ERP RT-060 - Intrinsic Dosimetry for Radioembolization utilizing PET-CT Imaging Data: A Prospective Registry Study.

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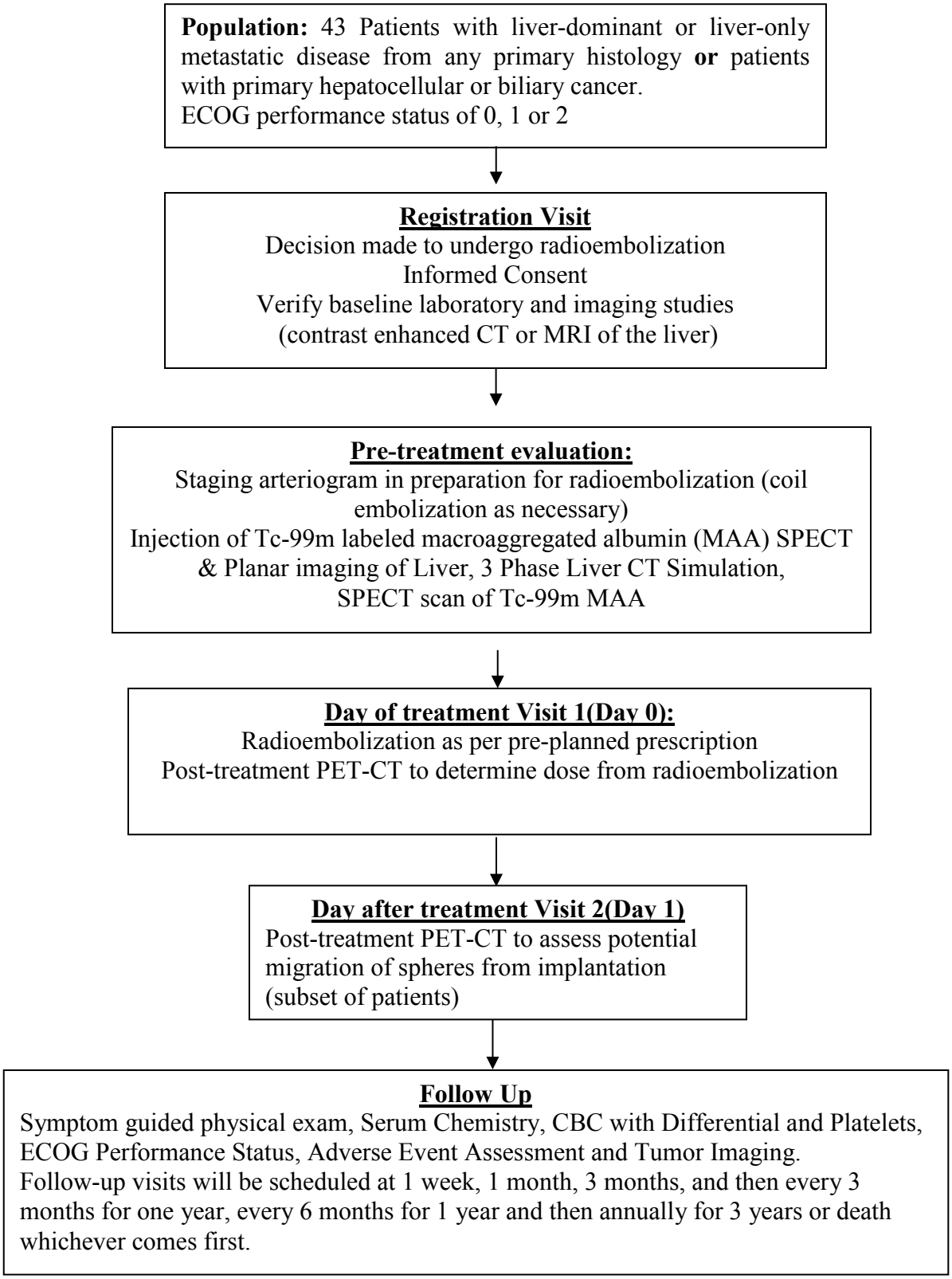

1.0 Introduction

1.1 Abstract

This protocol for human research study is conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization (ICH) Guidelines) and applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations).

The development of radioembolization with microspheres represents a significant advance in the treatment of patients with metastatic disease to the liver. [1,2] This technique uses semi-empirical formulas for dose calculation that rely on body surface area or crude volumes as the determinants of dose. Moreover, dose is assumed to be uniformly distributed throughout the treated volume. Although the efficacy of treatment and limited side effects are evidence of high intratumoral doses with minimal radiation to normal liver, there have been few attempts to quantify the actual doses delivered. Knowledge of these doses may allow more accurate determination of the effect of dose on response, improved algorithms for prescription of the safest and most effective dose for each patient, and safer integration of additional treatment to the area with either microspheres or external beam radiation. Therefore, we are proposing a new technique to better characterize the dose deposition of radioactive microspheres. The research plan will be based on the recent publication of positron emission from Yttrium 90 (Y-90), which can be utilized to image sphere distribution on a positron emission tomography (PET) scanner, without the administration of additional radiolabeled tracer. Three dimensional dose distributions will be generated and fused onto the CT data of patients to display doses to tumors and normal tissues.

1.2 Background

The current methodology for determining the prescribed dose for patients to be treated with radiolabeled microspheres likely leads to suboptimal treatment of hepatic malignancies, with most patients being either overtreated or undertreated. The development of a novel technique for defining actual dose delivered will better define the activity required to achieve specific doses, and begin to support the transition from a model of dose prescription based primarily on body surface area to one that predicts the dose to both tumor and normal tissues.

The current formulae for determining the prescribed activity to patients to be treated with radiolabeled microspheres are crude and do not take into account significant variations in tumor size, shape, or location. There are two radiolabeled microsphere products currently available for treating patients with liver tumors (metastatic or primary): SIR-Spheres (Sirtex Medical, North Sydney, Australia) and Therasphere (Nordion, Ottawa, Canada). The formula most commonly used for SIR-Spheres is largely driven by body surface area:

A [GBq] = BSA – 0.2 + (TV/TLV)

where A = activity, GBq = Gigabecquerels (units), BSA = body surface area, TV = tumor volume, and TLV = total liver volume. This may be multiplied by the lobe factor (fraction of the total liver volume being treated) for patients in whom whole liver treatment is not being pursued. The formula used for calculation of activity in Therasphere administration is:

A [GBq] = (D [Gy] x m [kg])/49.38

where D is the desired dose in Gy, m is the tumor mass in kg. Dose is set to a nominal 100-120 Gy, based on an expected uniform distribution of microspheres over the treated region. However, there is no data available to date that would definitely confirm this. Moreover, this should not be expected to be true. This is due to the existence of hypervascular malignancy with blood supply derived from the hepatic arterial system and normal tissue deriving its blood supply from the portal vein–all within the treated volume.

Neither one of these formulas, nor any others in routine use, takes into account the differences in expected dose based upon the size, shape, and location of tumors. In fact, the prescription is simply the total activity to be administered, without any calculation of the dose to be delivered from this activity. Additionally, there is almost no calculation of expected normal tissue doses, with the exception of the use of Tc-99m macro-aggregated albumin (MAA) in order to quantify the lung shunt at the time of angiography prior to treatment. These limitations in the current prescription methodology hamper the ability to move this treatment technique forward, because without doses to both normal tissues and tumors it is not possible to ascribe better responses or increased side effects to the doses received. Therefore, in the ten years since this treatment has become available, there has been little or minimal advancement in the treatment technique.

The emission of positrons from Y-90 has recently been used to generate positron emission tomographs of radiolabeled microsphere distribution [3]. A similar technique has been used to measure the absorbed dose in an anatomical phantom – a laboratory stand-in for a patient – after treatment with SIR-spheres [4]. However, to our knowledge this technique has not been routinely performed in patients.

With the availability of a new technique to quantify the dose to tumors and normal tissues, it will be possible to correlate response and toxicity with actual dose delivered. A second potential application will be the correlation of the activity on the MAA scan with the actual dose deposition. It will be valuable to determine whether the MAA scan is a reliable predictor of dose distribution. With this relationship better defined, we may be able to escalate the dose delivered in many patients in order to improve the control rates and decrease doses in patients who are expected to have higher doses to normal tissues.

1.2.1 Preliminary Data

The 3D dose absorbed in a patient is calculated by convolving the activity distribution A(x, y, z) with the dose kernel for Y-90 source, according to the following expression.

$$D(x,y,z) = \frac{1}{\lambda} \iiint K(x-x', y-y', z-z') A(x', y', z')\, dx'dy'dz',$$

where λ is the decay constant of Y-90 isotope and K is the dose kernel. The activity distribution in the equation above is due to electrons emitted by the source, but the measured PET scan data is the activity distribution due to emitted positrons. As a result, one can rewrite the above equation in the following from,

$$D(x,y,z) = \frac{1}{\lambda\gamma} \iiint K(x-x', y-y', z-z') A^{p}(x', y', z')\, dx'dy'dz',$$

where A^p is the measured activity due to positrons and γis the conversion factor. Since the PET scanner's resolution is not sufficient to resolve individual spheres, the dose kernel is calculated for a volume element of the size equal to that of the PET scanner's voxel size, which is 0.4 x 0.4 x 0.3 cm. The whole volume of the voxel is assumed to be filled with tissue, with uniformly distributed electron sources in it that emit electrons with energy spectrum corresponding to that of beta electrons of Y-90 [5]. The Fluka Monte Carlo code was used to calculate the voxel dose kernel (VDK) in tissue. All pertinent interactions were turned on during the simulations and up to 10^9 histories were simulated to reduce the uncertainties.

Care has to be taken in order to properly process the measured activity A^p (activity due to positrons). Current Siemens PET/CT scanners do not provide an option for specifying imaging-related parameters for Y-90 isotope. Therefore Y-86 template was used in our image acquisition procedure, which has its own tracer parameters that are different from those of Y-90. However, the Y-86 template can be used during image acquisition as long as one experimentally determines the calibration factor γ for Y-90 microspheres using the same PET scanner that is used for the subsequent in-patient dose reconstruction (one must use the same imaging template for determining the calibration factor as well as for patient scanning). It is interesting to note that in this case the herein defined calibration factor γ is the ratio between the branching ratios of Y-90 and Y-86.

The calibration factor γ for the Siemens Biograph 16 slice PET/CT scanner available at our center was determined by injecting 740 MBq of ^{90}Y-chloride into a 1 L water bag. Subsequently, the "hot" water bag was scanned together with a "cold" identical size water bag using the PET scanner (to account for the scanner's noise). After the scan, the activity in the "cold" water bag was subtracted from the activity value of the bag containing 90Y-chloride. The corrected measured activity was divided by the known total activity at the time of scanning to determine the calibration factor (an average value for the calibration factor was obtained out of seven measurements) that will be used in dose calculations of every patient treated with microspheres.

Figures 1 and 2 show the calculated isodose distribution as well as the dose volume histogram of one of the patients recently treated by Y-90 microspheres.

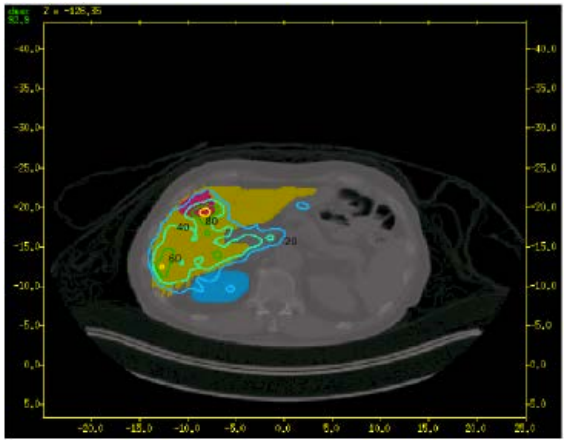

Fig. 1: Reconstructed in-patient dose distribution superimposed on patient's axial CT data. The red, green and blue contours designate the tumor, liver and right kidney, respectively.

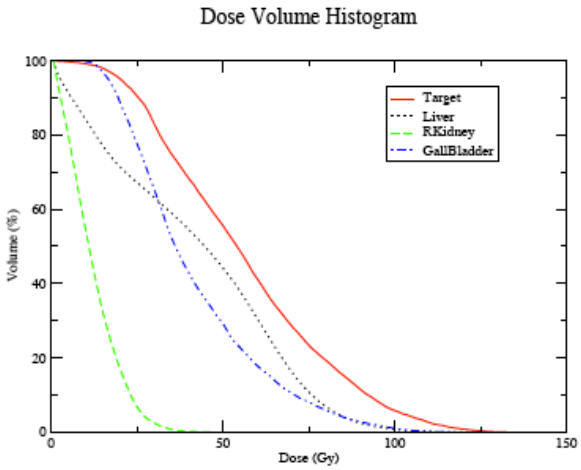

Fig 2: Dose volume histogram for tumor, liver, right kidney and gallbladder. The numbers indicate the percent line of the maximum dose, 134.7 Gy.

2.0 Objectives

2.1 Primary Objective

- To determine the relationship between radiation dose to 70% of the tumor volume as determined by post-treatment PET-CT and local control at 6 months.

2.2 Secondary Objectives

- To evaluate the ability of PET-CT to reproducibly determine dose to tumor, normal liver, and other surrounding organs
- To determine the stability of microsphere location by examining the changes in dose in a subset of patients with PET-CT scans performed on Day 0 and Day 1
- To determine the relationship of dose predicted by Tc-99m labeled Macro-aggregated albumin (MAA) imaged using SPECT versus post-treatment dosimetry
- To determine the effect of dose delivered on local control and normal tissue complications
- To measure the perfusion of the tumor for correlation with dose deposition, based on arterial phase CT measurements
- To evaluate overall survival for 5 years after Visit 1, Day 0.

3.0 Study Plan

This study will be a single arm registry study to evaluate the dose received by ability of PET-CT to determine dose delivered via radioembolization to the liver for metastatic disease. Patients will be staged and treated in the standard fashion, but will undergo a number of imaging studies in order to better analyze the dose of radiotherapy delivered. These imaging studies include a Tc-99m MAA SPECT scan (carrying no additional radiation exposure) as well as 1-2 PET-CT scans (a limited radiation exposure is necessary with each scan).

This is a prospective single-arm registry study being performed in order to validate a novel method of determining dose deposition from radioembolization by performing post-treatment PET-CT scan. Forty three patients will be enrolled over an expected recruitment time of 1.5 to 2 years. We will utilize these data to investigate the relationship between dose delivered to targets and local control. A subset of patients will undergo a second PET-CT with contrast CT on Day 0, and another subset of patient will have a second PET-CT on Day 1. All other procedures will be consistent with the standard of care. Details of the PET-CT procedure can be found in Appendix II.

4.0 Patient Selection Inclusion & Exclusion

4.1 Inclusion Criteria

4.1.1 Patients must be at least 18 years of age.

4.1.2 Patients must have liver-dominant or liver-only metastatic disease from any primary histology. Patients with primary hepatocellular or biliary cancer are also eligible.

4.1.3 Patients must be clinical candidates for radioembolization with either SIR-spheres or Therasphere due to metastatic or primary malignancies of the liver.

4.1.4 Women of child bearing potential must have a negative serum pregnancy test no more than 72 hours prior to registration.

4.1.5 ECOG performance status (PS) of 0, 1 or 2.

4.1.6 Ability to understand and willingness to sign a written informed consent and HIPAA authorization for release of medical information.

4.1.7 Complete Blood Count (CBC), Chemistry Panel (CMP) and Coagulation Panel (PT, & INR) no greater than 4 weeks prior to registration.

4.1.8 Diagnostic imaging of the abdomen utilizing either CT with contrast, MRI, or PET/CT no greater than 6 weeks prior to registration.

4.2 Exclusion Criteria

4.2.1 Patients not undergoing radioembolization to the liver

4.2.2 Women of childbearing potential (WOCBP) and men who refuse to comply with appropriate contraception as described in section 4.4 below.

4.2.2 Women who are either pregnant or breast feeding. Refer to section 4.4 for further detail.

4.3 Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Pregnancy

The effects of this clinical trial on the developing human fetus are unknown. For this reason and because radiation as well as other non-therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment, and for at least 3 months after the last radiographic evaluation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have a negative pregnancy test no more than 72 hours prior to registration. If the pregnancy test is positive, the patient must not receive the visit 1 scan and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), are considered to be WOCBP.

4.5 Patient Registration Procedure

Patients will be consented at the time when the decision to pursue radioembolization is made. No protocol-specific workup will take place prior to obtaining informed

consent. However, at this time it will be determined that the patient has had a complete staging workup within the last 4 weeks including:

- Diagnostic imaging of the abdomen utilizing either CT with contrast, MRI, or PET/CT
- Complete metabolic panel (CMP)
- Complete blood count (CBC)
- Coagulation studies (PT, INR)

Eligible patients will be entered on study centrally by the Fox Chase Cancer Center QA Coordinator or their designee. Following registration, participants must begin protocol related treatments and evaluations within 14 days of registration. If a participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study and will be replaced. The QA Coordinator must be notified of cancellations and withdraws as soon as possible.

Participants may be registered from 9:00 am to 5:00 pm excluding holidays and weekends by calling the QA Coordinator at 215-728-4770. The site's investigator or designee will then fax the completed registration form, entire, complete and signed informed consent document and HIPAA authorization documents and the completed eligibility checklist to 215-214-1511. The QA Coordinator or designee will notify the site's investigator or their designee by email when participant registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number assigned by the QA Coordinator prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 Study Procedures

Pretreatment Visit

A 3 Phase Liver CT simulation must be performed before Visit 1, Day 0 (The treatment Initiation Day). This simulation may occur before or after the staging angiogram, coil embolization, Tc-99m MAA injection, and planar and SPECT imaging of the participant's liver.

Visit 1 (Day 0)

Visit 1 will take place after the pretreatment visits, and will be referred to as Day 0, the day of radioembolization. Visit 1 will include the following procedures:

- Radioembolization as per standard clinical protocol
- PET-CT performed just after the radioembolization in order to measure Yttrium-90 activity for in-patient dose reconstruction
- Subset of patients will get contrast CT

Visit 2(Day 1)

Visit 2 will take place on Day 1, and will be pursued in only a subset of patients. This will include only a PET-CT for the purposes of determining the stability of microsphere

placement. The Visit 2, Day 1 PET-CT should be scheduled 24 hours +/- 3 hours after the Visit 1, Day 0 post-treatment PET-CT.

Follow-up Visits

Participants will be followed for 5 years or until death, whichever comes first. Follow-up visits will be scheduled at 1 week, 1 month, 3 months, and then every 3 months for one year, every 6 months for 1 year and then annually for 3 years or death whichever comes first

Additional Radioembolization Treatments

As a part of standard of care, many patients will require a second radioembolization.

Patients requiring a second radioembolization treatment will be scanned additionally at Visit 1 (Day 0) and Visit 2 (Day 1) after the second treatment.

Visit 2 of the second radioembolization will take place on Day 1, and will be pursued in only a subset of patients. This will include only a PET-CT for the purposes of determining the stability of microsphere placement. The Visit 2, Day 1 PET-CT should be scheduled 24 hours +/- 3 hours after the Visit 1, Day 0 post-treatment PET-CT.

In these cases the 1 month follow up visit may be conducted on the day of the second treatment.

Follow up visits may be conducted by any investigator and will include the following studies:

- CBC and CMP will be drawn at each follow-up visit
- Beginning at the 3-month visit, each visit should be accompanied by tumor imaging to evaluate local control. The modality of tumor imaging will be at the discretion of the investigator, but it is encouraged to use the same modality consistently over time.

6.0 Study Calendar

	Registration Visit	Pre treatment Visit(s)	Visit 1 / Day 0	Visit 2/ Day 1	Follow up
Informed consent & HIPAA[A]	X				
Medical history	X				
Symptom Guided Physical exam[G]	X				X
ECOG Performance Status	X				X
CBC w/diff, plts[B]	X				X
Serum chemistry[B]	X				X
EKG (as indicated)	X				
β-HCG	X[E]				
Coagulation Studies[B]	X	X			
3 Phase Liver CT Simulation		X			
Staging Angiogram		X			
Coil Embolization		X			
Tc-99m (approx 5mCi) MAA Injection		X			
Planar and SPECT Imaging of Liver		X			
Adverse Event Assessment			X	X	X[H]
PET-CT[C,D]			X	X	
Tumor Imaging[F]	X				X[I]

A: Must be completed less than 28 days prior to registration and prior to any protocol specific tests or procedures.
B: CBC and CMP will be drawn at each follow-up visit, Coagulation studies include PT and INR. Coagulation studies must be performed for eligibility however results will not exclude patient participation.
C:Visit 1, Day 0 post treatment PET CT and contrast CT for subset of participants, Day 1 PET CT.
D:24 hours +/- 3 hours after Day 0
E: See Section 4.4 for more information – Must be negative within 72 hours of first treatment related procedure or scan
F: Repeat imaging is encouraged to be the same modality (PET-CT, MRI, or contrast CT) as that in baseline study.
G: Physical exam with investigator where he/she reviews symptoms with the participant and addresses any issues that are identified by the participant. This is not the same as a complete physical exam, intentionally.
H: Record only AE's possibly, probably, or definitely related to the visit 2 / day 1 PET/CT scan. Possibly, probably or definitely related AE's must be followed until resolution or 30 days after visit 2.
I: Follow up tumor imaging begins with the month 3 follow up visit.

7.0 Adverse Events

For purposes of this clinical trial record only AE's possibly, probably, or definitely related to the visit 1 and visit 2 PET/CT scans. Possibly, probably or definitely related AE's must be followed until resolution or 30 days after visit 2 whichever comes first.

7.1 Standard Definitions of Adverse Events (AE) and Serious Adverse Events (SAE)

7.1.1 Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

7.1.2 Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

7.1.3 Severity Rating
The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

7.1.4 Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related

4. Unlikely – doubtfully related
5. Unrelated – clearly not related

7.1.5 Expectedness
An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event. *(OHRP Guidance on reviewing unanticipated problems 2007)*

7.2 Recording and Reporting Responsibilities of the participating investigative sites and the sponsor

7.2.1 Participating investigative site recording responsibilities:

These are the directions to be utilized by the site's investigator (sub-investigator) and/or study team at the participating site.

1. Upon identification of an AE or SAE, that is possibly, probably or definitely related to the investigational PET CT scans performed, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. Any AE or SAE that is possibly, probably or definitely related to the investigational PET CT scans performed ,will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events that are possibly, probably or definitely related to the investigational PET CT scans performed,will be recorded on case report forms for the duration of the study until they resolve.

3. All SAEs that are possibly, probably or definitely related to the investigational PET CT scans performed, will be recorded on the FDA

MedWatch form 3500a or other sponsor-provided SAE report form. After submitting the initial report it may be necessary to submit follow up reports to the Study Monitor, Sponsor and /or the FDA should the event require further investigation.

7.2.2 Investigative site reporting responsibilities:

1. The investigator/ site is responsible to report all SAEs that are possibly, probably or definitely related to the investigational PET CT scans performed, to the Study Monitor within 24 hours of becoming aware of the event.
2. Each investigator is responsible to report all AEs/SAEs that are possibly, probably or definitely related to the investigational PET CT scans performed; to their local IRB following guidelines set by that IRB. Fox Chase Cancer Center Quality Assurance (QA) reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent via fax to the Regulatory Coordinator at (215) 728-2914.
3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation from the PI.
4. If the results of an investigator or QA investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
5. Copies of all related correspondence and reporting documents must be submitted to the Regulatory Coordinator by the study monitor and will be maintained in a regulatory file.

The participating site should report events to:

Beth Adaire-Halenda, CCRP
Study Monitor
Fox Chase Cancer Center
Clinical Trials Operations
333 Cottman Avenue
Philadelphia, PA 19111
Telephone 215-214-3704
Fax 215-214-1511
beth.adaire@fccc.edu

7.2.2.1 Pregnancy

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Investigator must immediately notify the Fox Chase Cancer Center Study Monitor who will notify the Study PI (Joshua Meyer, MD).

7.2.3 ERP Reporting Responsibilities:

These are the reporting instructions for the study sponsor.

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
    i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
    ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
    iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the CTO for each site's IRB of record along with the report of the adverse event.
3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at CTO.

4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

   Food and Drug Administration:
   Telephone 1-800-FDA-1088
   Fax 1-800-FDA-0178
   http://www.fda.gov/medwatch/report.htm

   Mandatory Drug Reporting:
   Central Document Room
   Center for Drug Evaluation and Research
   Food and Drug Administration
   12229 Wilkins Avenue
   Rockville, MD 20852

   Office of Post-Marketing Drug Risk Assessment (HFD 730)
   Center for Drug Evaluation and Research
   Food and Drug Administration
   5600 Fishers Lane
   Rockville, MD 20857

   (301) 827-3169 for any further questions regarding where to send drug mandatory reporting forms

8.0 Statistical Considerations

In this study, we will evaluate the dosages received by tumors and surrounding tissue using PET-CT data. The primary objective is to determine the relationship between radiation dose to 70% of the tumor volume and local control at 6 months. We will conduct this analysis at the tumor level, as different tumors may receive different doses of radiation, and may have different progression statuses at 6 months. We will use standard summary measures such as means, medians, ranges, and standard deviations to characterize the dosages received by tumor and other tissue. We will use percentages and frequency tables to evaluate other characteristics such at tumor histology, number of liver tumors per patient, and volume of liver tumors.

We will determine the relationship between radiation dose and local control at 6 months using regression models with Generalized Estimating Equations (GEE) to account for within-patient correlation. We will use logistic regression to adjust for potentially confounding factors such as tumor volume, primary histology, and SIR-Spheres versus Therasphere intervention. We will also determine the relationship between radiation dose to healthy tissue, and side effects such as fatigue, nausea, pain and elevated liver function tests. Each

side effect will be characterized as present or absent, and we will test the relationship between radiation dose to the relevant type of healthy tissue and each side effect. For example, we will look at the relationship between dose to the normal liver and elevation of liver function tests.

In further secondary analyses, we will explore the relationship between the distribution of activity measured by PET-CT, and the distribution predicted by T-99m labeled MAA. This can be translated into predicted dose. We will calculate differences between PET-CT and MAA doses, and present the data graphically. We will use the method proposed by Bland & Altman (2007) to assess the agreement between the two methods. Finally, in a subset of patients, we will explore the change in dose measured by PET-CT scan between day 0 and day 1. The dose at day 1 will be adjusted to account for the decay of the yittrium-90 using A=A0e-(0.693t/T1/2). Observed changes in dose may be due to microsphere migration, and our main interest is to look for a systematic change in dose received based on this migration.

Sample size considerations
We will power our study to detect a 10 Gy difference in mean radiation doses between tumors with local control and 6 months vs those which progressed. Based on preliminary data, we expect that the standard deviation of doses will be 12Gy, and that approximately 60% of tumors will retain local control at 6 months. We will use a two-sided test with type I error of 0.05. In preliminary data, within-patient correlation was 0.6-0.7, and we saw an average of 2 tumors per patient. We therefore will enroll 43 patients in this study to have approximately 80% power to detect a difference of 10 Gy.

It is anticipated that 10 patients will be recruited for Day 1 PET-CT studies. This number of patients would be expected to detect a difference in the range of 12-20 Gy (Day 0 – Decay-adjusted day 1). Although we may not get a significant result, the point estimates may give an indication of whether the microspheres are moving. This level of certainty is felt to be appropriate for an exploratory aim.

9.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

9.1 Data Reporting

The FCCC Study Monitor will request case report form submission upon resolution of outstanding queries. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit. Participating sites are responsible for submitting case report forms to the QA Specialist / Study Monitor within two weeks of request.

The QA Coordinator is responsible for compiling and submitting data to the study PI and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Extramural Data and Safety Monitoring Committee.

All patient information will be stored on an electronic Microsoft Office Excel Spreadsheet on a drive accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in locked file cabinets with limited access.

The CTO Regulatory Coordinator is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

9.2 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the CTO and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the QA Specialist / Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

9.3 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

10.0 References

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APPENDIX I

Tc-99m MAA scan protocol

Purpose: To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs.

Agent: Technitium-99m labelled MAA (Macro-aggregated Albumin)

Dose: 150- 200 MBq

Equipment: Any large FOV gamma camera

Administration: The patient needs to have a trans-femoral catheter placed in the hepatic artery. The Technitium-99 labelled MAA is injected through the catheter into the hepatic artery by a qualified physician.

Imaging: The patient is positioned supine under the gamma camera and the images recorded.

Analogue:

- Anterior and posterior images of abdomen and thorax. Measure 700k -1000k cts for abdomen and equivalent time for thorax.
- Right lateral Abdo - same time acquisition as for Anterior.

Digital:

- 4 frames; 300"/ frame. 64 x 64 matrix Word mode.
- Image anterior and posterior abdomen
- Image anterior and posterior thorax

Analysis: Draw ROI around whole of liver and whole of lung fields. Calculate G mean for liver region and lung region.
Calculate Lung/liver ratio

Interpretation: If lung/liver ratio is >10% then there is need for dose reduction of SIR-Spheres

SPECT protocol:

SPECT acquisition: 360 arc, using a body-contoured elliptic orbit, optimally obtaining 120 (minimum of 60) projections at 15–25 s per projection (every 3–6_angle), depending on the number of projections and sensitivity of the detector. The SPECT acquisition takes, on average, approximately 25 min. The images are acquired into a 128 x128 (16-bit) matrix, corrected for attenuation, and reconstructed using a 2-dimensional orderedsubset expectation maximization iterative technique (at least 10 subsets and 2 iterations are typical, but the number may vary according to the manufacturer).

Processing: A 3-dimensional postprocessing filter, which should be specified in detail by the manufacturer (e.g., the Hanning postprocessing filter with a cutoff frequency of 0.85 cycles/cm) is typically applied to the SPECT dataset.

APPENDIX II

PET/CT scan protocol

Purpose: To assess the treatment dose distribution, and potential calculation of dosimetry of Y-90 Sir-Spheres and/or Theraspheres.

Instrumentation: PET/CT scanner **(**Siemens Biograph 16 in Fox Chase Cancer Center)

Postherapy Imaging: Within 5 hours after the administration of Sirsphere and/or Theraspheres, a PET/CT scan will be performed covering the liver area in order to verify localization of the Sirsphere/Therasphere in the targeted tumor. A proof of concept for such a technique has been reported (3).

Parameters: The patient will be positioned on the PET/CT scanner with arms raised up, and a localization scout scan will be performed in the abdominal region. A two-bed PET/CT acquisition will be set up centered on the liver. A low dose CT scan will be performed followed by a 10 minute per bed PET acquisition. The PET data will be reconstructed using manufacturer recommended procedure, and the data will be analyzed to determine the hepatic localization of microspheres.

For Subset of patients: Diagnostic (intravenous contrast) CT should be performed immediately after the PET scan without moving the participant, using portovenous phase for optimal visualization of the liver. The volume of IV contrast is per institution standard.