ammonia, is prepared by the BICOR on-site cyclotron/radiopharmacy facility at BWH. Brigham and Women's Hospital produces N-13 ammonia in a cyclotron target by proton irradiation of natural water with added ethyl alcohol. The irradiated solution is passed through an anion exchange column to remove extraneous anions and [$^{13}$N] Ammonia is captured on a cation exchange column while the target water passes to a waste vial. Normal saline is used to elute the [$^{13}$N] Ammonia and is sterile filtered into the product container. Sub-lots are produced each day in accordance with patient needs. The first

sub-lot is used exclusively for quality release testing. Subsequent lots are visually inspected and assayed. All sub-lots have individual sterile filters, each of which is integrity tested.



## Cyclotron and Target Preparation

Target water is prepared by mixing 145 uL of ethyl alcohol to 50 mL of LAL water. The target contains 1.5 mL of solution. The prepared vial supplies all target-fills for a day's production.

## Hot Cell Preparation

The target water delivery from the cyclotron leads to a clean hot cell (HC) where it is connected to the input of the [$^{13}$N] Ammonia purification apparatus. The columns in the apparatus are conditioned and assembled with the final product vial kit prior to closing the hot cell. Product vial kits are prepared in a sterile enclosure, one setup for each sub lot.

**Table 1. Ammonia Chemistry Setup Components**

| Item | Quantity | Specification |
|---|---|---|
| **Ammonia Kit** | **1** | **M0021** |
| **Maxi-Clean SAX cartridge** | **1** | **SB M0143** |
| **Sep Pak Accell Plus CM** | **1** | **SB M0178** |
| **LAL Water** | **20 mL** | **SB C0084** |
| **Product Filtering Y** | **2** | **SB M0123** |
| 0.9% Sodium Chloride Syringe 10mL | **1** | **SB C0139** |
| **Acrodisc 0.2 um 32 mm** | **1** | **SB M0131** |
| **Four Way Stopcock** | **1** | **SB M0009** |

**Table 2. Ammonia Chemistry Setup Components**

| Item | Quantity | Specification |
|---|---|---|
| **Ammonia Kit** | **1** | **M0021** |
| **Maxi-Clean SAX cartridge** | **1** | **SB M0143** |
| **Sep Pak Accell Plus CM** | **1** | **SB M0178** |
| **LAL Water** | **20 mL** | **SB C0084** |
| **Product Filtering Y** | **2** | **SB M0123** |
| 0.9% Sodium Chloride Syringe 10mL | **1** | **SB C0139** |
| **Acrodisc 0.2 um 32 mm** | **1** | **SB M0131** |
| **Four Way Stopcock** | **1** | **SB M0009** |

## Target Irradiation

The process to make [$^{13}$N]-Ammonia is irradiation of the target with 16.5 MeV protons. The proton current is set at 35 uAmp and the irradiation time is 15 minutes. The reaction $^{16}O(p,\alpha)^{13}N$ produces $^{13}$N ions that capture hydrogen from dissolved ethyl alcohol to form Ammonia ([$^{13}$N]$NH_3$). At the end of bombardment, the target water is transferred and the target dried.

## Post Irradiation Handling

The target water passes through the anion and cation columns before being diverted to the waste water collection vial leaving [$^{13}$N]-Ammonia captured on the cation column. 10 mL of normal saline elutes the [$^{13}$N]-Ammonia and passes through a sterilizing filter and into the final product vial. The first sub lot of the day is used only for quality control testing.

**Table 3. [$^{13}$N]-Ammonia Composition for each Sub-lot**

| Item | Quantity | Concentration |
|---|---|---|
| Sterile Normal Saline for Injection | 8 -10 ml | 9.0 mg/mL |
| [$^{13}$N]-Ammonia | 30 to 375 mCi | 3.75 to 37.5 mCi/mL |

**Analytical Procedures (N-13 ammonia injection)**

[$^{13}$N]-Ammonia quality control testing is conducted on material collected from the first irradiation (sub-lot) of a day's production. Samples are drawn and one part tested in the clean areas and the other sample taken to the quality testing lab for analysis

**Table 4. Summary of Analytical Procedures for Release Testing**

| Attribute | Procedure | Requirement |
|---|---|---|
| Appearance | Q0119, Visual Inspection of Clear Solution | Clear, colorless and particulate free |
| Radionuclidic Identity | Q0118, Radionuclide Identity – $T_{1/2}$ | Half-life is between 9.5 and 10.5 minutes |
| Radiochemical Identity | Q0041, [$^{13}$N]-Ammonia Radiochemical & Chemical Purity by HPLC | Determine retention times of product and reference standard. Ratio of retention times is 1.12 ± 5% |
| Radiochemical Purity and Chemical Purity | Q0041, [$^{13}$N]-Ammonia Radiochemical & Chemical Purity by HPLC | Radiochemical Purity ≥95%<br>No unknown chemical peaks identified |
| Radionuclidic Purity | Q0042, [$^{13}$N]-Ammonia Radionuclidic Purity by MCA | ≥99.5% of radiation associated with 511 Kev |
| Radioactive Concentration | M0009, [$^{13}$N]-Ammonia Batch Release Record | 3.75 to 37.5 mCi/mL |
| Specific Activity | NA – No Carrier Added | NA |
| pH | Q0045, [$^{13}$N] Ammonia pH Testing | 4.5-7.5 (USP) |
| Filter Integrity | Q0117 Filter Integrity Testing | ≥45 psi bubble point |
| Pyrogenicity (Bacterial Endotoxins) | Q0044, Pyrogen Testing | <175EU/V |
| Sterility | Q0043, Sterility Testing | No growth after 14 days |

**Dose administration**

The final dose-calibrated, sterile radiopharmaceutical is delivered to the AMIGO suite in a single syringe for intravenous administration through the patient's existing IV access.

# 8. CORRELATIVE/SPECIAL STUDIES – N/A

# 9. STUDY CALENDAR

- All research activity requiring patient participation occurs during the image-guided liver thermal ablation procedure on day 1. The only research activities are the one or two perfusion PET scans on day 1. All other calendar events fall within our routine clinical practice.

- **Arm 2:** the calendar for Arm 2 is identical to Arm 1; FDG PET/CT is substituted for Ammonia PET/CT
- Follow-up imaging examinations are performed as part of routine clinical practice and do not require extra patient time or commitment.

| | Visit 1 | Visit 2 | Visit 3 | Visit 4 |
|---|---|---|---|---|
| | Screening | Day 1 | Day 2-30 | Day 90-365 |
| Medical History & Physical Exam | X | | | |
| Blood Test | X | | | |
| Pregnancy Test | X | | | |
| Liver tumor ablation | | X | | |
| Perfusion PET/CT | | X | | |
| MRI, CT or PET/CT scan | | | X | X |

## 10. MEASUREMENT OF EFFECT

Drug response is not an endpoint of this trial. No therapeutic drugs are investigated in this trial. Patients undergoing liver ablation procedures will undergo follow-up contrast-enhanced MRI or CT at 24 hours (but not more than 30 days) after the ablation and then at 3-months to one year after the ablation. While obtaining a contrast-enhanced MRI or CT is routinely performed by our team at 24 hours, there are occasionally patient-specific clinical factors that may make it preferable to obtain the initial post-procedure scan up to 30 days later. This does not compromise our assessment of study endpoints. Then at least one scan is obtained between 3-months and one year, depending on routine clinical requirements. If there is severe renal insufficiency with EGFR < 30, the patient cannot be enrolled. CT and MRI with contrast can be performed with an EGFR ≥ 30. The assessment for incomplete tumor ablation and local tumor recurrence following thermal ablation procedures are study endpoints that are not based on standardized response criteria, such as RECIST. Instead, the interpretation of follow-up imaging tests is based on identification of findings that are now known to be specific for residual or recurrent tumor. These include new or enlarging nodular enhancing masses either in the ablation zone or at its margins. Enlargement of the ablation zone compared to baseline post-ablation imaging is a suspicious finding. Suspicious findings may undergo biopsy when possible and clinically indicated to prove the presence of tumor. Progressive imaging findings will be a secondary criterion for local tumor recurrence when biopsy is not clinically indicated. Other clinical parameters, such as serum tumor markers, cannot be used as the sole indication that the treated tumor was not treated completely because the marker activity could emanate from other liver tumors or tumor outside the liver. Thus serum tumor markers will not provide direct evidence of local tumor recurrence, but may

provide supportive evidence.

# 11. ADVERSE EVENT REPORTING REQUIREMENTS

## *11.1 Definitions*

### *Adverse Event (AE)*

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after enrollment into the study protocol or any procedure specified in the protocol, even if the event is not considered to be related to the study.

- Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

### *Serious adverse event (SAE)*

A serious adverse event (SAE) is any adverse event, occurring during the protocol and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person is at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event requires at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that does not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

### *Expectedness*

- Adverse events can be 'Expected' or 'Unexpected.'

### *Expected adverse event*

- Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

- Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

### *Unexpected adverse event*

- For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

### *Attribution*

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

## *11.2 Procedures for AE and SAE Recording and Reporting*

- Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

- All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

- 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 website at:

  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

## *11.3 Reporting Requirements*

- For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

- Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

## *11.4 Reporting to the Study Sponsor*

### *Serious Adverse Event Reporting*

- All serious adverse events that occur immediately after, during, or within 30 days of the research AP-PET scans must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

  - Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

  - All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

- Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Paul B. Shyn, MD
817-996-7208 (cell)
pshyn@partners.org
617-732-8353 (office)

- Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

### *Non-Serious Adverse Event Reporting*

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

## *11.5 Reporting to the Institutional Review Board (IRB)*

- Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

- Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to: N/A

- The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events. N/A

## *11.6 Reporting to the Food and Drug Administration (FDA)*

- N/A

## *11.7 Reporting to the NIH Office of Biotechnology Activities (OBA)*

- N/A

## *11.8 Reporting to the Institutional Biosafety Committee (IBC)N/A*

- N/A

## *11.9 Reporting to Hospital Risk Management*

- Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

## *11.10 Monitoring of Adverse Events and Period of Observation*

- All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

- For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

- Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

# 12. DATA AND SAFETY MONITORING

## *12.1 Data Reporting*

### *Method*

After review and approval by the QACT manager, Wendy Magnan, MPH, the decision was made that QACT will not collect, manage, or monitor data for this study. Note that this is not a therapeutic drug trial. The research activity involves only the IV administration of the PET radiopharmaceutical N-13 Ammonia or FDG. Instead, data will be collected and managed by the P.I. using a REDCap database.

## *12.2 Safety Meetings*

- The DF/HCC Data and Safety Monitoring Committee (DSMC) will review the protocol up to four times a year to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## *12.3 Monitoring*

- Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

- All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

# 13. REGULATORY CONSIDERATIONS

## *13.1 Protocol Review and Amendments*

- This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

- Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

- All decisions of the IRB concerning the conduct of the study must be made in writing.

## *13.2 Informed Consent*

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

## *13.3 Ethics and Good Clinical Practice (GCP)*

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

## *13.4 Study Documentation*

- The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

- Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.
- Photographs may be taken during the ablation procedures for illustration purposes in scientific publications or meetings, however, such photographs will not include the patient's face and will not in any way identify the patient.

## *13.5 Records Retention*

- All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

## *13.6 Multi-center Guidelines – N/A*

## *13.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA) – N/A*

# 14. STATISTICAL CONSIDERATIONS

## *14.1 Study Design/Endpoints*

**Arm 2:** Study design/endpoints are identical for Arms 1 & 2.

In this study of patients with liver lesions, it is expected that roughly two-thirds of patients will have FDG-avid tumors, one-third of patients will have non FDG-avid tumors, and although it is possible for a patient to have both types of tumor, that is considered rare. For sample size and power considerations we therefore conservatively assume that patients will have one type of tumor or the other and therefore target a sample size of 100 patients per arm, allowing for the potential for renal insufficiency in up to 25% of all patients (described in more detail below). Also, as the techniques focus on analysis by tumor and it is estimated that 70% of patients will have only a single lesion, the sample size considerations will focus on enrolling *patients* rather than *tumors*. Multiple tumors per patient, when they occur, will be treated and assessed in the statistical analysis, with appropriate adjustment for clustering of tumors within a patient to account for correlation of responses within a patient. Sample size considerations, however, focus on enrollment of patients. The study design and endpoints are identical for Arm 1 and Arm 2.

Primary Objectives:

1. Among FDG-avid liver tumors, comparison of imaging techniques will be done on paired tumor samples using McNemar's test, focusing on discordant pairs (AP-PET-1 adequate/CECT inadequate and AP-PET-1 inadequate/CECT adequate). For these comparisons it is expected that the rate of discordance will be high (near 60% of all pairs) and that differential in discordance will be large (difference between discordant pairs on the order of 50% or higher). In addition to comparing discordant pairs, there is interest in being able to precisely estimate the visibility rates under each imaging modality. With 50 paired samples in the FDG-avid liver tumor ablation group in each arm, visibility of the entire ablation margin can be estimated with a 95% binomial confidence interval that should be no wider than 24 percentage points (+/- 12%) in the expected range of visibility of each modality (80% for AP-PET and 20% for CECT). This sample size will provide greater than 90% power for McNemar's test using a 5% type I error given the assumptions above about discordance.

Since both imaging modalities are required for McNemar's test and the rate of renal insufficiency that would preclude a paired CECT scan is estimated to be roughly 25%, inflation for loss due to patients with renal insufficiency implies that the FDG-avid tumor target sample size for this trial is 67 patients per arm (=50/0.75). The trial will be monitored closely for

potential early closure if the rate of renal insufficiency is lower than 25% or potential extension of accrual if the yield of paired samples is lower than 75%.

2. With at least 50 evaluations in the FDG-avid liver tumor treated group per arm, the visibility rates for AP-PET-1 and intra-procedural PET/CECT will be estimated with an accuracy of +/- 12% using 95% confidence intervals for binomial proportions. With this sample size, if the observed visibility rate is near 90%, the 95% confidence interval width is expected to be shorter than 19 percentage points.

3. In patients with FDG-avid liver tumors, the goal of this objective is to assess the proportion of cases confirmed to have adequate ablation margins using 24-hour MRI or CT as the gold standard among those identified as nominally adequate at the time of final intra-procedural imaging. Note that for this objective, patients do not have to receive intra-procedural iodinated IV contrast, hence the reduction in sample size due to renal insufficiency does not apply to this objective. It is expected that nearly 95% of cases will be identified as nominally adequate by all available post-ablation intra-procedural imaging data (i.e. standard-of-care imaging plus AP-PET). With 75 cases per arm, this translates to roughly 71 nominally adequate cases. Among these cases, the ablation margin adequacy rates based on 24-hour MRI or CT will be estimated with 95% binomial confidence intervals and it is expected that the adequacy rates for all available post-ablation intra-procedural imaging will be high, in the range of 90% or higher. With the sample size stated above, the 95% confidence intervals to confirm adequate ablation after 24 hours will be no wider than 16 percentage points (+/- 8%). It is also of interest to confirm that margins that were deemed inadequate on AP-PET alone were confirmed inadequate based on 24-hour MRI or CT but this objective is largely exploratory since the sample size for cases labeled inadequate after AP-PET is expected to be very low, only 5% of the total cases. Finally, it is of interest to assess agreement of final intra-procedural AP-PET with 24-hour MRI or CT. Concordance rates are unknown but are estimated to be in the range of 50 to 80%. With 75 cases per arm, the 95% confidence intervals on the concordance rates are expected to be no wider than 24 percentage points (+/- 12%) assuming, conservatively, that the true concordance rate is near 50%.

4. Among non FDG-avid tumors (expected to be one-third of patient accrual) comparison of imaging techniques will be done on paired samples using McNemar's test, focusing on discordant pairs (AP-PET fused to pre-procedural MRI or CT adequate/CECT fused to pre-procedural MRI or CT inadequate and AP-PET fused to pre-procedural MRI or CT inadequate/CECT fused to pre-procedural MRI of CT adequate). For these comparisons it is expected that the rate of discordance will be high (near 70% of all pairs) and that differential in discordance will be large (difference between discordant pairs on the order of 60%). In addition to comparing discordant pairs, there is interest in being able to precisely estimate the visibility rates under each imaging modality. With 25 paired samples per arm in the non FDG-avid liver tumor ablation group, visibility of the entire ablation margin can be estimated with a 95% binomial confidence interval that should be no wider than 34 percentage points (+/- 17%) in the expected range of visibility of each modality (80% for AP-PET and 20% for CECT). This sample size will provide greater than 90% power for McNemar's test using a 5% type I error given the assumptions above about discordance.

Since both imaging modalities are required for McNemar's test and the rate of renal insufficiency that would preclude a paired CECT scan is estimated to be roughly 25%, inflation for loss due to patients with renal insufficiency implies that the non FDG-avid tumor target sample size for this trial is 33 patients per arm (=25/0.75). The trial will be monitored closely for potential early closure if the rate of renal insufficiency is lower than 25% or potential extension of accrual if the yield of paired samples is lower than 75%.

5. In patients with non FDG-avid liver tumors, the goal of this objective is to assess the proportion of cases confirmed to have adequate ablation margins using 24-hour MRI or CT as the gold standard among those identified as nominally adequate at the time of final intra-procedural imaging. Patients evaluated for this objective do not have to receive intra-procedural iodinated IV contrast. It is expected that nearly 95% of cases will be identified as nominally adequate by all available post-ablation intra-procedural imaging data (i.e. standard-of-care imaging plus AP-PET). With 33 cases per arm, this translates to roughly 31 nominally adequate cases. Among these cases, the ablation margin adequacy rates based on 24-hour MRI or CT will be estimated with 95% binomial confidence intervals and it is expected that the adequacy rates for all available post-ablation intra-procedural imaging will be high, in the range of 90% or higher. With the sample size stated above, the 95% confidence intervals to confirm adequate ablation after 24 hours will be no wider than 24 percentage points (+/- 12%). It is also of interest to confirm that margins that were deemed inadequate on AP-PET fused to pre-procedural MRI or CT were confirmed inadequate based on 24-hour MRI or CT but this objective is largely exploratory since the sample size for cases labeled inadequate after AP-PET fused to pre-procedural MRI or CT is expected to be very low, only 5% of the total cases. Finally, it is of interest to assess agreement of final intraprocedural AP/FDG PET fused to pre-procedural MRI or CT with 24-hour MRI or CT. Concordance rates are unknown but are estimated to be in the range of 50 to 80%. With 33 cases per arm, the 95% confidence intervals on the concordance rates are expected to be no wider than 36 percentage points (+/- 18%) assuming, conservatively, that the true concordance rate is near 50%.

Secondary Objectives:

Within arm, comparison of local tumor progression rates to ablation margin adequacy will be largely descriptive as this study does not have adequate power to make definitive conclusions about progression rates. Given the expected heterogeneity of the treated liver tumor populations at presentation and potential variability in clinical follow-up for local progression, this objective is therefore largely exploratory. Intra-procedural IV iodinated contrast is not required for patients analyzed for this objective. An independent radiologist will perform blinded reads for both the final intraprocedural AP-PET and 24-hour MRI or CT to classify cases as adequate or inadequate with respect to the ablation margins for both imaging techniques. Cases will be followed clinically for at least 3-12 months to identify local tumor progression. The method of Kaplan and Meier will be used to estimate the censored time-to-failure distributions for local tumor progression with the goal of estimating, in a preliminary and exploratory fashion, the local tumor progression rates by adequacy of the blinded AP-PET and 24-hour MRI or CT reads. Statistical

precision will be limited for these evaluations and no formal comparison of groups will be performed.

### *14.2 Sample Size/Accrual Rate*

**Target enrollment for each arm of the study is 100 patients. Each patient will be followed for 12 months after their study procedure(s). An accrual rate of 3-6 subjects/month is anticipated. Enrollment of 200 total patients is expected to be completed within 3-4 years.**

### *14.3 Stratification Factors – N/A*

### *14.4 Analysis of Secondary Endpoints*

*See above, Section 14.1*

### *14.5 Reporting and Exclusions*

*This is not a therapeutic drug trial. Please see Section 14.1*

## 15. PUBLICATION PLAN

The principal investigator holds primary responsibility for publication of the results of this study. The study results will be submitted for publication in a peer-reviewed journal within 24 months of the end of data collection, regardless of the outcomes.

## 16. REFERENCES

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## 17. APPENDICES

## Appendix A: Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Description | 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. |