Precision Dosimetry in Yttrium-90 Radioembolization through CT Imaging of Radiopaque Microspheres in a Rabbit Liver Model

E Courtney Henry (✉ courtney.henry@dal.ca)

Dalhousie University

Matthew Strugari

Dalhousie University

George Mawko

Dalhousie University

Kimberly Brewer

Dalhousie University

David Liu

The University of British Columbia

Andrew C. Gordon

Northwestern University

Jeffrey N. Bryan

University of Missouri

Charles Maitz

University of Missouri

Robert Abraham

Dalhousie University

S Cheenu Kappadath

The University of Texas MD Anderson Cancer Center

Alasdair Syme

Dalhousie University

Original research

Keywords: Radioembolization, Yttrium-90, Radiopacity, Microsphere, Dosimetry, PET, CT

Posted Date: August 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-806070/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at EJNMMI Physics on March 21st, 2022. See the published version at <https://doi.org/10.1186/s40658-022-00447-1>.

Precision Dosimetry in Yttrium-90 Radioembolization through CT Imaging of Radiopaque Microspheres in a Rabbit Liver Model

E. Courtney Henry¹, Matthew Strugari^{1,2}, George Mawko^{1,3,4,5}, Kimberly Brewer^{1,2,5,6}, David Liu⁸, Andrew C. Gordon⁹, Jeffrey N. Bryan¹⁰, Charles Maitz¹⁰, Robert Abraham^{5,7}, S. Cheenu Kappadath¹¹, and Alasdair Syme^{1,3,4}

¹ Department of Physics and Atmospheric Science, Dalhousie University, Halifax, NS, Canada

² Biomedical Translational Imaging Centre, Halifax, NS, Canada

³ Department of Medical Physics, Nova Scotia Health Authority, Halifax, NS, Canada

⁴ Department of Radiation Oncology, Dalhousie University, Halifax, NS, Canada

⁵ Department of Diagnostic Radiology, Dalhousie University, Halifax, NS, Canada

⁶ Department of Biomedical Engineering, Dalhousie University, Halifax, NS, Canada

⁷ ABK Biomedical Inc., Halifax, NS, Canada

⁸ School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada

⁹ Department of Radiology, Northwestern University, Chicago, IL, USA

¹⁰ Department of Veterinary Medicine and Surgery, University of Missouri, Columbia, MO, USA

¹¹ Department of Imaging Physics, University of Texas MD Anderson Cancer Centre, Houston, TX, USA

Corresponding Author: Courtney Henry

Email: Courtney.Henry@dal.ca

Abstract

Purpose: To perform precision dosimetry in yttrium-90 radioembolization through CT imaging of radiopaque microspheres in a rabbit liver model, and to compare extracted dose metrics to those produced from conventional PET-based dosimetry.

Materials and Methods: A CT calibration phantom was designed to contain posts having nominal microsphere concentrations of 0.5 mg/mL, 5.0 mg/mL, and 25.0 mg/mL. The mean Hounsfield unit was extracted from the post volumes to generate a calibration curve to relate Hounsfield units to microsphere concentration. A nominal bolus of 40 mg of microspheres was administered to the livers of 8 rabbits followed by PET/CT imaging. A CT-based activity distribution was calculated through the application of the calibration curve to the CT liver volume. Post-treatment dosimetry was performed through the convolution of yttrium-90 dose-voxel kernels and the PET- and CT-based cumulated activity distributions. The mean dose to the liver in PET- and CT-based dose distributions was compared through linear regression, ANOVA, and Bland-Altman analysis.

Results: A linear least-squares fit to the average Hounsfield unit and microsphere concentration data in the calibration phantom confirmed a strong correlation ($r^2 > 0.999$) with a slope of 14.13 HU/mg/mL. A poor correlation was found between the mean dose derived from CT and PET ($r^2 = 0.374$) while the ANOVA analysis revealed statistically significant differences ($p < 10^{-12}$) between the MIRD-derived mean dose and the PET- and CT-derived mean dose. Bland-Altman analysis predicted an offset of 15.0 Gy between the mean dose in CT and PET. The dose within the liver was shown to be more heterogeneous in CT than in PET with an average coefficient of variation equal to 1.99 and 1.02, respectively.

Conclusion: The benefits of a CT-based approach to post-treatment dosimetry in yttrium-90 radioembolization include improved visualization of the dose distribution, reduced partial volume effects, a better representation of dose heterogeneity, and the mitigation of respiratory motion effects. Post-treatment CT imaging of radiopaque microspheres in yttrium-90 radioembolization provides the means to perform precision dosimetry and extract accurate dose metrics used to refine the understanding of the dose-response relationship, which can permit an individualized approach to treatment planning that translates into improved patient outcomes.

Keywords: Radioembolization, Yttrium-90, Radiopacity, Microsphere, Dosimetry, PET, CT

1. Introduction

World-wide, hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer in men and the ninth in women with more than 840,000 new cases each year (1). It is responsible for the third most frequent cause of cancer related deaths and is one of a small number of cancers with a growing rate of incidence, particularly in Europe and North America where there have been historically low rates of incidence (1,2). Although liver transplant or surgical resection are considered the most effective treatments, 95% of patients are diagnosed after the disease has progressed beyond the point where these treatments are an option (3–6). For many of these patients, embolic therapies may prolong life expectancy (5).

Yttrium-90 (^{90}Y) radioembolization (RE) – indicated for primary and metastatic liver cancer – is a radiation-based embolic therapy that has been integrated into clinical practice for more than 20 years (7). In RE, ^{90}Y -labeled microspheres are administered into the hepatic arterial vasculature to preferentially target liver tumours while sparing the surrounding liver parenchyma. This preferential uptake is achieved by exploiting the process of tumour tissue angiogenesis, resulting in tumoural vascular inflow derived exclusively from the hepatic artery while the healthy liver parenchyma receives approximately 80% of its vascular inflow from the portal vein (8). The liver's dual blood supply is exploited to overcome the inherent limitation of external beam radiotherapy – the irradiation of healthy tissue when treating the intended target.

The two commercially available microspheres with FDA and CE approval are TheraSphere® glass microspheres (Boston Scientific Corp., Marlborough, MA, USA) and resin-based SIR-Spheres® microspheres (Sirtex Medical Inc., Woburn, MA, USA). As a therapeutic agent, both microspheres employ ^{90}Y – a pure β^- emitter that decays to zirconium-90 with a physical half-life of 2.67 days (64.1 hours), achieving 95% decay of the radioactivity within 11.5 days (9). Maximum and average β^- energies are 2.28 MeV and 0.93 MeV, respectively, corresponding to a range in water of 11.0 mm and 2.4 mm. The therapeutic range X_{90} in water is 5.4 mm, where X_{90} is defined as the radius of a sphere containing 90% of the absorbed dose (10).

With this localized energy deposition, the microsphere spatial distribution within the tumour plays a critical role in determining the absorbed dose. It has been previously demonstrated that microsphere distributions observed in *ex vivo* tissue samples can be highly heterogeneous with a wide range of microsphere cluster sizes (11–14). Furthermore, microspheres preferentially accumulate in the tumour's periphery and tend to remain localized within the portal tracts of the liver's vasculature (11,15). These combined effects result in a highly heterogeneous dose distribution. To demonstrate, Roberson et al. estimated that in a small tumour nodule, the minimum tumour dose was less than half of the average dose (14). A study performed by Kennedy et al. found that a TheraSphere administration intended to deliver a nominal dose of 150 Gy actually delivered doses between 100 and 8000 Gy, although only a small fraction of the volume received a dose exceeding 1000 Gy

(12). Cremonesi et al. later demonstrated the dose rate around a point source of ^{90}Y varied by approximately five orders of magnitude over a distance of only 2 mm (16).

To facilitate patient-specific estimates of the absorbed dose, post-treatment ^{90}Y PET and bremsstrahlung SPECT (bSPECT) imaging can approximate the ^{90}Y activity distribution. Voxel-based dosimetry formalisms can then be employed to calculate the absorbed dose distribution (17). Accumulated evidence from retrospective dose-response studies in ^{90}Y RE for the treatment of HCC with TheraSphere microspheres suggests a positive correlation between absorbed dose and tumour response, but the range of reported dose thresholds varies by a full order of magnitude (18). Some variance in the data may be attributed to tumour size, follow-up time, response assessment criteria, and the heterogeneity of study design, however, the poor spatial resolution of ^{90}Y PET and bSPECT arguably poses the most significant limitation to accurately quantifying dose thresholds for the prediction of toxicity, response, and survival in ^{90}Y RE (19). The spatial resolution, as measured by the full width at half maximum (FWHM), is reported to lie between 5.0 and 10.0 mm in ^{90}Y PET imaging and between 7.0 and 30.0 mm in bSPECT imaging (20–22). In either case, the resolution is insufficient to accurately estimate the true ^{90}Y activity distribution as the FWHM is consistently greater than the average ^{90}Y β^- emission range (2.4 mm) and orders of magnitude greater than the distance scale (microns) over which changes in microsphere concentration take place (12,13). This limitation results in the blurring of the true ^{90}Y activity distribution, which will diminish variations in the absorbed dose and incorrectly yield a more homogeneous dose distribution. Consequently, there exists an unmet clinical need to provide substantially higher spatial resolution imaging of microsphere distributions to facilitate high accuracy, high precision dosimetry in ^{90}Y RE.

CT-based imaging can provide significantly enhanced spatial resolution imaging relative to PET and bSPECT imaging, but CT-based evaluations of commercial microspheres are not performed as they lack sufficient radiopacity for their visualization to be of clinical use (23,24). Fortunately, a preclinical radiopaque microsphere product called Eye90 microspheres™ has recently been developed (ABK Biomedical Inc., Halifax, NS, Canada). By virtue of the high effective atomic numbers of the compounds within the material composition of these microspheres, they provide substantial radiopacity which permits high-resolution CT imaging to visualize the microspheres' spatial distribution. This accurate portrayal of the microsphere's spatial distribution, and hence ^{90}Y activity distribution, enables precise CT-based dosimetry (25). Furthermore, due to the fast scan time of CT relative to PET, uncertainties attributed to respiratory motion during the PET image acquisition can be effectively eliminated in CT as acquisitions can be performed with a breath hold technique.

Beyond the mean absorbed dose provided by PET and bSPECT dosimetry, CT-based dosimetry can provide accurate measures of dose-volume metrics, such as D_{70} – the minimum dose absorbed by at least 70% of the target volume. Previous

work has shown that the poor spatial resolution of PET and SPECT imaging may provide inaccurate estimates of D_{70} as this metric has been shown to correlate with the voxel size of the imaging modality (25).

The purpose of this study is to perform precision dosimetry in ^{90}Y RE through CT imaging of radiopaque microspheres in a rabbit liver model, and compare extracted dose metrics to those produced from PET-based dosimetry. This is the first study to provide an *in vivo* comparison of PET and CT-based dosimetry in ^{90}Y RE.

2. Materials and Methods

Numerical values are reported as mean $\pm$ standard deviation [minimum, maximum], unless otherwise stated.

2.1 Radiopaque Microspheres

Eye90 microspheres (Eye90) are composed of a proprietary, radiopaque glass composition and are similar in density and size to TheraSphere microspheres (20-30 μm diameter, $\rho = 3.3 \text{ g/cm}^3$). The ^{90}Y in Eye90 was produced through thermal neutron absorption of yttrium-89 embedded within the microsphere's glass matrix. A nominal bolus of 40 mg ($\sim 981,000$ microspheres) was measured for administration to each rabbit. The average microsphere specific activity A_{MS} at the time of administration was $156 \pm 18 \text{ Bq}$ [142, 182].

2.2 CT Calibration Phantom

It has been previously demonstrated that a linear relationship, defined by equation 1, exists between CT Hounsfield units HU and radiopaque microsphere concentration MS_{con} over a clinically relevant range of values,

$$HU = m_{cal} \cdot MS_{con} + b_{cal} \quad 1$$

where m_{cal} and b_{cal} are the slope and intercept (defined below) of the calibration curve, respectively (26). Based on this relationship, a calibration phantom was designed to contain cylindrical posts composed of a tissue-equivalent resin ($Z_{eff} = 6.45$, $\rho = 1.03 \text{ g/cm}^3$) and infused with Eye90 in nominal concentrations of 0.5 mg/mL, 5.0 mg/mL, 25.0 mg/mL. There were 9 posts per microsphere concentration with a post length of 40 mm and varying diameters ranging from 2 to 9 mm in 1 mm increments, with an additional post having a diameter of 15 mm. The central axis of all posts was placed equidistant (100 mm) from the central longitudinal axis and were embedded in the resin background material with a radius of 150 mm, as shown in figure 1(a).

This phantom was imaged with a clinical CT (Celesteion™ PET/CT, Canon Medical Systems, Ōtawara, Japan) using a tube potential of 100 kVp and an exposure of 270 mAs. Images were reconstructed with filtered back projection in a 16.2 cm field-of-view having voxel dimensions of 0.313 mm x 0.313 mm x 2.000 mm. An axial CT slice of the phantom shown in figure 1(b) and is displayed with a voxel intensity range of -100 to 200 HU. Within the MIM Software platform v6.9.4 (MIM Software Inc., Cleveland, OH, United States), structures were created for all 27 posts based on the known geometry of the phantom. Segmented post structures were reduced by a 1 mm radial margin and 5 mm longitudinal margin to reduce partial volume effects between the background-post and background-air interfaces, respectively. The 2 mm-diameter post segmentations were not reduced by the 1 mm radial margin as this would eliminate the structures entirely. Instead, they were reduced to a 1 mm-diameter cylinder centered on the post's central longitudinal axis. An additional cylindrical structure with a 30 mm diameter was segmented in the center of the background region to quantify the intensity of a uniform volume void of microspheres. All segmented structures within the calibration phantom are shown in figure 1(c).

Figure 1: (a) Image of the calibration phantom overlaid with physical dimensions. (b) Axial CT slice [-100 to 200 HU] of the calibration phantom with segmented structures for a background region (magenta) and three microsphere concentrations: 0.5 mg/mL (green), 5.0 mg/mL (red), and 25.0 mg/mL (blue). (c) Segmented structures in the calibration phantom.

The mean HU was extracted from each structure and a calibration curve based on equation 1 was determined through a linear least-squares fit of the HU and MS_{con} data. The slope m_{cal} was extracted from the fit while the intercept b_{cal} was calculated independently for each rabbit according to equation 2.

$$b_{cal} = \mu_{bkg} + 1.645\sigma_{bkg}$$

Here, μ_{bkg} and σ_{bkg} are the mean and standard deviation, respectively, of voxel values in a non-embolized background region L_{bkg} within each rabbit liver to account for HU variations in the liver parenchyma between rabbits. The factor 1.645 is the Z-score for a one-sided standard normal distribution with a false positive detection rate of $\alpha = 0.05$. As the voxel values within μ_{bkg} were normally distributed, voxels with $HU > b_{cal}$ have a 95% probability of containing Eye90.

To produce a CT-based ^{90}Y activity distribution A_{CT} with units of Bq, equation 1 was solved for MS_{con} and multiplied by three scalar factors: the number of microspheres per milligram MS_{mg} , the microsphere's specific activity A_{MS} measured at the time of administration, and the CT voxel volume V_{CT} , as shown in equation 3.

$$A_{CT} = MS_{con} \cdot [MS_{mg} \cdot A_{MS} \cdot V_{CT}] \quad 3$$

Theoretically, the administered ^{90}Y activity A_0 should be recovered by summing A_{CT} over the segmented rabbit liver volume L . A recovery coefficient RC_{CT} was defined as the ratio of this sum to A_0 , expressed as a percentage and shown in equation 4.

$$RC_{CT} = 100 \cdot \left[\frac{\sum_L A_{CT}}{A_0} \right] \quad 4$$

For comparison, equation 4 was applied to the PET-derived activity distribution A_{PET} for two structures, L and L_{shell} , where L_{shell} is defined as L plus a 1 cm isotropic margin. The corresponding recovery coefficients are RC_{PET} and RC_{PET}^{shell} , respectively.

2.3 Rabbit Liver Model

The University of Missouri Animal Care and Use Committee approved the animal protocol (#9786) whose data were analyzed for this study. Eight White New Zealand rabbits were included in this study (5 male, 3 female) weighing an average of 3.3 ± 0.2 kg [3.0, 3.5]. Rabbits are subsequently referred to as R01 through R08.

Prior to administration, each rabbit was induced with ketamine and dexmedetomidine then maintained on isoflurane and oxygen by mask. Eye90 was administered into either the left or proper hepatic arteries of the liver via a 2.4 Fr Progreat microcatheter. The average whole liver volume was 79 ± 11 mL [65, 97] and the average administered activity was $A_0 = 144.2 \pm 17.4$ MBq [128.1, 171.0] after accounting for residual activity within the administration equipment, where the average residual activity was 8.9 ± 2.0 MBq [6.0, 12.9]. The lung shunt fraction was expected to be negligible based on results from

pathologic studies of a rabbit VX2 liver tumour model following the administration of iron oxide nanoparticles (27). In this study, both intra-procedural fluoroscopic imaging and post-procedural PET imaging verified microsphere deposition only within L .

2.4 Post-Treatment Imaging

Following microsphere administration, each rabbit was imaged with a time-of-flight (TOF) PET/CT scanner (Celesteion™ PET/CT, Canon Medical Systems, Ōtawara, Japan). The radioisotope ^{90}Y was selected for the PET acquisition. Data was acquired using 4 overlapping bed positions with 7 minutes/position. The lower and upper energy level discriminators were set to 435 keV and 650 keV, respectively. Prior to reconstruction, sinograms were corrected for scatter, randoms, and attenuation. Images were reconstructed with the ordered subset expectation maximization algorithm using 3 iterations and 10 subsets in a $128 \times 128 \times 240$ matrix having isotropic voxel sizes of 2.039 mm x 2.039 mm x 2.039 mm. Postfiltering of reconstructed images was performed with a 4 mm FWHM Gaussian filter.

Following the PET/CT acquisition, an additional four-phase CT was acquired with acquisition parameters set to match the parameters used during CT imaging of the calibration phantom. CT scans included a baseline unenhanced, arterial, portal, and delayed venous phase. Within MIM, the liver volume L was contoured using arterial phase CT to provide maximum contrast between liver parenchyma and surrounding soft tissue. The second structure L_{shell} was generated by isotropically extending L by a 1.0 cm margin. This margin was chosen to account for the reduced PET spatial resolution relative to CT as well as perceived ^{90}Y activity outside of L resulting from respiration, which was shown during intra-procedural angiographic imaging to displace the rabbit livers by a maximum of 1.0 cm in the cranial-caudal direction. A third structure B was generated around the exterior of the rabbit body. In the unenhanced CT, a final structure L_{bkg} was generated in a non-embolized, homogeneous background region of the liver to account for HU variations in the non-embolized liver parenchyma between rabbits. In figure 2, all structures in R03 are visible in a baseline, unenhanced axial CT slice with a voxel intensity range of -100 to 200 HU.

Figure 2: Baseline unenhanced axial CT slice [-100 to 200 HU] of R03 following the administration of Eye90 showing four structures: the rabbit's body B (yellow), the liver L (blue), the liver extended by an isotropic 1 cm margin L_{shell} (red), and the non-embolized, homogeneous background region L_{bkg} (magenta).

2.5 Dosimetry

2.5.1 MIRD

Treatment planning for commercially available TheraSphere microspheres is based on a MIRD model that assumes a uniform ^{90}Y activity distribution within a target volume (28). In this model, the mean dose D_{MIRD} to a target volume is defined in equation 5.

$$D_{MIRD} = \frac{A_0 \cdot 50 \cdot (1 - R)}{M} \quad 5$$

Here, A_0 is the administered ^{90}Y activity in GBq, M is the mass of the target in kg, and R is the fractional residual activity. To serve as a reference for PET- and CT-based dosimetry, D_{MIRD} was calculated for each rabbit liver given R , A_0 , the treated liver volume, and an assumed liver density of 1.03 g/mL.

2.5.2 Convolution

Pathohistological studies performed on explanted human livers following ^{90}Y RE demonstrate a highly heterogeneous *in vivo* microsphere distribution (12,13,29). Currently, no clinical imaging modality is capable of resolving individual microspheres, so all relevant imaging methods present a reduced resolution approximation of the true ^{90}Y activity distribution. Within the constraints of this limitation, dose-voxel kernel (DVK) convolutional dosimetry can be used to calculate the dose distribution based on a heterogeneous ^{90}Y activity distribution. The dose distribution D can be determined through the convolution of a cumulated activity distribution $\tilde{A}$ with a spatially invariant DVK, as described in equation 6.

$$D = \tilde{A} \otimes \text{DVK} = \sum_{x'} \sum_{y'} \sum_{z'} \tilde{A}(x', y', z') \cdot \text{DVK}(x - x', y - y', z - z') \quad 6$$

As microspheres are permanent implants, it is unnecessary to image at multiple time points post-administration to determine the cumulated activity. Instead, $\tilde{A}$ can be calculated using equation 7,

$$\tilde{A}(x', y', z') = \int_0^\infty A(x', y', z', t) e^{-\lambda t} dt = \frac{A(x', y', z')}{\lambda} = \tau A(x', y', z') \quad 7$$

where λ is the decay constant and τ is the mean lifetime of ^{90}Y . The convolution of $\tilde{A}$ and DVK was performed in the frequency domain using the fast Fourier transform. The resulting PET- and CT-based dose distributions are subsequently referred to as DD_{PET} and DD_{CT} , respectively. Dosimetry calculations were performed in MATLAB R2020b (MathWorks Inc., Natick, MA, United States).

2.5.3 Dose-Voxel Kernels

The DVKs in this study were calculated through simulations of ^{90}Y radiation transport in a voxelized sphere of water with the GATE v9.0 Monte Carlo toolkit encapsulating Geant4 10.06.p01 (30). Physics processes were enabled according to the standard electromagnetic physics list option 4 and electron transport was performed with an energy cutoff of 1 keV. The DVKs were calculated specific to voxel sizes of A_{CT} and A_{PET} , referred to as DVK_{PET} and DVK_{CT} , respectively. Prior to each simulation, a ^{90}Y source was uniformly distributed within the origin voxel of a spherical water phantom where 40 million histories were set to decay. Voxels whose center of mass was ≤ 25 mm from the origin were assigned to water and the remaining voxels were set to air. From the simulation output, the mean absorbed dose per decay was calculated in each voxel. Voxels whose center of mass was > 25 mm were masked to zero to ensure convolution with spherically symmetric DVKs.

2.5.4 Statistical Analysis

Dosimetric evaluations were carried out through a comparison of standard dose metrics including the median dose D_{med} , maximum dose D_{max} , mean dose D_{μ} , standard deviation σ , and coefficient of variation (COV) defined as σ/D_{μ} . Cumulative dose-volume histograms (cDVHs) were calculated to determine D_{70} . The mean dose D_{μ} across all rabbits was compared between DD_{PET} and DD_{CT} through linear regression, ANOVA, and Bland-Altman analysis. For DD_{CT} , D_{μ} was calculated for the structure L . For DD_{PET} , D_{μ} was calculated for the structure L_{shell} to account for reduced spatial resolution and respiratory motion during PET image acquisition.

3. Results

3.1 CT Calibration Phantom

In figure 3, the mean HU is given as a function of post diameter for all three microsphere concentrations within the phantom. The data show that the mean HU is independent of the post diameter for diameters > 2 mm.

Figure 3: The mean Hounsfield unit within post structures as a function of post diameter for the three microsphere concentrations within the CT calibration phantom – 0.5 mg/mL, 5.0 mg/mL, and 25.0 mg/mL. Error bars represent the standard deviation of the voxel values within a post.

A least-squares linear fit presented in figure 4 shows a strong correlation ($r^2 > 0.999$) between HU and MS_{con} with upper and lower 95% prediction intervals (PIs) defined by the dashed lines. The slope is $m_{cal} = 14.13$ with 95% confidence intervals (CIs) between 13.14 and 15.12. For display purposes, data were offset such that $\mu_{bkg} = 0$.

Figure 4: A calibration curve derived from the analysis of the calibration phantom. The coefficient of determination is $r^2 \geq 0.999$. Voxel values were extracted for the 15 mm-diameter posts only.

The microsphere concentration MS_{con} within the liver L was determined using equation 1 with $m_{cal} = 14.13$ and b_{cal} specific to each rabbit according to equation 2. Rabbit liver backgrounds μ_{bkg} varied by 40.6 HU with a range of 69.2 to 109.9 HU, while σ_{bkg} was relatively constant across all rabbits. Values for μ_{bkg} , σ_{bkg} , and b_{cal} are reported in table 1.

Rabbit Index	$\mu_{bkg} \pm \sigma_{bkg}$ (HU)	b_{cal} (HU)	A_0 (MBq)	A_{CT} [95% CI] (MBq)	A_{PET} (MBq)	A_{PET}^{shell} (MBq)	RC_{CT} (%)	RC_{PET} (%)	RC_{PET}^{shell} (%)
R01	99.1 ± 5.6	110.0	132.4	122.6 [114.6 – 131.9]	93.5	138.4	92.6	70.6	104.6
R02	69.2 ± 3.0	75.1	171.0	119.8 [111.9 – 128.8]	124.3	176.1	70.1	72.7	103.0
R03	84.4 ± 3.7	91.7	155.9	141.9 [132.6 – 152.6]	86.5	143.2	91.1	55.5	91.9
R04	103.8 ± 4.2	112.1	128.1	117.9 [108.7 – 126.8]	51.4	81.9	92.1	40.1	63.9
R05	96.5 ± 3.3	102.9	133.7	132.5 [123.8 – 143.9]	99.9	144.8	99.1	74.7	108.3
R06	109.9 ± 3.8	117.2	171.0	158.2 [147.9 – 171.5]	109.9	164.6	92.6	64.3	96.2
R07	105.4 ± 4.0	113.1	131.6	119.2 [110.4 – 128.2]	103.3	145.0	90.6	78.5	110.2
R08	94.8 ± 4.9	104.3	130.2	100.8 [91.7 – 108.4]	61.5	101.4	77.4	47.2	77.9

Table 1: Average Hounsfield units, calibration curve intercepts, activity parameters, and recovery coefficients for all rabbits.

3.2 Activity Distributions

The CT recovery coefficient RC_{CT} was equal to 70.1% in R02 and 77.4% in R08. In the remaining six rabbits, it was found that $RC_{CT} \geq 90.0\%$ while the average RC_{CT} across all eight rabbits was $88.2 \pm 8.9\%$ [70.1, 99.1]. There was more variation in RC_{PET} with an average of $62.9 \pm 13.0\%$ [40.1, 74.7], although only R02 had A_{PET} within the 95% CIs of A_{CT} . Within L_{shell} , the recovery coefficient RC_{PET}^{shell} had an average of $94.5 \pm 15.1\%$ [63.9, 110.2] and R03, R06, and R08 had A_{PET}^{shell} within the 95% CIs of A_{CT} . Activity parameters (A_0 , A_{CT} , A_{PET} , A_{PET}^{shell}) and recovery coefficients (RC_{CT} , RC_{PET} , RC_{PET}^{shell}) are reported in table 1.

3.3 Dose-Voxel Kernels

The absorbed dose per decay in the central voxel of DVK_{CT} and DVK_{PET} was 2.21×10^{-8} Gy/Decay and 3.55×10^{-9} Gy/Decay, respectively. Both DVK_{CT} and DVK_{PET} had uncertainties $\leq 0.01\%$ in the central voxel. A 3D surface plot and 2D cross-section through the central voxel are shown for DVK_{CT} in figures 5(a, b). The analogous plots for DVK_{PET} are shown in figures 5(c, d). The vertical axis limits in the surface plots of figures 5(a, c) share the same maximum to emphasize differences in the magnitude of the central voxel as a result of discrete sampling.

Figure 5: (a) 3D surface plot through the central voxel in the CT dose-voxel kernel DVK_{CT} . (b) 2D cross section through the central voxel in the CT dose-voxel kernel DVK_{CT} . (c) 3D surface plot through the central voxel in the PET dose-voxel kernel DVK_{PET} . (d) 2D cross section through the central voxel in the PET dose-voxel kernel DVK_{PET} .

3.4 Dose Distributions

For R05, the dose distribution DD_{CT} is shown in figures 6(a-c) and DD_{PET} is shown in figures 6(d-f). For R06, DD_{CT} is shown in figures 7(a-c) while DD_{PET} is shown in figures 7(d-f). Dose distributions are overlaid on an axial CT slice with a voxel intensity range of -100 to 200 HU. Rabbits R05 and R06 are presented as they qualitatively represent the worst and best agreement between DD_{CT} and DD_{PET} . Both dose distributions are displayed with a dose range between 50 and 500 Gy.

In figures 6(a-c), from a qualitative perspective, DD_{CT} appears to contain significant dose gradients and is highly correlated with the radioembolized vasculature as it was derived from the radiopaque microsphere distribution itself. In figures 6(d-f), the corresponding PET-based dose distribution DD_{PET} demonstrates a clear discordance with multiple regions containing radioembolized vasculature. Furthermore, DD_{PET} is more homogeneous with a COV of 0.98 relative to 1.63 in DD_{CT} . At the intersection of the red crosshair in figure 6, there is an absolute dose difference of 134.3 Gy between DD_{PET} and DD_{CT} .

In figure 7(a-f), the dose distributions DD_{PET} and DD_{CT} in R06 share more correspondences than in R05, although DD_{CT} is mostly confined within L while DD_{PET} shows dose spilling beyond L , thereby predicting a low dose to the surrounding soft tissue. This may be attributed to respiratory motion due to the longer scan duration in PET imaging. At the intersection of the red crosshair in figure 7, the absolute dose difference is 1411.2 Gy between DD_{PET} and DD_{CT} . Quantitative dose metrics from all rabbits are reported in table 2.

Figure 6: (a-c) Axial, sagittal, and coronal views of the CT-based dose distribution DD_{CT} in R05 overlaid on an axial CT [-100 to 200 HU]. (d-f) Axial, sagittal, and coronal views of the PET-based dose distribution DD_{PET} in R05 overlaid on an axial CT [-100 to 200 HU].

Figure 7: (a-c) Axial, sagittal, and coronal views of the CT-based dose distribution DD_{CT} in R06 overlaid on an axial CT [-100 to 200 HU]. (d-f) Axial, sagittal, and coronal views of the PET-based dose distribution DD_{PET} in R06 overlaid on an axial CT [-100 to 200 HU].

Rabbit	Modality	Structure	D_{med}	D_{max}	D_{μ}	σ	COV	D_{70}
R01	CT	L	5.4	1124.3	42.0	78.9	1.9	0.8
		L _{shell}	0.0	1124.3	10.9	42.9	3.9	0.4
		B	0.0	1124.3	3.5	24.9	7.1	0.3
	PET	L	36.7	372.0	65.3	66.0	1.0	11.3
		L _{shell}	6.0	372.0	24.3	44.7	1.8	2.2
		B	1.6	372.0	8.9	27.3	3.1	1.1
R02	CT	L	9.6	1155.8	32.6	57.8	1.8	1.8
		L _{shell}	0.0	1155.8	9.2	33.2	3.6	0.4
		B	0.0	1155.8	3.1	19.6	6.4	0.3
	PET	L	53.3	309.0	68.3	63.0	0.9	16.4
		L _{shell}	9.3	309.1	27.3	44.4	1.6	3.7
		B	1.9	309.0	10.2	27.8	2.7	1.1
R03	CT	L	2.6	1585.5	32.5	84.7	2.6	0.9
		L _{shell}	0.0	1585.5	10.5	48.2	4.6	0.4
		B	0.0	1585.5	4.5	31.8	7.2	0.3
	PET	L	15.9	345.0	42.0	55.0	1.3	10.3
		L _{shell}	8.2	345.0	21.3	37.7	1.8	5.3
		B	3.1	345.0	10.4	25.8	2.5	2.0
R04	CT	L	14.3	754.8	41.9	68.3	1.6	4.3
		L _{shell}	0.0	754.8	11.3	39.0	3.4	0.2
		B	0.0	754.8	3.9	23.5	6.0	0.1
	PET	L	23.4	266.0	36.9	36.3	1.0	15.4
		L _{shell}	8.5	266.0	15.8	23.8	1.5	6.1
		B	3.7	266.0	7.4	15.0	2.0	2.0

R05	CT	L	2.9	1812.3	38.4	96.3	2.5	0.8
		L _{shell}	0.1	1812.3	16.4	64.3	3.9	0.4
		B	0.0	1812.3	3.7	31.0	8.4	0.3
	PET	L	21.7	389.0	58.5	66.0	1.1	9.4
		L _{shell}	6.5	389.3	22.7	43.0	1.9	2.1
		B	1.6	389.0	9.0	27.1	3.0	1.0
R06	CT	L	13.6	1375.6	49.7	91.2	1.8	3.3
		L _{shell}	0.0	1375.6	13.5	50.5	3.7	0.5
		B	0.0	1375.6	4.4	29.7	6.7	0.3
	PET	L	67.5	337.0	72.0	54.2	0.8	39.3
		L _{shell}	9.9	336.8	28.4	41.3	1.5	4.6
		B	1.9	337.0	10.5	26.2	2.5	1.0
R07	CT	L	6.1	1005.1	30.8	63.2	2.0	1.1
		L _{shell}	0.0	1005.1	9.1	36.1	4.0	0.2
		B	0.0	1005.1	3.2	21.9	6.8	0.2
	PET	L	30.6	316.0	54.5	55.0	1.0	12.4
		L _{shell}	6.5	316.4	22.1	38.5	1.7	3.4
		B	1.9	316.0	8.8	24.5	2.8	1.2
R08	CT	L	11.8	966.2	30.2	49.1	1.6	4.0
		L _{shell}	0.1	966.2	8.3	27.7	3.3	0.2
		B	0.0	966.2	3.5	18.5	5.3	0.2
	PET	L	22.5	304.0	39.9	41.2	1.0	11.8
		L _{shell}	7.7	304.4	16.7	27.2	1.6	5.0
		B	3.2	304.0	8.4	18.6	2.2	2.0

Table 2: Dose metrics for all structures within the CT-based dose distribution DD_{CT} and the PET-based dose distribution DD_{PET} across all rabbits. All values are in units of Gy except for the unitless COV.

The results from linear regression are shown in figure 8(a) and results from Bland-Altman analysis are shown in figure 8(b). Linear regression reveals a poor correlation with a coefficient of determination of $r^2 = 0.374$ between D_μ in DD_{CT} and in DD_{PET} . The slope of the curve is 0.586 with 95% CIs between 0.482 and 0.693. Bland-Altman analysis predicts a mean offset of 15.0 Gy between D_μ in DD_{CT} and in DD_{PET} with 95% CIs between 1.8 Gy and 28.2 Gy.

Figure 8: (a) Linear regression analysis with 95% confidence intervals (dashed) and identity line (dotted) for the mean dose D_μ in the CT-based dose distribution DD_{CT} and in the PET-based dose distribution DD_{PET} . (b) Bland-Altman analysis with 95% confidence intervals (dashed).

Figure 9 shows a box-and-whisker plot of D_μ from DD_{CT} and DD_{PET} , as well as the MIRD-derived dose D_{MIRD} . The data indicate a larger dispersion in D_μ for DD_{CT} relative to DD_{PET} . Median values for PET, CT and MIRD are 22.5 Gy, 35.5 Gy, and 90.0 Gy, respectively, with interquartile ranges between 19.0 and 25.5 Gy, 31.5 and 42.0 Gy, and 79.5 and 96.5 Gy, respectively. Results from ANOVA indicate D_{MIRD} and D_μ from DD_{CT} and DD_{PET} are all significantly different with $F(2,21) = 113.2$, $p = 5.65 \times 10^{-12}$. If the absorbed dose is averaged over every constituent voxel of the dose matrices DD_{CT} and DD_{PET} , the discrepancy in D_μ is resolved. In this case, the average difference in D_μ between DD_{CT} and DD_{PET} is only 1.6 ± 0.2 Gy [1.31, 1.95].

Figure 9: Box-and-whisker plot for the mean dose D_μ across all rabbits extracted from the CT-based dose distribution DD_{CT} , the PET-based dose distribution DD_{PET} , and D_{MIRD} . The red line represents the median value, the blue box contains data between the 25th and 75th percentiles, and the black whiskers extend to the most extreme data points that are not considered outliers.

3.5 Dose-Volume Histograms

Shown in figure 10 are cDVHs in L and L_{shell} for all rabbits. The broader shoulder of the cDVH curves for DD_{PET} indicates a bias toward lower doses relative to DD_{CT} . The long tail of the liver cDVH derived from DD_{CT} implies that a small fraction of volume L received an exceedingly high dose, with the highest dose in R05 greater than 1800 Gy. However, maxima never exceed 389 Gy in DD_{PET} . In most cases, there is better agreement in the cDVH curves of L for DD_{CT} and L_{shell} for DD_{PET} .

Figure 10: Cumulative dose volume histograms (cDVHs) for L and L_{shell} across all rabbits.

4. Discussion

4.1 CT Calibration Phantom

The calibration curve used to determine the microsphere concentration within the rabbits was derived from an analysis of the 15 mm-diameter posts only, despite the presence of radioembolized vasculature with vessel diameters < 15 mm. An analysis of the 3 to 15 mm-diameter posts in the calibration phantom shows that m_{cal} is independent of the post diameter ($14.01 \leq m_{cal} \leq 14.26$) as demonstrated in figure 11(a). The adjacent scatter plot in figure 11(b) shows that the 2 mm-diameter post ($m_{cal} = 11.63$) has a slope outside the 95% CIs of the slopes for the remaining posts, likely due to partial volume effects.

Figure 11: (a) Calibration curves derived for all post sizes within the calibration phantom. (b) Calibration curve slope as a function of post diameter with error bars representing 95% confidence intervals.

To justify the use of m_{cal} for vessels with diameters ≤ 2 mm, additional contours were drawn around the 2 mm-diameter post containing 25.0 mg/mL in an attempt to recover the nominal mass of Eye90 within the post. Figure 12(a) shows the recovered mass in the post as a function of an expanding radial shell thickness up to ~ 1 mm and figure 12(b) shows the placement of the shells relative to the true post boundary. The data indicate that, despite the use of m_{cal} derived exclusively from the 15 mm-diameter posts, the nominal mass of Eye90 within the smallest post can still be recovered within 3%. This suggests that diffusion of HU enhancement to surrounding voxels, in part due to CT image acquisition and reconstruction parameters, may introduce additional blurring of the dose over small distance scales (100% of the microsphere mass is recovered within a 0.85 mm-thick shell), but the total microsphere quantification could be highly accurate.

Figure 12: (a) The microsphere mass in the 2 mm-diameter post with a microsphere concentration of 25.0 mg/mL as a function of contour shell thickness. The nominal mass of Eye90 within the contour is represented by the dashed horizontal line. (b) Axial CT slice [-50 to 400 HU] of the 2 mm-diameter post with a microsphere concentration of 25.0 mg/mL. The red contours represent extended shell thicknesses.

In figure 6 and figure 7, many high intensity regions are clearly larger in cross sectional area than the equivalent area of the 2 mm-diameter post, further suggesting the impact of these partial volume effects may not be clinically consequential. This can be verified by the similar values for RC_{CT} and RC_{PET} reported in table 1. An experimental calibration phantom featuring conical inserts that taper to a point is under development to further explore the dependence of the calibration curve slope on diameters ≤ 2 mm.

4.2 Minimum Detectable Activity

An alternative approach in the development of CT calibration curves would require pre- and post-CT imaging of a liver tumour before and after microsphere administration to determine a relative HU enhancement, ΔHU . This approach was not taken in this work as respiratory motion artifacts produced undesirable results following image co-registration with the post-treatment CT. Human patients can perform breath holds during their pre- and post-treatment CT to reduce these image discrepancies. However, we can still apply the ΔHU calibration approach to the calibration phantom in an effort to determine a theoretical limit of detection (LOD_{HU}), as described by the Clinical and Laboratory Standards Institute (31) and previously implemented in determining the detectable iodine concentrations within anthropomorphic phantoms (32).

If the population of voxels within the background is normally distributed with a mean voxel value $\mu_{bkg_phant} = 0$ (following the ΔHU calibration approach) and a standard deviation σ_{bkg_phant} , the limit of blank (LOB_{HU}) is the voxel value found when replicates of μ_{bkg_phant} are repeatedly measured, and is defined in equation 8.

$$LOB_{HU} = \mu_{bkg_phant} + 1.645\sigma_{bkg_phant} \quad 8$$

The LOD_{HU} is the lowest microsphere concentration to be reliably distinguished from the LOB_{HU} , and is determined measuring replicates of a sample known to contain a low microsphere concentration (0.5 mg/mL), as defined in equation 9.

$$LOD_{HU} = LOB_{HU} + 1.645\sigma_{0.5} \quad 9$$

We apply the calibration curve parameters to find LOD_{HU} in terms of microsphere concentration, $LOD_{mg/mL}$ using equation 10.

$$LOD_{mg/mL} = \frac{LOD_{HU} - b_{cal}}{m_{cal}} \quad 10$$

The minimum detectable ^{90}Y activity concentration from CT imaging MDA_{CT} can be determined from MS_{mg} , A_{MS} , and $LOD_{mg/mL}$, as shown in equation 11.

$$MDA_{CT} = LOD_{mg/mL} \cdot MS_{mg} \cdot A_{MS} \quad 11$$

Given $MS_{mg} = 24,526$ MS/mg, the average specific activity of $A_{MS} = 156$ Bq, and $LOD_{mg/mL} = 0.22$ mg/mL, equation 11 yields $MDA_{CT} \approx 0.84$ MBq/mL. The corresponding value in TOF ^{90}Y PET imaging has previously been estimated as $MDA_{PET} = 1.0$ MBq/mL for small lesions (33). We can apply equation 5 to determine the corresponding dose in a voxel volume given $A_0 = MDA_{CT} \cdot V_{CT}$, $M = 1.03$ g/mL $\cdot V_{CT}$, and $R = 0$. For a single PET voxel, the MIRD dose corresponding to MDA_{PET} is 49 Gy, while the MIRD dose for a single CT voxel is 40 Gy. These threshold dose values justify the lower limit of the dose distribution color bar in figure 6 and figure 7 and are also well below the estimated dose threshold required to produce a therapeutic response. This implies that CT is not inferior to PET in terms of detectable activity and dose levels while still being

capable of producing more realistic heterogeneous dose distributions. The value of MDA_{CT} also suggests that CT-based dosimetry will be sensitive enough to characterize regions of the target volume that may be at risk for disease progression. Accurately assessing the tumour coverage is essential as low dose regions correlate with reduced local control and an increased probability of local recurrence (34).

4.3 Dose Discrepancies

Since CT and PET imaging were performed 30 minutes apart in this study, differences between DD_{CT} and DD_{PET} cannot be attributed to changes in hepatic vascularization, catheter positioning, or flow characteristics between macroaggregates and microspheres, as is the case when comparing dose distributions derived from ^{90}Y PET imaging and technetium-99m aggregated albumin (^{99m}Tc -MAA) SPECT imaging (19,35). Instead, dose discrepancies can be attributed to imaging modality-specific characteristics.

4.3.1 PET

The chief limitations in ^{90}Y PET imaging result from the low positron fraction (~ 32 ppm). At very low counts, PET images are noisy, and the resulting scatter correction might lead to significant under or overestimation of the scatter contribution (36). Moreover, bremsstrahlung photons and prompt gammas can result in a very high fraction of random coincidences when imaging ^{90}Y . Corrections for scatter and randoms generate noise in the true coincidence sinogram of count-deprived images, with the potential for a large fraction of negative counts. Reconstruction algorithm positivity constraints truncate negative values which can cause an overestimation of ^{90}Y activity due to a positive bias in low or zero activity regions in the reconstructed image (36).

An additional limitation lies in the choice of scintillator material. Most modern TOF PET scanners utilize lutetium-based scintillators, such as cerium-doped lutetium oxyorthosilicate LSO(Ce) or cerium-doped lutetium-yttrium oxyorthosilicate LYSO(Ce). Although these have desirable characteristics in terms of temporal resolution, light output, and detection efficiency, the presence of naturally occurring radioisotope lutetium-176 produces undesirable intrinsic background counts within the scintillator that can reduce quantitative accuracy in the case of low counts and a high randoms fraction (37).

Furthermore, due to the low positron fraction in ^{90}Y PET imaging, scan times typically require between 15 and 30 minutes over which many respiratory cycles occur (38). This effectively smears the measured ^{90}Y activity distribution over a larger volume, reducing the total activity within the CT-derived liver contour. To quantify the “loss” of activity in A_{PET} , the ratio of ^{90}Y activity outside of L_{shell} to the activity within B was calculated and is reported in table 3. On average, 14% of administered ^{90}Y activity in A_{PET} lies outside L_{shell} . A rationale for the extreme activity loss in R04 ($RC_{PET} = 40.1\%$) is the relatively high

ratio (27%) of ^{90}Y activity beyond L_{shell} . The reduced spatial resolution of PET imaging relative to CT imaging may also contribute to this effect.

Rabbit Index	R01	R02	R03	R04	R05	R06	R07	R08
PET Activity Ratio	11%	12%	14%	27%	10%	12%	12%	16%

Table 3: Ratio of ^{90}Y activity outside of L_{shell} to the activity within B to quantify extrahepatic ^{90}Y activity in the PET-based activity distribution A_{PET} .

In this study, given the range of liver motion observed during intra-procedural angiographic imaging (1.0 cm), there may be a degree of dosimetric uncertainty as a result of PET/CT coregistration. A study by Vogel et al. reported 40% of patients encounter an absolute PET/CT coregistration error exceeding 1 cm in the cranial-caudal dimension when employing an expiration breath hold technique during CT imaging (39). The same study found CT-based attenuation correction artifacts caused a deformation of the liver dome in the PET image > 1 cm in 50% of patients. Based on these results, deviations in D_μ can be expected between DD_{PET} and DD_{CT} , particularly for tumours proximal to the liver dome.

4.3.2 CT

An issue specific to post-treatment CT imaging in ^{90}Y RE is the use of vascular contrast agents when guiding the catheter through the hepatic arterial vasculature. Although a rabbit-specific b_{cal} accounts for varying μ_{bkg} , non-uniform contrast agent uptake within L was still observed. In these cases, μ_{bkg} may be sensitive to the spatial location of L_{bkg} , so it is essential to place multiple L_{bkg} structures within L to average over any nonuniformities.

An additional drawback in implementing a CT-based approach to dosimetry in ^{90}Y RE is that it requires an indirect method of ^{90}Y activity quantification that requires the intermediate step of imaging and analyzing a calibration phantom. This may introduce additional uncertainty in DD_{CT} . For example, the calibration curve slope m_{cal} was calculated with 95% CIs. In R05, when using the upper 95% CI in m_{cal} to determine DD_{CT} , D_μ decreased by 2.5 Gy, from 38.6 Gy to 35.9 Gy. When using the lower 95% CI in m_{cal} , D_μ increased by 3.3 Gy, from 38.6 Gy to 41.7 Gy. The corresponding A_{CT} values for the upper and lower 95% CIs are 123.8 MBq and 143.9 MBq, respectively, while A_0 was 133.7 MBq.

CT image artifacts may present additional complications. High-Z objects proximal to the intended treatment target, such as clips, coils, or calcifications, could produce image artifacts that may be mistaken for radiopaque microsphere uptake. In these cases, image artifacts could be mitigated by implementing the ΔHU calibration approach discussed previously. Note the Eye90 in this study did not produce any image artifacts as a result of their material composition.

4.4 Dose Heterogeneity

This study has demonstrated that a significant benefit of CT-based dosimetry is its ability to reveal the high dose heterogeneity known to exist from pathohistological studies on explanted livers following ^{90}Y RE (12,13). The COV values in table 2 verify this heterogeneity as the COV within L in DD_{CT} is consistently greater than the corresponding values in DD_{PET} with an average of 1.99 ± 0.35 [1.63, 2.61] in DD_{CT} and 1.02 ± 0.15 [0.75, 1.31] in DD_{PET} . The high spatial resolution of CT also provides an opportunity to further investigate dose-volume metrics for predicting response in ^{90}Y RE. One of the earliest studies reporting dose-volume metrics in ^{90}Y RE was performed by a Kao et al. where $D_{70} > 100$ Gy was suggested as a threshold to predict treatment response in HCC (40). A subsequent study by Fowler et al. indicated dose-volume metrics predict response better in hypovascular lesions than in hypervascular ones, and suggested one incorporate a measure of tumor dose heterogeneity, such as the COV, into the dose response analysis to improve the positive predictive value (41). Willowson et al. later found D_{70} resulted in a stronger correlation with outcome than D_{μ} in metastatic colorectal cancer patients (42). More recently, a study performed by Kappadath et al. found D_{μ} and D_{20} to D_{80} were correlated with mRECIST response criteria (43). We have previously shown that D_{70} is dependent on the spatial resolution of the imaging modality (25), and in this study, the data show D_{70} in L (and in L_{shell}) are consistently overestimated in DD_{PET} relative to their corresponding values in DD_{CT} . Although these results are not derived from a hypervascular tumour model, they suggest that existing dose-response data based on dose-volume metrics derived from PET and bSPECT may be improved with CT-based dosimetry in ^{90}Y RE.

5. Conclusions

The recovery of the radiopaque microsphere mass within the rabbits validates CT-based dosimetry in ^{90}Y RE. Due to the high resolution of CT imaging, the benefits of this novel approach include improved visualization of the dose distribution, reduced partial volume effects in dose reporting, and a better representation of dose heterogeneity allowing for the extraction of more accurate dose-volume metrics. Effects of respiratory motion are also mitigated when compared to post-treatment PET or bSPECT imaging. Future work aims to validate these benefits in a hypervascular tumour model.

Ultimately, post-treatment CT imaging of radiopaque microspheres provides the means to perform precision dosimetry in ^{90}Y RE and extract accurate dose metrics used to refine the understanding of the dose response relationship in ^{90}Y RE. Understanding the dose-response relationship can permit an individualized approach to treatment planning and should translate into improved patient outcomes.

List of Abbreviations

HCC – Hepatocellular Carcinoma
⁹⁰ Y – Yttrium-90
RE - Radioembolization
CT – Computed Tomography
PET – Positron Emission Tomography
SPECT – Single Photon Emission Computed Tomography
FWHM – Full Width Half Maximum
HU – Hounsfield Units
TOF – Time-of-Flight
MIRD – Medical Internal Radiation Dose
DVK – Dose-Voxel Kernel
COV – Coefficient of Variation
cDVH – Cumulative Dose-Volume Histogram
PI – Prediction Interval
CI – Confidence Interval
LOD – Limit of Detection
LOB – Limit of Blank
MDA – Minimum Detectable Activity

Declarations

Ethics Approval and Consent to Participate

The University of Missouri Animal Care and Use Committee approved the animal protocol (#9786) whose data were analyzed for this study.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

RA is a shareholder, cofounder, and Chief Medical Officer of ABK Biomedical. AS, ECH, ACG, and DL have provided consulting services to ABK Biomedical. JNB has received research support from ABK Biomedical. SCK has received research support from and served as a consultant for Boston Scientific, Sirtex Medical, and ABK Biomedical. DL has received research support from Boston Scientific and served as a consultant for Sirtex Medical and ABK Biomedical.

Funding

This work was funded through a Nova Scotia Health Authority graduate student scholarship.

Author's Contributions

ECH performed the bulk of the data analysis and wrote the manuscript. MS and KB performed dose-voxel kernel calculations and validation. DL provided editorial review. JNB and ACG contributed to the protocol development, execution of the experiments, and interpretation of the data. CM performed structure delineation in rabbit CT volumes. RJA contributed to the protocol development, data analysis, and interpretation of the data. SCK contributed to the data analysis and interpretation of the data. AS and GM contributed to the conceptualization and review of the study. All authors contributed to the drafting and revision of the manuscript.

Acknowledgements

Not applicable.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018 Nov 1;68(6):394–424.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87–108.
3. Rognoni C, Ciani O, Sommariva S, Facciorusso A, Tarricone R, Bhoori S, et al. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. *Oncotarget.* 2016;7(44):72343.
4. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. *CA Cancer J Clin.* 2012;62(6):394–9.
5. Moreno-Luna LE, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol.* 2013;36(3):714–23.
6. Sacco R, Mismas V, Marceglia S, Romano A, Giacomelli L, Bertini M, et al. Transarterial radioembolization for hepatocellular carcinoma: An update and perspectives. *World J Gastroenterol.* 2015 Jun 7;21(21):6518.
7. Saini A, Wallace A, Alzubaidi S, Knuttinen MG, Naidu S, Sheth R, et al. History and Evolution of Yttrium-90 Radioembolization for Hepatocellular Carcinoma. *J Clin Med.* 2019 Jan 7;8(1):55.
8. BREEDIS C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol.* 1954;30(5):969.
9. Volchok HL, Kulp JL. Half-life of yttrium-90. *Phys Rev.* 1955;97(1):102.
10. Mainegra-Hing E, Rogers DWO, Kawrakow I. Calculation of photon energy deposition kernels and electron dose point kernels in water. *Med Phys.* 2005;32(3):685–99.
11. Ae JIB, De A, Ae M, De E, Ae L, Díaz-Dorransoro L, et al. Biocompatibility, Inflammatory Response, and Recanalization Characteristics of Nonradioactive Resin Microspheres: Histological Findings.
12. Kennedy AS, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of 90Y microspheres in man: Review of four explanted whole livers. *Int J Radiat Oncol Biol Phys.* 2004;60(5):1552–63.
13. Campbell AM, Bailey IH, Burton MA. Analysis of the distribution of intra-arterial microspheres in human liver following hepatic yttrium-90 microsphere therapy. *Phys Med Biol.* 2000 Apr 1;45(4):1023–33.
14. Roberson PL, Ten RKH, McShan DL, McKeever PE, Ensminger WD, Haken RKT, et al. Three-dimensional tumor dosimetry for hepatic yttrium-90-microsphere therapy. *J Nucl Med Off Publ Soc Nucl Med.* 1992;33(5):735–8.
15. Gulec SA, Szejnberg ML, Siegel JA, Jevremovic T, Stabin M. Hepatic Structural Dosimetry in 90 Y Microsphere Treatment: A Monte Carlo Modeling Approach Based on Lobular Microanatomy. *J Nucl Med.* 2010;51:301–10.
16. Cremonesi M, Chiesa C, Strigari L, Ferrari L, Botta F, Guerriero F, et al. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective. *Front Oncol.* 2014 Aug;4:210.
17. O’ Doherty J, O’Doherty J, O’Doherty J. A review of 3D image-based dosimetry, technical considerations and emerging perspectives in 90Y microsphere therapy. *J diagnostic imaging Ther.* 2015;2(2):1–34.
18. Roosen J, Klaassen NJM, Westlund Gotby LEL, Overduin CG, Verheij M, Konijnenberg MW, et al. To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer. *European Journal of Nuclear Medicine and Molecular Imaging.* Springer Science and Business Media Deutschland GmbH; 2021. p. 1–15.
19. Kim SP, Cohalan C, Kopek N, Enger SA. A guide to 90Y radioembolization and its dosimetry. Vol. 68, *Physica Medica.* 2019. p. 132–45.
20. Gates VL, Esmail AAH, Marshall K, Spies S, Salem R. Internal pair production of 90Y permits hepatic localization of microspheres using routine PET: proof of concept. *J Nucl Med.* 2011;52(1):72–6.
21. Elschot M, Nijssen JFW, Dam AJ, de Jong HWAM. Quantitative evaluation of scintillation camera imaging characteristics of isotopes used in liver radioembolization. *PLoS One.* 2011;6(11):e26174.
22. Pasciak AS, Bourgeois AC, Bradley YC. A Comparison of Techniques for (90)Y PET/CT Image-Based Dosimetry Following Radioembolization with Resin Microspheres. *Front Oncol.* 2014 May;4:121.
23. Sato K, Lewandowski RJ, Bui JT, Omary R, Hunter RD, Kulik L, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere®): Assessment of hepatic arterial embolization. *Cardiovasc Intervent Radiol.* 2006;29(4):522–9.
24. Spina JC, Hume I, Pelaez A, Peralta O, Quadrelli M, Monaco RG. Expected and unexpected imaging findings after 90 Y transarterial radioembolization for liver tumors. *Radiographics.* 2019;
25. Henry EC, Strugari M, Mawko G, Brewer KD, Abraham R, Kappadath SC, et al. Post-administration dosimetry in yttrium-90 radioembolization through micro-CT imaging of radiopaque microspheres in a porcine renal model. *Phys Med Biol.* 2021 May 7;66(9):095011.
26. Henry C, Mawko G, Tonkopi E, Frampton J, Abraham R, Boyd D, et al. The Quantification and Comparison of the Inherent Radiopacity of Glass Microspheres Used in Transarterial Radioembolization. In: 60th Annual Meeting of AAPM. Medical physics; 2018. p. E566.
27. Chen J, White SB, Harris KR, Li W, Yap JW, Kim D-H, et al. Poly(lactide-co-glycolide) Microspheres for MRI-Monitored Delivery of Sorafenib in a Rabbit VX2 model HHS Public Access. *Biomaterials.* 2015;61:299–306.
28. Medicine BTGI. Package Insert - TheraSphere® Yttrium-90 Glass Microspheres.
29. Högberg J, Rizell M, Hultborn R, Svensson J, Henrikson O, Mölne J, et al. Heterogeneity of microsphere distribution in resected liver and tumour tissue following selective intrahepatic radiotherapy. *EJNMMI Res.* 2014;4(1):48.
30. Jan S, Santin G, Strul D, Staelens S, Assié K, Autret D, et al. GATE: A simulation toolkit for PET and SPECT. *Phys Med Biol.*

2004;49(19):4543–61.

31. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition. 2012.
32. Jacobsen MC, Cressman ENK, Tamm EP, Baluya DL, Duan X, Cody DD, et al. Dual-energy CT: Lower limits of iodine detection and quantification. *Radiology*. 2019;292(2):414–9.
33. Carlier T, Eugène T, Bodet-Milin C, Garin E, Ansquer C, Rousseau C, et al. Assessment of acquisition protocols for routine imaging of Y-90 using PET/CT. *EJNMMI Res*. 2013;
34. Chang BK, Timmerman RD. Stereotactic body radiation therapy: A comprehensive review. Vol. 30, *American Journal of Clinical Oncology: Cancer Clinical Trials*. 2007. p. 637–44.
35. Alsultan AA, Braat AJAT, Smits MLJ, Barentsz MW, Bastiaannet R, Bruijnen RCG, et al. Current Status and Future Direction of Hepatic Radioembolisation. *Clin Oncol*. 2021 Feb 1;33(2):106–16.
36. Carlier T, Willowson KP, Fourkal E, Bailey DL, Doss M, Conti M. 90Y -PET imaging: Exploring limitations and accuracy under conditions of low counts and high random fraction. *Med Phys*. 2015 Jul 1;42(7):4295–309.
37. Conti M, Eriksson L, Rothfuss H, Sjöholm T, Townsend D, Rosenqvist G, et al. Characterization of 176Lu background in LSO-based PET scanners. *Phys Med Biol*. 2017;62(9):3700–11.
38. Kao YH, Steinberg JD, Tay YS, Lim GKY, Yan J, Townsend DW, et al. Post-radioembolization yttrium-90 PET/CT-part 1: Diagnostic reporting. Vol. 3, *EJNMMI Research*. 2013. p. 1–28.
39. Vogel W V, Van Dalen JA, Wiering B, Huisman H, Corstens FHM, Ruers TJM, et al. Evaluation of Image Registration in PET/CT of the Liver and Recommendations for Optimized Imaging. *J Nucl Med*. 2007;48:910–9.
40. Kao YH, Steinberg JD, Tay YS, Lim GK, Yan J, Townsend DW, et al. Post-radioembolization yttrium-90 PET/CT - part 2: dose-response and tumor predictive dosimetry for resin microspheres. *EJNMMI Res*. 2013 Jul;3(1):5–57.
41. Fowler KJ, Maughan NM, Laforest R, Saad NE, Sharma A, Olsen J, et al. PET/MRI of Hepatic 90Y Microsphere Deposition Determines Individual Tumor Response. *Cardiovasc Intervent Radiol*. 2016;39(6):855–64.
42. Willowson KP, Hayes AR, Chan DLH, Tapner M, Bernard EJ, Maher R, et al. Clinical and imaging-based prognostic factors in radioembolisation of liver metastases from colorectal cancer: a retrospective exploratory analysis. *EJNMMI Res*. 2017;7(1).
43. Kappadath SC, Mikell J, Balagopal A, Baladandayuthapani V, Kaseb A, Mahvash A. Hepatocellular Carcinoma Tumor Dose Response After 90Y-radioembolization With Glass Microspheres Using 90Y-SPECT/CT-Based Voxel Dosimetry. *Int J Radiat Oncol Biol Phys*. 2018 Oct 1;102(2):451–61.