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Feasibility of a personalized dosimetry-based treatment planning for Radioembolization in the treatment of Secondary Malignancies in Liver

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Feasibility of a personalized dosimetry-based treatment planning for Radioembolization in the treatment of Secondary Malignancies in Liver

1. Abstract

Trans-arterial Radio-embolization (TARE) therapy of liver neoplasia using ^{90}Y-theraspheres has a long history (see Background section). The device is FDA approved for the treatment of primary and secondary liver neoplasia, clinically performed under Humanitarian Device Exemption protocols, previously approved IRB00078140 / CR00021884. This protocol seeks to acquire the imaging information from additional 3-5 patients that will demonstrate feasibility of a personalized dosimetry-based treatment planning for TARE.

The rationale for this proposed personalized ^{90}Y treatment planning is due to a current clinical Therasphere dose calculation (as a targeted radioactive therapy), and within radiopharmaceutical therapy (RPT) overall presents as an opportunity gap. The current TARE dose calculation suffers from an imprecise efficiency characterization of the ^{90}Y radiopharmaceutical therapy (RPT) in general; namely, that the activity to treat the patient is not optimized to normal organ tolerated absorbed dose and tumor efficacy thresholds. The current amount of activity to be administered is calculated from tissue volumetrics established from imaging, either MRI or X-ray CT. The total volume of irradiated tissue is considered as irrigated by the supply hepatic artery selected for administration, including both liver tumor and normal tissue. From this volume determination, the activity necessary to deliver an average pre-determined safe absorbed dose (120 Gy) to the entire irradiated region is calculated and administered. We propose a more accurate personalized treatment planning technique in a small group of patients.

As a generalization, RPT in the theranostic paradigm, a quantity of predetermined activity of a pre-therapeutic surrogate is administered to the patient; 3D imaging (SPECT/CT or PET/CT) is then acquired at several time points. Then the individual patient's pharmacokinetics are determined, the normal organ and tumor dosimetry are performed and the optimal administered activity calculated that will deliver safe and efficacious treatment for the individual patient is determined, generally limited by the normal organ at risk maximum tolerated dose.

TARE presents a number of unique characteristics that enable a simpler version of this approach than is typical for most RPT. The method of hepatic intra-arterial administration means that only the normal liver and lungs are the potential organs at risk as the microspheres embolize and do not circulate systemically. The lack of associated photons in the ^{90}Y decay chain means that a simple

activity-to-dose-rate conversion can be used. In addition, the embolization means that only a single imaging time point is necessary, as there is no redistribution of activity over time and the dose rate is converted to absorbed dose using the physical decay parameters of ^{90}Y. These natural simplifications are already exploited in the current volumetric paradigm, where a ^{99m}Tc-macro albumin aggregate (MAA) surrogate and planar imaging are used to determine the fraction of total activity that is shunted to the lung and where a derived conversion factor is used to convert activity to absorbed dose.

The technical weakness in TARE planning is that the surrogate (^{99m}Tc-MAA) has a different nature from the therapeutic device (^{90}Y-theraspheres), and thus the reliability of the predictive quality of the surrogate is regarded as suboptimal, albeit accepted in current clinical practice and presents an opportunity for improvement. With precise advanced imaging reconstruction and dosimetry, we have shown previously, it is possible to accurately and precisely predict normal liver and tumor average ^{90}Y-therasphere uptake and absorbed dose from ^{99m}Tc-MAA surrogate. This protocol seeks to acquire the imaging information from 3-5 patients that will demonstrate feasibility of future implementation of personal dosimetry-based treatment planning for TARE.

The proposed changes to the existing clinical protocol for this small cohort are:

1. A single SPECT/CT instead of the current planar imaging will be acquired of the surrogate ^{99m}Tc-MAA;
2. An additional single 3D imaging study (either SPECT/CT or PET/CT, depending on machine availability) will be acquired up to 12 hours post-administration of the therapeutic ^{90}Y-microspheres for comparison. The images in institutional PACS (Carestream) will be de-identified, stored on JH OneDrive for analysis, and analyzed with study partners Radiopharmaceutical Imaging and Dosimetry, LLC (RAPID).

2. Objectives:

To investigate whether the dose predicted by pre-therapy ^{99m}Tc MAA SPECT predicts the dose to the liver from the ^{90}Y microspheres as assessed by post-therapy by either ^{90}Y SPECT/CT or PET/CT.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Primary and secondary liver cancer patients are treated in this institution under the HUD protocol IRB00078140 / CR00021884. More specifically, the group to be studied are patients with secondary malignancies (e.g.: Colorectal cancer (CRC), which is the third most common cancer diagnosed among both men and women in the US). The American Cancer Society estimates that approximately 148,810 new cases of colorectal cancer and 49,960 deaths were expected in 2008. Hepatic metastases are present in 15–25% of patients at presentation, and an additional 25–50% will develop liver metastases within 3 years following resection of the primary tumor [1, 2]. In approximately half of these patients, metastatic disease is confined to the liver, and 20% of all patients who die of metastatic colorectal cancer have metastases limited to the liver.

Previously reports of Radioembolization used in CRC patients include Benson et al., [3] reported the results of the first prospective multi-institutional phase II study of TheraSphere® in a heavily pretreated metastatic liver neoplasia population. One hundred-fifty one patients with liver metastasis (Colorectal n=61, neuroendocrine n=43 and other tumor types n=47) were enrolled. The primary endpoint was progression-free survival (PFS); secondary end-points included safety;

hepatic progression-free survival (HPFS), response rate and overall survival. Median PFS was 2.9 month (CRC) and 2.8 month (other primaries). PFS was not achieved in the neuroendocrine group. Median survival was 8.8 months (CRC) and 10.4 months (the other populations). Median survival for neuroendocrine patients had not been reached. No new safety issues were reported. In addition, treatment parameters including dose delivery were reproducible among centers.

TheraSphere® was recently evaluated in a cohort of seventy-two patients with unresectable hepatic colorectal metastases who were treated at a targeted absorbed dose of 120 Gy with a median delivered dose of 118 Gy [4]. TheraSphere® was well tolerated with a tumor response rate of 40.3%. The median time to hepatic progression was 15.4 months, the median response duration was 15 months, and the overall survival from the first TheraSphere® treatment was 14.5 months. The presence of unresectable metastatic lesions in the liver remains a key cause of mortality in patients with colorectal cancer requiring intensive treatment [5].

An expanded analysis was conducted, which included patients from Mulcahy et al. [4], where subsequent outcomes in unresectable hepatic colorectal metastases were reported by Lewandowski et al. in a cohort of two hundred and fourteen (214) patients [6]. All patients were refractory to previous systemic/locoregional therapy. As with Mulcahy et al., decision to treat was determined by a multidisciplinary team of medical/surgical oncologists and interventional radiologists. The median radiation dose to the liver was 122 Gy with no evidence of radiation induced liver disease or gastric ulceration although Grade 4 absolute lymphocyte and ALP toxicities were observed in 5% and 3% of patients respectively. Median overall survival was 43.0 months from diagnosis of primary tumor, 34.6 months from diagnosis of hepatic metastases and 10.6 months from first TheraSphere® treatment. The presence of extrahepatic disease (42%), poor performance status and poor liver function negatively affected survival outcomes following TheraSphere® treatment.

Johns Hopkins Hospital has been an early and active participant in various clinical trials and has an active RE program for the treatment of liver cancer. From July 16, 2001 through February 2015, a total of 363 TheraSphere treatments were performed, with similar procedure volumes since.

We have recently performed an IRB approved study comparing ^{90}Y PET and quantitative bremsstrahlung SPECT (QBSPECT) and a study in HCC to validate the use of MAA imaging and CBCT tumor delineation to provide estimates of ^{90}Y activity distribution in normal organs and liver. Excellent agreement was obtained on a voxel, whole organ, and sub-organ level. This work is published [7].

We have performed 3D dosimetric computations on MAA SPECT and ^{90}Y QBSPECT and PET images. The resulting 3D dose distributions were registered via the CT images. We compared AD estimates in lung, treated normal liver, and tumor volumes from MAA imaging to from ^{90}Y QBSPECT in 20 patients receiving lobar therapy for HCC. VOIs for the normal treated liver and tumor volumes were defined on CBCT (18 patients) or contrast-enhanced MR images (2 patients where CBCT was not available), which were then registered to the nuclear medicine images. Lung VOIs were defined in CT images for the MAA and QBSPECT images. ADs in these 3 regions were computed and compared. For the lung region, we also computed the dose using standard planar imaging methods.

From these data, we observed that the MAA planar imaging overestimated the *lung* dose compared to the estimate from MAA SPECT in 9 out of 10 patients, with an average overestimate by a factor of 4.2 ± 4.3 (range 0.96-12.7). In one patient, the planar estimate of lung dose was 38 Gy, greater than the 30 Gy lung dose limit for TheraSphere, and thus required reducing the administered activity. The MAA SPECT overestimated the lung dose compared to the dose estimated from ^{90}Y

QBSPECT in all cases: the ^{90}Y dose was < 0.1 Gy for 7 out of 10 patients, and the MAA dose was larger than the ^{90}Y dose by factors of 8.9, 32, and 5.2 for the remaining cases. In the patient with a 38 Gy lung dose estimated from MAA planar imaging, the doses from MAA and ^{90}Y SPECT were 14, and 1.57 Gy, respectively. These data justify the use of MAA SPECT instead of planar imaging to estimate the lung dose, and indicate that MAA AD estimates provide a significant margin for error over the actual dose from ^{90}Y. The differences can be explained by the presence of small particles or free Tc (size <15 μm) in the MAA.

Most importantly from the standpoint of being able to predict normal organ dose and therefore provide safe and effective treatment planning, we also compared the tumor and treated normal liver doses estimated from MAA SPECT with those from post-therapy ^{90}Y QBSPECT. The differences in the liver AD ranged from -8 to 6% (mean 1% ± 6%), indicating that the MAA can predict normal liver AD very accurately, even in extreme cases where the correlation is not visually apparent. Moreover, as is consistent with experience from a wide range of experience in all RPTs (refs), the average absorbed dose to the dose limiting normal organ (liver) varied widely from patient to patient indicating the potential for a significant safe increase in potential activity administered (average of 60 %) and consequently a proportionately higher absorbed dose to the tumor and a probable increase in the chance of tumor control (calculated as 99.8 % of tumor control probability vs. 72 % using the tumor control threshold of 235 Gy as established by Garin et al. [8]).

4. Study Procedures

This is an observational treatment use protocol that will provide IRB oversight and documentation of the clinical experience of patients undergoing treatment for metastatic colorectal cancer in the liver using TheraSphere® under an HDE, IRB00078140 / CR00021884. We proposed to enroll 3-5 patients from this clinical treatment group. Study participation involves an additional post-treatment SPECT/CT or PET/CT scan (up to 12 hours post-treatment). Patients will be followed for treatment-related adverse experiences for a minimum of 30 days after each treatment per clinical protocol.

Patients shall be screened to be enrolled and, if eligible, the physician and patient will discuss a standard of care TheraSphere® treatment plan. The patient will be asked to provide consent in accordance with IRB approval.

Prior to initial treatment, standard of care Shunt Study, the ^{99m}Tc MAA SPECT/CT scan of the liver and lungs will be performed using standard institutional practices.

The TheraSphere® dose will be ordered (per standard of care) and initial treatment scheduled. TheraSphere® treatment will be performed in an outpatient setting.

Following treatment, patients will remain at the hospital under medical observation until the physician determines that they can safely be discharged to home. The patient will undergo an additional SPECT/CT or PET/CT scan of the liver and lungs which is not part of the standard of care at up to 12 hours post-treatment. All patients will be evaluated 3-6 weeks post-treatment to assess clinical experience and adverse experiences. Subsequently, patient status will be followed via communication with the referring physician to determine disease status and long term treatment outcome according to standard of care practice.

Patients will have 1-2 outpatient visits for pre-treatment evaluation to determine initial eligibility to receive TheraSphere®, followed by a treatment visit for outpatient delivery of TheraSphere®, and at least 1 follow-up visit 3-6 weeks after initial treatment.

If more than one treatment is given, additional follow-up visits will occur after each treatment following institutional guidelines. Subsequent follow-up contacts will be made with the referring physician. Patients will be asked to provide consent for medical record review after treatment.

No scheduled hospitalizations will be required for the study. Description of the procedure (standard of care) is detailed in previously approved IRB00078140 / CR00021884,

Pre-Treatment Evaluation

The clinician will explain the procedure and treatment options to the patient and, if the patient wishes to proceed with treatment, the patient will indicate their informed consent in accordance with JHU IRB requirements.

Pre-treatment evaluation will include initial screening by history, physical examination, laboratory and diagnostic studies (hepatic angiography and ^{99m}Tc MAA SPECT/CT). A treatment plan will be developed, dosage will be calculated, and the TheraSphere® dose vial will be ordered from Boston Scientific.

Clinical and Laboratory Diagnostic Procedures

A history, physical examination and clinical interview will be completed. The diagnostic laboratory studies usually performed within 30 days of beginning TheraSphere® treatment are:

- Complete blood count with differential and platelet count
- Prothrombin Time/Partial Thromboplastin Time
- Serum Chemistry Panel, including: Electrolytes, BUN, AST, ALT, Creatinine, LDH, Glucose, Alkaline Phosphatase, Albumin and Total Bilirubin; Serum alphafetoprotein level (optional)

Diagnostic Imaging Studies

The following diagnostic radiographic studies may be performed:

- Chest X-Ray: Standard views of the chest may be taken (at discretion of physician)
- Computed Tomography Scanning or Magnetic Resonance Imaging or Cone-beam Computed Tomography or Angiography of the Abdomen/Liver
- ^{99m}Tc MAA SPECT/CT Scan
- Post-therapy ^{90}Y SPECT/CT or PET/CT scan

CT/MR/CBCT/angiography scanning of the liver will be performed and the images used to calculate the appropriate liver volume for TheraSphere® dose determination. Reasonable attempts will be made to use the same imaging modality as that used for pre-treatment for all subsequent evaluations of the patient related to dose determination.

The dose is calculated as described below using the appropriate reference liver volume and mass. Dosimetric techniques for TheraSphere® are discussed in detail in the peer-reviewed literature.[48-51] The imaging scan also is used to document the location and size of the hepatic lesion(s) and vascular anatomy (MRI only) where possible.

Prior to first TheraSphere® treatment, a ^{99m}Tc MAA SPECT/CT scan will be performed to obtain a preliminary assessment of hepatic infusion and any potential extrahepatic shunting or gastrointestinal flow. Lung Shunt Fraction will be determined as the ratio of total lung activity divided by administered activity. If the entire lung cannot be imaged in a single scan, the measured activity concentration in the lungs will be used and scaled to the lung volume.

If gastrointestinal flow is detected, steps will be undertaken (embolization, change in catheter position) to correct this flow, prior to TheraSphere® administration. If gastrointestinal flow cannot be corrected using established angiographic techniques, the patient may not receive TheraSphere® treatment. Only after extrahepatic exposure has been evaluated and the patient deemed to meet eligibility criteria, may TheraSphere® be administered. Comprehensive and exhaustive reviews of the angiographic and technical considerations prior to TheraSphere® have been published.[48-51]

To be eligible to receive TheraSphere® treatment, the potential absorbed dose to the lungs must be <30 Gy (<16.5mCi of injected activity) per single injection, and < 50 Gy for multiple injections. Any uncorrected detectable gastrointestinal flow is a contraindication to TheraSphere® treatment.

Treatment Planning

The principal clinician or Authorized User will formulate the initial treatment plan, indicating the number and sequence of planned TheraSphere® treatments. The clinician will assure that the patient understands the two-stage screening process that is necessary for this treatment procedure. The physician and patient will discuss and agree on a contingency treatment plan, including the option of no treatment, in the event that the patient is found ineligible to receive TheraSphere® after catheter placement. The Treatment Plan may be modified following initial treatment, based on clinical experience and patient response to treatment. Treatment of a second target tissue will be timed to occur within 30-90 days of initial TheraSphere® treatment. Patients whose treatment plan includes subsequent treatment with TheraSphere® must satisfy all applicable exclusion criteria again, prior to treatment.

TheraSphere® Dose Calculation

The most commonly used target dose of TheraSphere®, within the approved dose range of 80-150 Gy, is 110-120 Gy. Depending on the timing of the product order relative to the TheraSphere® production schedule, and the treatment date proposed for the patient, it may be necessary to allow TheraSphere® to physically decay to the appropriate targeted activity before injection.

The amount of radioactivity required to deliver the dose to the selected liver target is calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{ Mass of Selected Liver Target (kg)}]}{49.8[1\text{-}F]0.99}$$

Where F is the fraction of injected activity deposited into the lungs as measured by Tc-99m MAA SPECT, 49.8 is a conversion factor and the 0.99 anticipates a residual activity of 1 %.

In nearly all cases, more than 95% of the glass microspheres are delivered. Calculation of the average dose (Gy) to the treated area delivered after injection uses the following formula:

$$\text{Dose (Gy)} = \frac{49.8[\text{Injected Activity (GBq)}][1\text{-}F][1\text{-}R]}{\text{Mass of Selected Liver Target (kg)}}$$

Where F is the fraction of injected activity deposited into the lungs as measured by Tc-99m MAA SPECT and R is the calculated residual [9].

No blinding, placebo or non-treatment group exists; the research component only includes an additional SPECT/CT or PET/CT 0-12 hours after administration (treatment). The patient may decline the extra scan at any point of the procedure including after administration, which will not affect the therapy. The results of the post-implant scan will not affect the patient therapy.

Data Analysis

We propose to use the data obtained from the 3 patients participating in this study along with data from 17 patients available from a previous IRB-approved study to assess the ability of ^{99m}Tc MAA SPECT/CT images to predict ^{90}Y dose to the liver estimated from post-Therapy ^{90}Y imaging. To do this, the MAA and ^{90}Y images with be reconstructed and quantified to obtain 3D activity distribution images. Tumors and normal liver regions will be delineated with the aid of CBCT and diagnostic CT or MRI images. We will use the average activities in the tumors and normal liver parenchyma obtained in the MAA images to estimate the ^{90}Y activity activity that would be delivered to each region. We will then apply 3D dosimetry methods [10, 11] to calculate the average doses to the tumors and normal liver parenchyma from both the ^{90}Y images and the

estimated ^{90}Y distribution obtained from the SPECT/CT images. We will then compare the dose estimates to these to tumors and normal liver obtained by these two methods.

5. Inclusion/Exclusion Criteria

Inclusion Criteria (per current clinical criteria)

- The Diagnosis of secondary malignancy to the liver for patients who have failed or are intolerant to other systemic or liver directed therapies. *A patient is considered to have failed other systemic or liver-directed therapies when, in the opinion of the referring physician, the patient has progression of disease after receiving standard approved therapies. Specifically, if a patient has failed first line chemotherapy (or the standard approved therapies for secondary malignancy), in the time period designed to assess that particular regimen (at least 30 days), then they may be enrolled on this protocol.A patient is considered to be intolerant to other systemic or liver-directed therapies when, in the opinion of the referring physician, the patient is unable to tolerate appropriate chemotherapy. Patients may have residual toxicity from previous therapies (e.g., neuropathy from oxaliplatin), have performance status such that treatment with systemic therapies would result in excessive toxicity.*
- The histopathology confirmation criterion may be waived in patients with a radiographically identifiable liver mass, known laboratory or clinical risk factors for cancer or elevated tumor markers such as alphafetoprotein (AFP)[47] and clinical findings. Guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) describe in detail the approach and algorithm for diagnosing.
- Patients with a diagnosis of metastatic cancer to the liver
- Liver metastases are unresectable
- Tumor replacement ≤ 70% of total liver volume based on visual estimation by the Investigator
- Tumors are hypervascular based on visual estimation by the Investigator
- Target tumors are measurable using standard imaging techniques
- ECOG Performance Status Score 0 - 2
- Age ≥18 years
- Life expectancy ≥3 months
- >4 weeks since prior radiation, surgery or chemotherapy
- Able to comprehend and provide written informed consent in accordance with institutional and federal guidelines
- At least one month has elapsed since most recent prior cancer therapy with the following exception:
    - Chemotherapy may continue if there is evidence of progression in the liver on treatment providing there is no change in the chemotherapy regimen in the 1 month prior to TheraSphere treatment and that any immediate chemotherapeutic toxicity that could complicate TheraSphere treatment is resolved. In this case, chemotherapy may continue after a minimum of 7 days following TheraSphere treatment for the purpose of controlling extrahepatic disease.
- Patient is willing to participate in the study and has signed the study informed consent

Exclusion Criteria

Patients may not be treated with TheraSphere® if they have any of the following exclusions:

- Any pre-treatment laboratory findings within 15 days of treatment demonstrating liver dysfunction:
  - AST or ALT >5 times UNL
  - Serum creatinine >2.0 mg/dL, unless on dialysis
  - Serum total bilirubin ≥ 2.0 mg/dL
  - Albumin < 2.0 g/dL
  - Any history of hepatic encephalopathy
- Any contraindications to angiography and hepatic artery catheterization such as:
  - History of severe allergy or intolerance to any contrast media, narcotics, sedatives or atropine that cannot be corrected or premedicated
  - Bleeding diathesis, not correctable by usual forms of therapy
  - Severe peripheral vascular disease that would preclude catheterization.
- Evidence of potential delivery of greater than 30 Gy absorbed dose of radiation to the lungs in a single injection, or greater than 50 Gy for multiple injections
- Evidence of pulmonary insufficiency
- Evidence of any detectable ^{99m}Tc MAA flow to the stomach or duodenum, after application of established angiographic techniques to stop or mitigate such flow
- Significant extrahepatic disease representing an imminent life-threatening outcome
- Active uncontrolled infection
- Significant underlying medical or psychiatric illness
- Co-morbid disease or condition that would preclude safe delivery of TheraSphere® treatment or, in the judgment of the physician, place the patient at undue risk
- Pregnancy
- Special Categories of Patients: Not applicable
- Research in Mentally Disabled People: No. All participants or legal guardians will be fully able to give informed consent.

6. Drugs/ Substances/ Devices

TheraSphere® consists of insoluble glass microspheres where ^{90}Y is an integral constituent of the glass. The mean sphere diameter ranges from 20 to 30 μm. Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® is supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vee-bottom vial secured within a 12 mm clear acrylic vial shield. TheraSphere® is available in six activity sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi) and 20 GBq (540 mCi). TheraSphere® is also available in custom dose sizes in increments of 0.5 GBq between 3 GBq and 20 GBq.

TheraSphere® is delivered into the liver tumor through a catheter placed into the hepatic artery. The hepatic artery provides the main blood supply to the tumor in the liver, whereas the portal vein supplies blood to normal liver parenchyma. TheraSphere® is embolized within the tumor and exerts a local beta radiation radiotherapeutic effect with relatively limited concurrent injury to surrounding normal tissue.

Hepatic resection of liver metastases is currently the only potentially curative therapy. Unfortunately, curative resection is possible in less than 20% of those patients with metastases to the liver [4]. Over the past two decades, more frequent screening and the introduction of new anticancer agents has resulted in decreases in the incidence and mortality associated with colorectal cancer, *inter alia*. According to SEER data, the annualized percent change in incidence decreased 2.5% between 1998 and 2008 while the annualized percent change in mortality was negative in every period analyzed between 1978 and 2007.

As an example of secondary malignancy, systemic therapies for CRC include cytotoxic agents (fluoropyrimidines, irinotecan, oxaliplatin) and targeted therapies that inhibit tumor growth (vascular endothelial growth factor and epidermal growth factor targeting agents). The identification of the KRAS biomarker has further refined therapeutic options. Patients with CRC who fail first-line chemotherapy, typically an oxaliplatin based therapies have a poor prognosis. According to a recent study by Peeters et al, patients treated with second-line FOLFIRI have a median PFS of 3.9 months (wild-type KRAS) to 4.9 months (mutant type KRAS). Adding panitumumab was shown to improve median PFS to 5.9 months in wild-type KRAS patients and had no impact on PFS (median 5.0 months) in mutant-type KRAS patients [12].

While CRC metastatic to the liver is considered Stage IV disease, advances in perioperative care, imaging and surgical techniques have supported development of liver-directed therapies which may be used alone, in combination with chemotherapy, or integrated with surgical approaches.

Liver directed radiotherapy using external beam radiotherapy to the liver is limited by the higher sensitivity to radiation of normal liver parenchyma versus tumor and the subsequent risk of radiation induced liver disease. Localized delivery of radiation through radioembolization using ^{90}Y microspheres has shown encouraging results as a well-tolerated treatment with good response rates in an increasing body of literature [13].

7. Study Statistics

We propose to combine the studies acquired here with those from a previous study that included data from 17 patients. Statistical Considerations. The goal is to test whether the pre-therapy estimate of liver dose is within 10% of that of the post-therapy estimates. Based on simulation and phantom experiments, we assume that the standard deviation for ^{90}Y estimates of liver dose is 5%. A sample size of 20 will have 95% power to detect such a difference at a significance level of 0.05.

8. Risks

The medical risk of our study includes an additional SPECT/CT or PET/CT post-administration as well as a SPECT/CT of the pre-therapeutic ^{99m}Tc-MAA. The estimated equivalent dose to the patient from these two scans is on the order of 10-20 mSv or 10-20 mGy. While this may in theory represent an increased stochastic risk of cancer induction, the value must be taken in comparison with the 120 Gy of absorbed dose from the therapy itself, a value ~ 10000 times higher than the absorbed dose from the diagnostic 3D imaging scans; in fact the dose from the scans represent about 0.1 % of the potential error or variability in the dose allowed in the treatment.

Minimization of this risk includes only obtaining one field of view per time point. Also, a low-dose CT scan appropriate for attenuation correction will be performed as part of the of SPECT/CT or PET/CT scans in order to reduce X-ray exposure.

Legal risks include the existence of a patient key on the secure department drive that is encrypted. This list is necessary for recovering clinical data elements needed for study follow-up. After the study, all documents with the patient's name will be destroyed except for the initial consent which will be maintained in a locked cabinet. The consent will be destroyed within one year of death of patient or after 3 years if lost to follow up. There are no financial risks to the participants.

9. Data Safety and Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

10. Benefits

Results from this study could benefit society as they could be used to identify the patients with liver neoplasia who many benefit from personalized dosimetry-based treatment planning for TARE and therefore increased activity and dose to the disease site.

11. Payment and Remuneration

The participants will not be compensated for participation in this study.

12. Costs

The cost for the additional post-implant PET/CT or SPECT/CT scan will be paid for by the investigators. No additional costs will be incurred by the patient for the research component.

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