High Quality Imaging and Dosimetry of Yttrium-90 (^{90}Y) SIRT Using a Digital PET/CT

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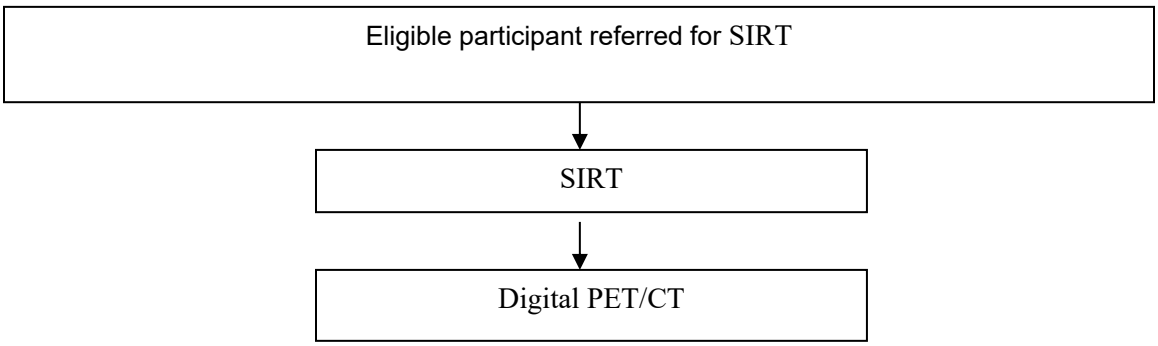
SCHEMA


Eligible participant referred for SIRT
SIRT
Digital PET/CT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

MAA	Macro aggregated albumin
IRB	Institutional Review Board
IV	Intravenous
IA	Intra-arterial
SIRT	Selective internal radiation therapy
PET/CT	Positron emission tomography – computed tomography
ROC	Receiver-Operative-Characteristic
SUV	Standardized Uptake Value

1. OBJECTIVES

1.1 Primary Objective

- To evaluate the image quality of ^{90}Y PET/CT post SIRT images as compared to ^{99m}Tc MAA SPECT/CT.

1.2 Secondary Objective

- To determine the superior accuracy in both distribution and dosimetry of ^{90}Y PET/CT post SIRT imaging compared to ^{99m}Tc MAA planar and SPECT/CT imaging

2. BACKGROUND

2.1 Preliminary information

Yttrium-90 (^{90}Y) selective internal radiation therapy (SIRT) is a rapidly emerging radionuclide treatment modality for hepatic liver malignancy. The majority of patients with hepatocellular carcinoma are being treated with glass microspheres (TheraSphere®; Biocompatibles Inc., London, UK), while most patients with liver metastasis are being treated with resin microspheres (SIR-Spheres®; Sirtex Medical Limited, Lane Cove, Australia). SIRT leads to improvements in progression free and overall survival (*1-4*). Complications are either caused by inadvertent deposition of radioactive microspheres outside the liver, in the lungs (radiation pneumonitis) or in the gastrointestinal tract (gastroduodenal ulceration), or by direct injury to functional liver parenchyma itself (*5-7*). Reported hepatic toxicity is mostly limited to symptoms related to the so-called post-radioembolization syndrome including mild pain, nausea, vomiting and fatigue, but may include a more serious clinical syndrome, called radioembolization induced liver disease (REILD), with liver insufficiency characterized by elevated liver enzymes and bilirubin, jaundice and ascites. REILD occurs in about 5% of the patients. It is difficult to treat and often fatal (*8*).

Individualized dose planning should aim for maximum treatment effect while keeping toxicity acceptably low. The current dose calculation methods however are based on empirical evidence with regard to both efficacy and safety, without established dose-response relationships (*9*). Resin microsphere activity doses are calculated by body surface area (BSA) and fractional liver involvement, while glass microsphere dose calculation is based on a whole liver partition model, derived from the medical internal radiation dosimetry pamphlet No. 17 (*10*). Although the latter method is more robust it does not take the radiation absorbed dose in the tumors or the normal liver tissue into account.

Despite success, there are currently no reliable methods to demonstrate and quantify distribution of the treatment doses to the target lesion(s). ^{90}Y PET/CT represents a technological leap from ^{90}Y bremsstrahlung SPECT/CT by coincidence imaging of low abundance internal pair production. However, image acquisition times are long and the resulting quality is suboptimal when using currently available PET/CT scanners.

More than a decade ago, multimodality imaging was introduced into clinical routine with the development of the PET/CT. Since then, PET/CT has been widely accepted in clinical imaging and has emerged as one of the main cancer imaging modalities. With the recent development of combined PET/MRI systems for clinical use, a promising new PET detector technology using silicon photomultiplier tubes has become available. The combination of functional information delivered by highly sensitive novel PET detectors with the morphologic imaging of

CT offers exciting possibilities for clinical applications as well as basic research. However, the differences between standard and digital PET detectors are fundamental. Digital PET/CT is expected to show advantages over standard PET/CT by decreasing required dose of PET radiopharmaceuticals, higher sensitivity and temporal resolution. However, as of now, only assumptions can be made about the future clinical role of digital PET/CT, as data about the performance of digital PET/CT in the clinical setting are still limited (*11*). The first ever GE-made digital PET/CT scanner worldwide will be installed in the Nuclear Medicine and Molecular Imaging Clinic. This novel digital PET/CT may allow for faster and higher quality images of the therapy agent distribution when compared to historical published data from standard PET/CT.

2.2 Study Agent/Device
Digital PET/CT Scanner

2.3 Clinicaltrials.gov
This study will be registered on clinicaltrials.gov

2.4 Rationale
Selective internal radiation therapy (SIRT) is a form of radiation therapy used in interventional radiology to treat cancer. It is used for selected patients with unresectable cancers, those that cannot be treated surgically, especially hepatic cell carcinoma or metastasis to the liver. Despite success, there are currently no reliable methods to demonstrate and quantify distribution of the treatment doses to the target lesion(s). ^{90}Y PET/CT represents a technological leap from ^{90}Y bremsstrahlung SPECT/CT by coincidence imaging of low abundance internal pair production. However, image acquisition times are long and the resulting quality is suboptimal when using currently available PET/CT scanners. However, the first ever GE-made digital PET/CT scanner worldwide will be installed in the Nuclear Medicine and Molecular Imaging Clinic. This novel digital PET/CT may allow for faster and higher quality images of the therapy agent distribution when compared to historical published data from standard PET/CT.

2.5 Study Design
This is a non-randomized prospective trial. Patients who are referred to Nuclear Medicine and Interventional Radiology for ^{99m}Tc MAA SPECT/CT followed by SIRT will be asked to have imaging done using the digital PET/CT scanner following the ^{90}Y SIRT injection. This could be done during their mandatory 2-hr rest while lying flat (due to closure device), after their 2-hr rest period, or the next day after the participant's SIRT procedure. We will administer 50mL of IsoVue 370 contrast to the participant during the CT scan, if there are no contraindications. We will not inject additional radiopharmaceutical; instead, we will use the already administered ^{90}Y from SIRT. This is possible because the digital PET/CT has very sensitive PET detectors. A very small amount of radiation (5 mSv) will be given by the attenuation correction CT scan in the second PET/CT.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria
- Patient is ≥ 18 years old at the time of the scan
- Patient provides written informed consent
- Patient is referred for ^{90}Y SIRT radioembolization of liver tumor(s)
- Patient is capable of complying with study procedures

- Patient is able to remain still for duration of imaging procedure (approximately 30 minutes total for digital PET/CT)

3.2 Exclusion Criteria

- Patient is pregnant or nursing

3.3 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive 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.

3.4 Study Timeline

3.4.1 Primary Completion:

The study will reach primary completion 36 months from the time the study opens to accrual. We estimate 75 patients will be enrolled.

3.4.2. Study Completion:

The study will reach study completion 36 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agent/Device

Digital PET/CT Scanner

4.2 Specify the source of the study agent/device.

GE Healthcare

4.3 Describe how the agent will be requested and provide mailing address and phone number.

Digital PET/CT Scanner present on Stanford Campus in the hospital.

4.4 Agent Accountability

N/A

5. IMAGING SPECIFICS

5.1 Modality or Modalities to be used

Digital PET/CT

5.2 Details of Imaging (i.e. dynamic, static, number of scans, etc.)

Patients will have ^{99m}Tc MAA planar and SPECT/CT imaging as part of the standard SIRT planning protocol. These images are acquired after administration of 4 mCi of ^{99m}Tc MAA in the Interventional Radiology suite. The patient will then be given ^{90}Y Spheres (Glass or Resin), and after SIRT procedure, will be arrive to NM for digital PET/CT image acquisition with diagnostic contrast enhanced CT of the abdomen. We will be administering 50mL of iodinated contrast through IV during the CT scan. Next, PET images will be acquired in 3D mode using a single bed located over the liver, with a total acquisition time of approximately 30-minutes. The PET emission scan is corrected using the segmented attenuation data from the CT scan. The PET images are reconstructed both with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets), as well as a regularized reconstruction algorithm provided by GE Healthcare. All images are reformatted into axial, coronal, and sagittal views and viewed with the software available in the Nuclear Medicine and Molecular Imaging Clinic (MIM Software, Cleveland, OH).

5.3 Details of processing/analysis

The ^{99m}Tc MAA planar and SPECT/CT imaging and the PET/CT scans will be interpreted by ABNM certified Nuclear Medicine physicians. All investigators have significant clinical experience and will be blinded to the participant's medical history and the results of other imaging modalities. A consensus read will be obtained for each scan to assess image quality. Each lesion will be tabulated and a comparison of lesion detection and radiation absorbed dose by each scanner will be conducted.

Currently, ^{99m}Tc MAA planar and SPECT/CT images only simulate ^{90}Y radiopharmaceutical biodistribution within the liver and tumor(s). Incorporating SurePlan software (MIM) to analyze the PET/CT images will determine final dose-volume histogram (DVH) within the liver and tumor (s) post ^{90}Y injection. Additionally, ^{90}Y PET/CT and ^{99m}Tc MAA planar and SPECT/CT biodistribution images can be compared to evaluate ^{99m}Tc MAA simulation accuracy. Results of this image comparison could potentially impact clinical decision-making moving forward. This information will be reported and shared with the referring physicians involved in the care of the patient.

6. STUDY PROCEDURES

6.1 Criteria for Removal from Study

The Protocol Director may withdraw subjects from the study for one or more of the following reasons: failure to follow the instructions of the Protocol Director and/or study staff; determination that continuing the participation could be harmful to the subject; the study is cancelled or other administrative reasons.

6.2 Alternatives

The alternative is to not participate in the study.

7. STUDY CALENDAR

	Pre-Study	Day 1-2	1 Months
Informed consent	X		
Demographics	X		
Medical history	X		
^{99m}Tc MAA planar and SPECT/CT imaging	X		
SIRT followed by digital PET/CT		X	
Data analysis			X

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

We will not inject additional radiopharmaceutical; instead, we will use the already administered ^{90}Y from SIRT. This is possible because the digital PET/CT has very sensitive PET detectors. There will be additional radiation from the contrast-enhanced CT used in the research scan. This research study involves exposure to radiation from CT scans that is not necessary for participant's medical care and is for research purposes only. The additional amount of radiation exposure is up to about 5.0 mSv, which is approximately equal to 10% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

There is a small volume (50 ml) of iodinated contrast to be given during the CT scan. This will require the introduction of an intravenous (IV) catheter. As with any IV catheter, there is some discomfort associated with introduction of the catheter. There can also be some redness and swelling associated with the catheter placement, but these will usually subside quickly. With the contrast injection, there is a risk of contrast extravasation (leakage) into the skin which can cause swelling and mild pain. You will be offered a hot or cold compress to help mobilize any extravasated contrast, and if very severe, you would be offered the appropriate supportive care, which in rare instances includes transfer to the emergency room and surgical consultation.

If there is any reason for you not to have the iodinated contrast, it will be omitted at physician discretion.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (i.e., each dose will be double checked for dosimetry and quality by a researcher and technologist). Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochures, and related to the investigation. For the purposes of this study, the reporting period ends at scan completion. There will be no follow-up procedures for this study. Adverse events will be reported in adherence to Stanford University's internal Adverse Event SOP.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review of Protocol

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

9.2 Data Management Plan

Electronic CRF's and patient records will both be stored electronically using OnCore.

9.3 Data and Safety Monitoring

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring of the trial will occur every 12 weeks and a record of monitoring activities will be maintained by the study team.

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

10. MEASUREMENTS

10.1 Primary outcome measure

We will evaluate the image quality of the lesions detected with the digital PET/CT scanner

and compare with the image quality of the lesions seen on the standard of care pre-therapy ^{99m}Tc-MAA SPECT/CT.

10.2 Measurement Methods

We will use a 5-point Likert scale to assess image quality.

10.3 Measurement Time Points

Images will be analyzed after completion of scanning and processing. Goal is to complete this within one month of acquisition.

10.4 Response Review

The 5-point Likert scale will be determined by Nuclear Medicine physicians blinded to the diagnosis and results of the other scan, in a randomized order to avoid bias. Two physicians will review all scans independently. Both scans of a given patient will be analyzed by one physician, then separately by the second physician.

10.5 Secondary outcome measure

We will assess the radiopharmaceutical distribution and dosimetry accuracy of ^{90}Y PET/CT by comparing visual distribution discrepancies (if any) and numerical values calculated by SurePlan from both ^{99}mTc MAA SPECT/CT and ^{90}Y PET/CT images.

10.6 Measurement Methods

We will use SurePlan software to edge-contour and calculate tumor radiation absorbed dose values in both ^{99m}Tc MAA SPECT/CT and ^{90}Y PET/CT images. This software will convert counts/pixel on the images to radiation absorbed dose measure in Gray.

10.7 Measurement Time Points

Images will be analyzed after completion of scanning and processing. Goal is to complete this within one month of acquisition.

10.8 Response Review

After radiation absorbed dose is measured in both ^{99m}Tc MAA SPECT/CT and ^{90}Y PET/CT images, the values will be compared on a lesion-by-lesion basis.

11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design

Single arm prospective study of paired imaging studies.

11.2. Randomization

This study is to compare the images from two different scans: standard SPECT/CT and digital

PET/CT and patients are scanned with both scanners. No randomization will be done.

11.3. Accrual estimates

We expect accrual of 75 patients. There are approximately 100 patients receiving SIRT each year at Stanford University. We plan to enroll 25 participants/year (33%) and this is easily achievable given our experience with other protocols.

11.4. Criteria for future studies

At this time, there are no future studies planned beyond the initial 75 participants.

11.5 Statistical Analysis

Statistical analysis is not required for this study since the comparison is between two separate modalities with inherently different properties.

Appendix: Inclusion/Exclusion Criteria Checklist

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	Supporting Documentation*
1. Patient is ≥ 18 years old at the time of the scan	☐	☐	
2. Patient provides written informed consent	☐	☐	
3. Patient is referred for ^{90}Y SIRT radioembolization of liver tumor(s)	☐	☐	
4. Patient is capable of complying with study procedures	☐	☐	
5. Patient is able to remain still for duration of imaging procedure (approximately 30 minutes total for digital PET/CT)	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Patient is pregnant or nursing	☐	☐	

***All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-support, and medical record review.**

Statement of Eligibility

By signing this form of this trial I verify that this subject is ☐ **eligible** / ☐ **ineligible** for participation in the study. The study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

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