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STUDY TITLE: Comparison of yttrium-90 absorbed doses using PET/CT versus PET/MR imaging in patients undergoing selective internal radiation therapy for hepatic malignancies

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Title: Comparison of yttrium-90 absorbed doses using PET/CT versus PET/MR imaging in patients undergoing selective internal radiation therapy for hepatic malignancies

Principal Investigator: Ram Gurajala, M.D.

PRINCIPAL INVESTIGATOR SIGNATURE:

Date: 2/4/2020

SUMMARY OF CHANGES

Protocol Date	Section	Change
11/4/2019		Initial IRB approval reviewed on 11/26/19
1/16/2020		Revised protocol (version 1) for Initial IRB approval
2/4/2020		Revised protocol (version 2) for Initial IRB approval
6/10/21		Revised protocol (version 3) Dosimetry and volumetry results from an earlier pilot series of 8 cases (IRB#17-823 Effect of PET/MR Attenuation correction in Y90 dosimetry analysis compared to PET/CT); will be compared to verify their consistency and evaluate the validity of using them interchangeably and will be included in the statistical analysis

PROTOCOL SUMMARY

12 consecutive cases undergoing yttrium-90 radioembolization (Y-90 RE) for hepatic malignancies at our institute are consented to participate at this trial. Within 6 hours after the procedure, the patients undergo PET/CT and PET/MR imaging (less than 1 hour apart) for evaluation of the treatment and software-assisted measurement of yttrium-90 absorbed doses in the tumor and surrounding liver tissue. Dosimetry data acquired from the two imaging modalities from these cases, in addition to the post-Y90 RE dosimetry and volumetry results from an earlier pilot series of 8 cases (IRB#17-823 Effect of PET/MR Attenuation correction in Y90 dosimetry analysis compared to PET/CT; similar protocol design), will be compared to each other to verify their consistency and evaluate the validity of using them interchangeably.

ABBREVIATIONS

CT	Computed Tomography
DSMP	Data and Safety Monitoring Plan
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RDC	Reproducibility Coefficient
RE	Radioembolization
SD	Standard Deviation
SIRT	Selective Internal Radiation Therapy
SPECT	Single Photon Emission Computed Tomography

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1.0 INTRODUCTION

1.1 Selective Internal Radiation Therapy

The liver is one of the most common sites for metastatic diseases. Moreover, primary cancers in the liver are a major global matter of concern, with incidence rates that have increased substantially within the past two decades [1]. Selective internal radiation therapy (SIRT) with yttrium (Y)-90 is a well-established modality for palliative treatment of primary and metastatic liver malignancies and constitutes delivery of radioactive-emitting embolic microspheres through selection of arteries that directly feed the tumor. Radioembolization (RE) through this method achieves prolonged patient survival with limited systemic adverse effects and acceptable safety profile [2, 3].

1.2 Post Y-90 Radioembolization Imaging

Various imaging modalities including single-photon emission computed tomography (SPECT) and positron emission tomography (PET), in combination with computed tomography (CT) or magnetic resonance imaging (MRI), are incorporated as part of standard patient care after Y-90 RE to evaluate the distribution of radionuclide particles within the liver (and elsewhere in the body) and to calculate the radionuclide absorbed doses in the tumors, which in turn would permit optimal planning for continuation of patient's care [4]. Accurate tumor Y-90 dosimetry is crucial for determination of the treatment efficacy and prediction of the response to therapy. In comparison to SPECT, post-Y-90 RE imaging with PET/CT has been proven to serve as a favorable modality for this purpose as it delivers better spatial resolution and higher precision in quantifying tumor absorbed doses. These advantages improve Y-90 RE treatment planning by generating more pertinent dose-response and dose-toxicity data [5]. Hence, Y-90 PET/CT has become the modality of choice for post-Y-90 RE imaging in many centers across the US including our institute. Y-90 PET/MR is another imaging modality that may be performed after SIRT with Y-90 and confers superior soft tissue contrast and determination of the liver/tumor contours, compared to Y-90 PET/CT imaging [6]. For this reason, post-Y-90 RE PET/MR is frequently performed at our institute, encompassing over 200 cases since 2016. Despite this, Y-90 PET/CT still provides a better quantification of PET images, due to the better attenuation correction, and remains as the gold standard method [6]. This necessitates assessment of the validity of dosimetry results acquired by Y-90 PET/MR, in comparison to PET/CT imaging.

1.3 Rationale of Study

In a prior pilot study to compare post-Y-90 RE dosimetry results between PET/CT and PET/MR imaging, the current investigators observed significant inconsistencies

between the two modalities; in other words, tumor absorbed doses were on average 36% (SD = 43%) lower in PET/MR-based calculations than in PET/CT [7]. This resulted in PET/MR software upgrades which predominantly included a few improvements in the attenuation correction as well as the respiratory motion correction methods. In order to validate these PET/MR-based dosimetry upgrades, this protocol was designed including another pilot trial of 8 cases, to compare Y-90 dosimetry data between PET/CT and PET/MR. Given the promising results of the second pilot trial (IRB#17-823 Effect of PET/MR Attenuation correction in Y90 dosimetry analysis compared to PET/CT), the investigators are proposing this study (with similar design) to extend their research on more cases.

2.0 OBJECTIVE

2.1 Primary Objective

To assess the agreement between post-Y-90 RE absorbed doses (Gy) in the liver tumor tissues based on PET/CT versus PET/MR imaging. This objective would permit the comparison of Y-90 tumor absorbed doses, acquired from PET/MR, with the current standard of care PET/CT imaging to verify the data consistency and to validate its application for the prediction of tumor response to treatment. The endpoint for this objective would be the measurement of the reproducibility coefficient (RDC) between the two imaging modalities for post-Y-90 RE absorbed doses (Gy) in the liver tumor tissues (please see the Study Design for further details).

2.2 Secondary Objective

To assess the agreement between post-Y-90 RE absorbed doses (Gy) in the background liver tissues (surrounding tumors), based on PET/CT versus PET/MR imaging. This objective would permit the comparison of Y-90 background liver absorbed doses, acquired from PET/MR, with the current standard of care PET/CT imaging to verify the data consistency and to validate its application for the prediction of dose toxicity. The endpoint for this objective would be the measurement of the RDC between the two imaging modalities for post-Y-90 RE absorbed doses (Gy) in the background liver tissues (please see the Study Design for further details).

3.0 STUDY DESIGN

3.1 Number of Subjects

Upon IRB approval and patient's informed consent, 12 new consecutive cases will be enrolled in the study. The sample size calculation (n = 12) is based on the fact that the

RDC should be $\leq$ 5% for clinical use. The following table summarizes the estimated upper 95% confidence bound for the RDC as a function of the unknown RDC. Based on this table and our expectation that our new technique will have an excellent reproducibility with PET, a sample size of 12 will provide sufficient precision to determine if the RDC with our new technique is near 5%.

Estimated Upper 95% Confidence Bound for RDC

	Magnitude of RDC			
# Cases	RDC=2%	RDC=3%	RDC=4%	RDC=5%
10	3.2	4.8	6.4	8.0
12	3.0	4.5	6.1	7.6
15	2.9	4.3	5.7	7.2

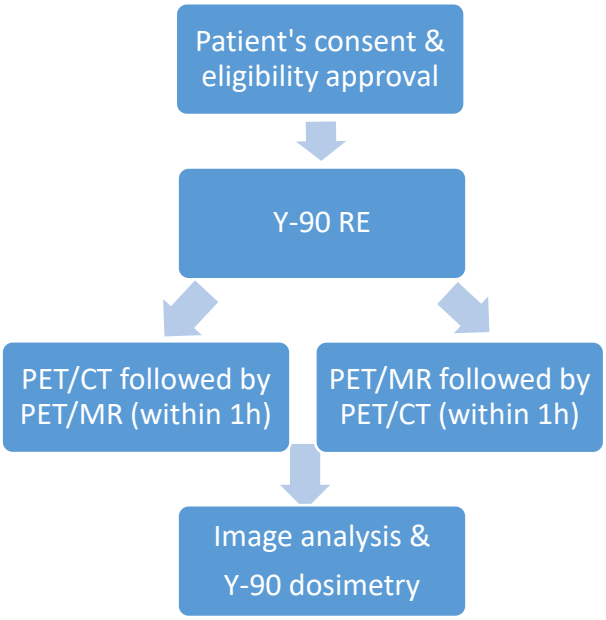
3.2 Study Protocol

The study protocol is outlined in the diagram below. Upon the patient's informed consent and eligibility approval (according to the inclusion/exclusion criteria below) for participation in the trial, they undergo PET/CT (standard imaging) and PET/MR (additional imaging), within 6 hours after SIRT with Y-90 for palliative treatment of the liver malignancy. Patients will be randomized to receive either of the imaging modalities first, based on the availability of the imaging device, and less than 1 hour apart. This limited time threshold allows to ignore the trivial amounts of β^- decay in radionuclide emission that happens after trans-arterial delivery of Y-90 microspheres into the liver, with regards to its half-life of ~64 hours. Upon acquirement and construction of PET/CT and PET/MR images, a software (MIM SurePlan LiverY90) would be utilized for semi-automatic determination of the liver/tumor contours and calculation of the Y-90 absorbed doses (Gy) in the regions of interest (including within tumor and background liver outlines) using the Local Deposition Method.

Dosimetry/volumetry data from the two modalities from these cases, in addition to the results from the pilot cases (IRB#17-823 Effect of PET/MR Attenuation correction in Y90 dosimetry analysis compared to PET/CT ; similar protocol design), will be compared using the Bland Altman method to assess the pattern of differences between dosimetry values and to measure the reproducibility of the methods [8]. The RDC is the minimum difference between the two measurements that can be considered a true difference, with 95% confidence. It will be calculated as 2.77 times the within-subject SD (wSD), where wSD is the square root of the mean variance across the N subjects, and the variance for each subject is calculated from their two dosimetry values [9,10]. In addition, the reproducibility coefficient will also be expressed as a percentage of a subject's PET/CT value of dose, using the within-subject coefficient of variation

(wCV) instead of wSD. An upper 95% confidence bound for the RDC will be constructed using a chi square statistic as the pivotal statistic, as follows:

$2.77 \times \sqrt{N \times \%wCV^2/\chi^2_{M,\alpha}}$, where $\chi^2_{M,\alpha}$ is the αth percentile of the chi square distribution with N degrees of freedom.



3.3 Expected Duration of Subject Participation

The study involves one-time PET/MR imaging in addition to the standard PET/CT imaging, both performed on the same day of the treatment procedure (Y-90 RE). Upon completion of the imaging procedures, the patient's involvement in the study would be completed. The researchers, however, will need to access the patient's medical records to record basic medical information including the patient demographics, diagnosis, and treatment and to analyze the imaging data and dosimetry.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

A) The patient has a liver malignancy and is scheduled for SIRT with Y-90; AND
B) The patient is an adult (18 years or above), self-competent, and able to provide informed consent to participate in the study

4.2 Exclusion Criteria

A) The patient loses competence, has a condition that questions their ability to provide informed consent independently (e.g. cannot communicate in English), or withdraws consent to participate within any time in the study period; OR
B) The patient is not eligible to undergo MRI due to the presence of metal devices or implants in their body; OR
C) Both imaging modalities cannot take place within 6 hours after Y-90 RE; OR
D) Both imaging modalities cannot take place within 1 hour apart from each other

4.3 Inclusion of Women and Minorities

Adult patients who are able to communicate in English efficiently may participate in the study, regardless of their gender, age, race, or ethnic origin.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

6.0 POTENTIAL RISKS

6.1 Adverse effects

The additional PET/MR imaging in this study does not involve any extra radiation to the patient, besides what one would receive as part of the standard protocol during Y-90 RE and PET/CT imaging. There are no known biological risks associated with PET/MRI. A PET/MRI procedure may cause possible anxiety in some individuals, due to the confined space of the testing area resulting in feelings of claustrophobia and the loud banging made by the machine. The patients retain the right to withdraw from participating in the study in such conditions.

Since the MRI is a powerful magnet, patients cannot be scanned if they have certain metal devices in their body. There is also a risk of injury if metal is brought into the imaging room, which may be pulled into the magnet. Patients will be asked to remove any magnetic objects from their clothes and body in order to prevent any injuries. A safety zone is established around the MR scanner to prevent objects containing iron from coming into contact with the scanner.

6.2 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

7.0 RECORDS TO BE KEPT/REGULATORY CONSIDERATIONS

7.1 Data Reporting

The OnCore™ Database would be utilized, as required by the Case Comprehensive Cancer Center, in order to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password. OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study would utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

7.2 Regulatory Considerations

The study would be conducted in compliance with the IRB-approved protocol, HIPAA and ICH guidelines, as well as all applicable federal (including 21 CFR parts 56 & 50), state and local regulations.

7.2.1 Written Informed consent

Provision of written informed consent would be obtained prior to any study-related procedures. The Principal Investigator would ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects would also be notified that they are free to discontinue from the study at any time. The subject would be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form would be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form would be given to the subject. Additionally, documentation of the consenting process would be located in the research chart.

7.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), all study subjects would sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review

Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

7.2.3 Retention of records

The Principal Investigator of the Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records would be destroyed until the Principal Investigator confirms destruction is permitted.

7.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

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