Dosimetry of a ^{90}Y -Hydroxide Liquid Brachytherapy Treatment Approach to Canine Osteosarcoma Using PET/CT

Jien Jie Zhou^a, Arnulfo Gonzalez^a, Mark W. Lenox^b, Theresa W. Fossum^b, R. Keith Frank^c, Jaime Simon^c, Stan Stearns^d, Catherine M. Ruoff^b, Richard E. Wendt^e, Gamal Akabani^{a,b}

^aDepartment of Nuclear Engineering, Texas A&M University, College Station, Texas

^bTexas A&M Institute for Preclinical Studies, Texas A&M University, College Station, Texas

^cIsoTherapeutics Group, LLC, Angleton, Texas

^dThe Gabriel Institute, Houston, Texas

^eDepartment of Imaging Physics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Corresponding author:

Gamal Akabani, Ph.D.. Department of Nuclear Engineering. Texas A&M Institute for Preclinical Studies . Texas A&M University. College Station, TX 77843-3133
Tel: 979-458-1699. E-mail address: akabani@tamu.edu

Abstract:

A new treatment strategy based on direct injections of ^{90}Y -hydroxide into the tumor bed in dogs with osteosarcoma was studied. Direct injections of the radiopharmaceutical into the tumor bed were made according to a pretreatment plan established using ^{18}F -FDG images. Using a special drill, cannulas were inserted going through tissue, tumor and bone. Using these cannulas, direct injections of the radiopharmaceutical were made. The *in vivo* biodistribution of ^{90}Y -hydroxide and the anatomical tumor bed were imaged using a time-of-flight (TOF) PET/CT scanner. The material properties of the tissues were estimated from corresponding CT numbers

using an electron-density calibration. Radiation absorbed dose estimates were calculated using Monte Carlo methods where the biodistribution of the pharmaceutical from PET images was sampled using a collapsing 3-D rejection technique. Dose distributions in the tumor bed and surrounding tissues were calculated, showing significant heterogeneity with multiple hot spots at injection sites. Dose volume histograms showed that approximately 33.9% of bone and tumor and 70.2% of bone marrow and trabecular bone received an absorbed dose over 200 Gy; approximately 3.2% of bone and tumor and 31.0% of bone marrow and trabecular bone received a total dose of over 1000 Gy.

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor, affecting mainly children and adolescents. According to the Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review, the age-adjusted incidence rate of osteosarcoma from 2004 to 2008 was 5.2 per million for ages 0-19, accounting for 57.8% of all malignant bone tumors in the same age group (Howlader N, 2011). The incidence of osteosarcoma was slightly higher in males than in females, with a rate of 5.4 per million in males versus 4.0 per million in females (Jaffe et al., 2009). Osteosarcoma develops from propagation of malignant mesenchymal tumor cells which have the ability to produce osteoid extracellular matrix or immature bone (Dorfman and Czerniak, 1998). Generally, the tumor is a combination of bony and soft tissues showing significant heterogeneity. Osteosarcoma exhibits an invasive and bone-destroying pattern of growth where the borders between the tumor tissue and adjacent structures are indistinct and irregular (Dorfman and Czerniak, 1998). Osteosarcoma often occurs near the metaphyseal growth plates of the long bones of the extremities, such as femur, tibia, and humerus. Other sites where osteosarcoma occurs include the skull or jaw, vertebra, and the pelvis (Jaffe et al., 2009). The most common metastases site is the lung, followed by the knees and other bones.

Current treatment options for osteosarcoma include surgery, chemotherapy, external beam radiotherapy and targeted radionuclide therapy (TRT). Surgical resection accompanied by pre- and post-operative multi-agent chemotherapy has improved the 5-year relative survival of osteosarcoma considerably since the 1980s, and has now become the standard of care for patients with non-metastatic osteosarcoma (Chou et al., 2008). External beam radiotherapy is seldom used for primary treatment, but it is an important option for the treatment of unresectable primary tumors and metastases and for palliation purposes. The most widely studied radiopharmaceutical for the treatment of osteosarcoma is Quadramet® (¹⁵³Sm-EDTMP, EUSA Pharma (USA), Inc.), which is often administered intravenously in combination with chemotherapy or external beam radiotherapy (Chou et al., 2008; Schwarz et al., 2009).

There has been little improvement in the overall survival rate of osteosarcoma in the last twenty years. A recent SEER report suggested that the 5-year relative survival rate, based on data from 2001-2007, was 68.5% for ages 0-19 (Howlader N, 2011). A prior report based on SEER data from 1973-2004, determined that the relative 5-year survival rate was 61.6% for patients ages 0-24, 58.7% for ages 25-59, and 24.2% for ages 60-85+ (Mirabello et al., 2009). For patients with metastatic disease or local relapse, the 5-year survival rate is lower than 30% (Chou et al., 2008). Therefore, there is a tremendous need to develop improved treatment strategies for loco-regional control.

Canine osteosarcoma serves as an excellent translational model for human osteosarcoma due to conspicuous similarities, such as male sex predilection, affected sites, histopathological characteristics, and treatment response (Legare et al., 2011; Rodriguez, 2014). Moreover, the feasibility of *in vivo* ⁹⁰Y PET imaging has been demonstrated (Carlier et al., 2013; Lhommel et al., 2009), allowing for direct imaging and subsequent dosimetry for the treatment site(s).

Yttrium-90 hydroxide is an early prototype of BetaBrach^{TM}(Patent Pending), a novel beta-emitting source being developed for interstitial brachytherapy (Frank et al., 2007). In this study we provide a description of the treatment strategy, imaging of ⁹⁰Y-hydroxide using PET-CT, and computational methods for dosimetry in dogs with osteosarcoma using TOF PET/CT and present a dose assessment in tumors and surrounding tissues.

2. Material and Methods

2.1 Preclinical protocol

Prior to intervention, an ¹⁸F-FDG PET/CT scan was performed to assess the metabolic activity of tumors and predefine the treatment sites for direct injections. Injection sites were determined with the intent of covering as much of the total tumor volume as possible. Injection sites, moreover, were distributed uniformly throughout the treatment volume and sites were spaced approximately 1 cm from each other. After an injection site was chosen, a needle-like adaptor was inserted through the skin until it made contact with the tumor-bone region. The adaptor consisted of three parts: a) an outer cannula, b) an inner cannula, and c) a cap (see Figure 1a). A specially designed miniature electric drill was used to drill into the osteoid tumor bed through the adaptor, to allow the direct injection of the radiopharmaceutical. After drilling, the adaptor was left *in situ* to stop blood from filling up the orifice, and a cap was inserted to isolate it from air-borne contaminants.

Figure 1. (a) The picture shows the adaptors in place as well as the drill used to produce the cannulas. (b) A radiographic check using a fluoroscopy unit was carried out to assure maximum tumor coverage. (c) The ^{90}Y radiopharmaceutical was injected using a micro-needle syringe through each cannula at different depths.

After all the adaptors were inserted, a radiograph was taken to document the placement and integrity of the adaptors and to ensure that the tumor volume was completely covered (see Figure 1b). The radiopharmaceutical formulation was prepared as a solution with an approximate activity concentration of $3.7 \text{ MBq } \mu\text{L}^{-1}$ ($100 \text{ } \mu\text{Ci } \mu\text{L}^{-1}$). A micro-needle syringe was used to perform the injections (Figure 1c). For each adaptor, approximately $15 \text{ } \mu\text{L}$ of ^{90}Y radiopharmaceutical was injected at either three or four spots, at different depths, spaced 1 cm from each other. Each adaptor was removed from the tumor site immediately following the injection. The volume of radioactive solution in the syringe was recorded before and after each injection to determine the net volume injected.

The decay of ^{90}Y has a small branch to the 0^+ first excited state of ^{89}Zr and its de-excitation is constrained to follow internal conversion, or $e^- e^+$ creation with an overall yield of $(31.8 \pm 0.47) \times 10^{-6}$ (Nickles et al., 2004; Selwyn et al., 2007). After treatment, a PET/CT scan was performed using a Siemens Biograph mCT scanner to assess the *in vivo* distribution of the

radiopharmaceutical. The scan lasted approximately 1 hour and images were reconstructed using ultraHD and TOF information.

2.2 CT number conversion

Reconstructed CT images were used to build the patient specific geometry and the composition of the tumor and tissues for Monte Carlo simulations. CT numbers (Hounsfield Unit, HU) were used to establish the mass density and elemental composition for each voxel making up the CT image. A calibration curve was used to convert CT numbers into material properties and density. This quasi-linear relationship between CT numbers and electron density and tissue composition has been shown in prior studies (DeMarco et al., 1998; du Plessis et al., 1998; Parker et al., 1979; Schneider et al., 2000). The calibration was carried out using a CIRS 062 electron density phantom (CIRS, Norfolk VA) on the scanner. The phantom consisted of a two-part body made of soft tissue equivalent epoxy resin, holding eight pairs of tissue equivalent inserts and a solid water insert with known electron densities. For each pair of tissue equivalent inserts, one of the inserts was placed in the inner ring while the other in the outer ring. The solid water insert was placed in the center of the phantom. For each insert, the average CT number was determined by drawing a circular ROI with a diameter of approximately 2 cm on a central slice CT image. The CT number for each tissue equivalent material was the average of the inner and outer ring measurements. A calibration curve was obtained by plotting the average CT number against relative electron density (electron density normalized to that of water). Once the calibration was established, the relative electron density of each voxel in the CT images could be calculated using a linear interpolation. The relevant materials in this study are listed in Table 1. The material density, electron density, and elemental composition data for all the materials were

obtained from ICRU Report 46 (International Commission on Radiation Units and Measurements., 1992).

Table 1. Material groups used for Monte Carlo simulations based on ICRU 46 (International Commission on Radiation Units and Measurements., 1992).

	Group	Material or Tissues	Reference Mass Density (g cm⁻³)	Relative Electron Density^a	Relative Electron Density Range
1	Air	Air	1.20×10 ⁻³	1.08×10 ⁻³	[0, 0.1)
2	Soft Tissues	Yellow Marrow Soft Tissue Red Marrow	0.98 1.00 1.03	0.982 0.991 1.02	[0.1, 1)
3	Bone Marrow	Muscle Blood Cartilage	1.05 1.06 1.10	1.04 1.05 1.08	[1.0, 1.1)
4	Bone and Tumor	Trabecular Bone Cortical Bone^b	1.16 1.92	1.14 1.78	[1.1, 1.1+)

^aThe electron density of the material divided by that of water.

^bThe elemental composition of this group is determined by interpolation of cortical bone and blood.

The materials were divided into four groups according to their relative electron density: Air, Soft Tissue, Bone Marrow, and Bone and Tumor. Voxels can be sorted into these groups according to the relative electron density ρ_e^w calculated from CT numbers. The materials in Table 1 with their names in bold are specified as the reference materials by ICRU Report 46 (International Commission on Radiation Units and Measurements., 1992).

The elemental composition of voxels in each of the four groups was determined by the reference material of the group, except for those in the Bone and Tumor group. The Bone and Tumor group includes trabecular bone, tumor, and cortical bone, with the density of material varying over a broad range. Osteosarcoma tumors, as previously noted, are composed of bony and soft tissue, with an electron density in the range of the Bone and Tumor group; trabecular bone is a mixture of dense bone, bone marrow and blood. As such, the material in the Bone and Tumor group is defined as a mixture of cortical bone (high density component) and blood (low

density component) to effectively simulate the composition of osteosarcoma tumors and trabecular bone. The elemental composition of voxels pertaining to the air, soft tissue, and bone marrow groups is fixed, while their mass density was adjusted based on relative electron density. For groups 1, 2, and 3, the mass density for a given voxel ρ should comply with the following equation:

$$\frac{\rho}{\rho_e^w} = \frac{\rho_{ref}}{\rho_{e,ref}^w} \quad (1)$$

where ρ_e^w is the relative electron density of the voxel estimated from CT numbers, $\rho_{e,ref}^w$ is the relative electron density of the reference material in that group, and ρ_{ref} is the mass density of the reference material as per ICRU Report 46. For voxels in group 4 (Bone and Tumor), the elemental composition and mass density both change with step sizes corresponding to 0.1 of relative electron density. For each bin in the Bone and Tumor group, the relative electron density at the mid-point was used. If $\rho_e^w \leq \rho_{e,c}^w$, where ρ_e^w is the relative electron density of the voxel and $\rho_{e,c}^w$ is the relative electron density of cortical bone, the fractions of cortical bone and blood for each voxel were calculated by interpolation, as shown in the following equation:

$$\begin{aligned} f_c \rho_{e,c}^w + f_b \rho_{e,b}^w &= \rho_e^w \\ f_c + f_b &= 1 \end{aligned} \quad (2)$$

where $\rho_{e,b}^w$ is the relative electron density of blood, f_c is the fraction of cortical bone and f_b is the fraction of blood. If $\rho_e^w > \rho_{e,c}^w$, the fraction of cortical bone was assumed to be 1 and the fraction of blood is 0. The elemental composition of the voxel was then expressed as:

$$w_i = f_c w_{c,i} + f_b w_{b,i} \quad (3)$$

where w_i is the elemental weight of element i for that voxel, $w_{c,i}$ is the elemental weight of element i for cortical bone, and $w_{b,i}$ is the elemental weight of element i for blood. The mass density is calculated using the following equation:

$$\rho = f_c \frac{\rho_e^w}{\rho_{e,c}^w} \rho_c + f_b \frac{\rho_e^w}{\rho_{e,b}^w} \rho_b \quad (4)$$

where ρ_c is the mass density of cortical bone and ρ_b is the mass density of blood.

The electron mass stopping power of the materials in the Soft Tissue and Bone Marrow groups were calculated using the program ESTAR (Berger et al., 2005). The total mass stopping power for all the materials were similar with deviations of less than 2%. The electron mass stopping power was thus negligibly affected by elemental composition. Therefore, it was proper to use the elemental composition of the reference material for the whole group.

2.3 Activity Sampling of ^{90}Y

The activity distribution of ^{90}Y was sampled using PET images to determine the decay sites for use in Monte Carlo simulations. PET images in DICOM format were read as a 3-D array and a collapsing 3-D triple rejection technique was used for fast sampling (Akabani et al., 1997). Once the voxel indices (i, j, k) were determined, the decay site was randomized within the selected voxel. The coordinates (x, y, z) were calculated as:

$$\begin{aligned} x &= (i + r_x) \Delta_x + O_x \\ y &= (j + r_y) \Delta_y + O_y \\ z &= (k + r_z) \Delta_z + O_z \end{aligned} \quad (5)$$

where Δ_x , Δ_y , and Δ_z are the dimensions of voxel size along the x , y , z axis respectively, r_x , r_y and r_z are random numbers between -0.5 and 0.5, and (O_x, O_y, O_z) are the coordinates of the voxel with indices (0, 0, 0).

2.4 Monte Carlo Simulations

The Geant4 Monte Carlo transport code was used for dosimetry calculations purposes (Agostinelli et al., 2003; Allison et al., 2006). In Monte Carlo simulations, a computational geometry was built using anatomical data obtained from CT images. The material properties of the tumor and surrounding tissues were obtained from CT numbers by using the CT number-electron density calibration that was previously described. The decay sites of ^{90}Y were sampled from PET images using a collapsed 3-D rejection technique. The initial kinetic energy of the beta particles was sampled using the ^{90}Y β^- spectrum (Soppera et al., 2011). Particle transport was carried out, and the energy deposition in each voxel was recorded. Dosimetry results are given as specific absorbed dose (S-values) in each voxel, with a unit of $\text{Gy Bq}^{-1} \text{s}^{-1}$. The S-value for a given voxel was calculated as $S_{\text{voxel}} = \varepsilon_{\text{voxel}} / (\tilde{A} \cdot m_{\text{voxel}})$ where $\varepsilon_{\text{voxel}}$ is the energy deposited in a given voxel for a cumulative activity $\tilde{A}$ over the whole phantom, and m_{voxel} is the mass of the voxel. Therefore, the absorbed dose to a given voxel was calculated as,

$$D_{\text{voxel}} = S_{\text{voxel}} \tilde{A} = S_{\text{voxel}} A \tau \quad (6)$$

where A is the net administered activity (Bq), and τ is the residence time (s). The residence time τ is given as:

$$\tau = \frac{1}{\lambda_p + \lambda_b} \quad (7)$$

where λ_p is the physical radioactive decay constant of ^{90}Y and λ_b is the biological clearance

constant of the radiopharmaceutical.

2.5 3-D CT Segmentation

To evaluate the dose delivered to the bone, tumor and bone marrow separately, 3-D CT image segmentations were performed morphologically using the segmentation software ITK-SNAP (Yushkevich et al., 2006). A segmentation can be generated either manually by drawing regions of interest on the CT images, or automatically by specifying a CT-number range and a smoothness filter for the structure of interest. The segmentation result was saved as a 3-D binary array. The dose volume histogram (DVH) of a structure of interest was obtained by applying the segmentation array as a mask with the dose distribution array.

3. Results

3.1 CT Number - Electron Density Calibration

The average CT number for each tissue equivalent insert, and its standard deviation, were measured from the central slices of the reconstructed DICOM files and plotted against the relative electron density, as shown in Figure 2. CT numbers from patient images were converted to relative electron densities by linear interpolation of data points and converted into material properties as previously described.

Fig. 2 CT numbers as a function of relative electron density for all tissue equivalent inserts. Material groups are shown with corresponding relative electron density range.

3.2 Activity Administration and PET/CT Imaging

A 5 year-old male dog with osteosarcoma in its left tibia was treated with ^{90}Y liquid brachytherapy. The activity concentration of ^{90}Y -hydroxide solution was $2.88 \text{ MBq } \mu\text{l}^{-1}$ ($78 \text{ } \mu\text{Ci } \mu\text{l}^{-1}$), and the total administered activity was 611.83 MBq (16.536 mCi). After administration, a 60 min PET/CT scan was performed to assess the distribution of ^{90}Y . The collected PET data were reconstructed using ultraHD (including TOF) with 3 iterations, 21 subsets and a post-smoothing filter of 5 mm. A 3-D co-registered ^{90}Y PET/CT image is shown in Figure 3.

Fig. 3. 3-D co-registered PET/CT image showing the distribution of ^{90}Y in the left tibia of a dog with osteosarcoma. A high activity hot spot was found in the bone marrow and multiple isolated hotspots in the tumor bed, corresponding to the sites of administration.

3.3 Monte Carlo Simulation

Geometry and Physics

The reconstructed PET DICOM images had 200×200 pixels in 100 slices ($203.6 \text{ mm} \times 203.6 \text{ mm} \times 300 \text{ mm}$). The pixel size was $1.018 \text{ mm} \times 1.018 \text{ mm}$ and the slice thickness was 3 mm. A voxelized phantom was built based on the cropped CT images. The phantom consisted of an array with $209 \times 209 \times 100$ voxels ($204.0 \times 204.0 \times 300.0 \text{ mm}$). The voxel size was $0.976 \text{ mm} \times 0.976 \text{ mm} \times 3 \text{ mm}$.

In the Geant4 Monte Carlo simulations, the position of each primary particle was determined by sampling the ^{90}Y distribution from the PET images. The momentum direction of primary particles was assumed to be isotropic. The energy of each primary particle was determined by sampling the β -particle energy spectrum of ^{90}Y obtained from JANIS (Soppera et al., 2011). The cut value of Monte Carlo transport for all particles was set to 0.01 mm (i.e., particles with a range smaller than 0.01 mm would not be tracked and were assumed to deposit all of their remaining energy locally).

Dosimetry Calculations

The Geant4 Monte Carlo simulation was performed in 10 runs to assess the uncertainties of all calculations with a total number of 10^8 particles transported. The S -value for each voxel was recorded in binary files with units $\text{Gy Bq}^{-1} \text{s}^{-1}$. The absorbed dose was calculated using equation 6. A 3-D volume rendering of CT images fused with the dose distribution is shown in Figure 4. The resulting dose distribution consisted of multiple hot spots corresponding to the injection sites.

Fig. 4. 3-D volume rendering of CT fused with dose distribution of ^{90}Y -hydroxide liquid brachytherapy in a dog with osteosarcoma in the left tibia.

Isodose curves were plotted on an axial plane, as shown in Figure 5. The osteolytic lesions were covered in a total dose over 200 Gy, with a central hot spot of over 1200 Gy. However, the bone marrow was also irradiated with a hotspot of over 1000 Gy.

Fig. 5. Isodose curves on an axial plane, showing the dose distribution in the tumor bed, adjacent bone and bone marrow.

Dose Volume Histograms

Osteosarcoma tumors primarily consist of bony tissue, with intensity close to that of bone; therefore, separating the tumor from adjacent bone posed severe difficulties. Consequently, two 3-D CT segmentations were generated. Segmentation (1) consisted bone and tumor, and segmentation (2) of bone marrow (including trabecular bone). Segmentation (1) was generated using threshold CT number of 400 HU and a smoothness filter of 2 mm. Segmentation (2) was generated by manually selecting the low density volume in the bone, including the red marrow, trabecular bone, and yellow marrow in the medullary cavity. The two segmentations are shown in Figure 6.

Fig. 6. 3-D CT segmentations in the (a) axial, (b) sagittal and (c) coronal planes. Segmentation (1) bone + tumor is marked in red and (2) bone marrow (including trabecular bone) is marked in green.

The CT number histograms for these two segmentations are shown in Figure 7. Corresponding material groups are marked in the figure. Segmentation (1) as bone and tumor is in the range of the Muscle and Bone and Tumor group. Segmentation (2) as bone marrow (including trabecular bone) is in the range of Soft Tissue and Bone Marrow groups.

Fig. 7. CT number histograms for segmentation (1) as bone and tumor, and (2) as bone marrow (including trabecular bone).

Fig. 8. (a) Normalized dose volume histograms for bone and tumor and bone marrow (including trabecular bone), and (b) co-registered PET/CT images showing a hot spot in the medullary cavity, resulting in high doses to the bone marrow and trabecular bone.

Normalized dose volume histograms were calculated by applying the segmentation masks to the 3-D dose distribution and are shown in Figure 8(a). The dose distribution in the tumor and other tissues highly varied. From the DVH data approximately 33.9% of bone and tumor and 70.2% of bone marrow and trabecular bone received a total dose over 200 Gy; approximately 3.2% of bone and tumor and 31.0% of bone marrow and trabecular bone received a total dose of over 1000 Gy. The hot spot in the center of the bone, shown in Figure 8(b), explained the high dose to the bone marrow and trabecular bone. The uncertainties in absorbed dose to bone and tumor in each voxel were also calculated. The average percentage standard deviation among all voxels was 13.4%, with a range from 0% to 250%.

4. Discussion

4.1 Limitations in the Current Dosimetry Calculations

There are two major limitations in the current dosimetry calculations. Foremost, improvement on quantitative imaging of ^{90}Y activity concentration from PET images should be further studied for small activity volumes, as described by Carlier et al (Carlier et al., 2013), to allow for accurate acquisition and reconstruction of images and quantitative activity assessment. Secondly, the pharmacokinetics of the ^{90}Y radiopharmaceutical should be further investigated, and the residence time τ in different regions should be estimated with biological clearance as in equation 7. It is important to note that the clearance of the ^{90}Y radiopharmaceutical in the bone and tumor and in the soft tissue could be different. While the current dosimetry calculations were performed based on the ^{90}Y distribution from a PET/CT scan acquired immediately after injection for a period of one hour, changes in the ^{90}Y activity distribution with time should be considered to improve the accuracy of the dose estimates.

4.2 Dose Distribution of ^{90}Y Hydroxide

The heterogeneous dose distribution of ^{90}Y liquid brachytherapy is a primary result of the injection pattern: for each adaptor the ^{90}Y radiopharmaceutical was injected at either 3 or 4 spots spaced approximately 1 cm from each other. An alternative was to administer the radiopharmaceutical as a continuous line, along the drilled hole, to introduce a uniform dose distribution. However, because the injection was performed manually, administering the radiopharmaceutical in such a fashion proved to be extremely difficult.

A heterogeneous dose distribution can lead to complications, namely an inadequate dose at the tumor site and a high dose in normal tissues, including bone marrow. Osteosarcomas tend to have an indistinct tumor margin with an irregular border with adjacent cortex. Therefore, it is difficult to separate the tumor from adjacent bone and to estimate the activity distribution and corresponding dose delivered to the normal bone. Concurrently, it is also difficult to evaluate the dose received by the red marrow in the treated bone. Low-density volume in the bone represents a mixture of red marrow, trabecular bone, and yellow marrow in the medullary cavity; it is quite difficult to separate each of these tissues from each other. The dose delivered to the red marrow should be carefully estimated according to the bone type and the tumor location in the bone. In this study, all segmentations were performed using CT images morphologically. MRI with its superior tissue differentiation ability should be considered as an alternative for the definition of target treatment volume and segmentations.

4.3 Efficacy and Potential Utility

The evaluation of the efficacy of ^{90}Y liquid brachytherapy cannot be established without

acquiring further preclinical data, including longitudinal data for individual dogs. Comparable to ^{153}Sm -EDTMP targeted radionuclide therapy, ^{90}Y -hydroxide liquid brachytherapy might be applied as a primary treatment method for osteosarcoma. The potential utility of liquid brachytherapy includes being used as an addition to chemotherapy or adjuvant therapy after surgery, being used for the treatment of unresectable tumors or metastases, as well as for pain palliation.

5. Conclusion

A novel ^{90}Y -hydroxide liquid brachytherapy radiopharmaceutical is currently being studied for the treatment of osteosarcoma using a preclinical translational model in dogs to assess its potential efficacy and toxicity. The present strategy has the potential to be used as an adjuvant therapy or for palliation purposes. In the present study, dosimetry calculations were carried out in a dog with osteosarcoma. The dose distribution of ^{90}Y -hydroxide showed significant heterogeneity with multiple hot spots corresponding to injection sites, and the dose-Volume histograms indicated that approximately 33.9% of bone and tumor and 70.2% of bone marrow and trabecular bone received a total dose over 200 Gy; approximately 3.2% of bone and tumor and 31.0% of bone marrow and trabecular bone received a total dose of over 1000 Gy.

As for future work, dosimetry calculations should be performed for more cases, and comparison should be made for osteosarcoma at different sites, with varied tumor volume, treated with different activity concentration and total activity. Moreover, PET scanners should be calibrated to establish a direct quantitative assessment of ^{90}Y activity concentration and pharmacokinetics of the radiopharmaceutical. These studies allow the assessment of hematological toxicity and accurate dosimetry calculations.

Acknowledgments: This project is partially funded by the U.S. Department of Energy, grant numbers DE-SC0007371 and DE-SC0008433, as well as the U.S. Nuclear Regulatory Commission, grant number NRS-38-10-923.

References:

Agostinelli, S., Allison, J., Amako, K.a., Apostolakis, J., Araujo, H., Arce, P., Asai, M., Axen, D., Banerjee, S., Barrand, G., 2003. GEANT4—a simulation toolkit. *Nuclear Instruments & Methods In Physics Research Section A-Accelerators Spectrometers Detectors And Associated Equipment* 506, 250-303.

Akabani, G., Hawkins, W.G., Eckblade, M.B., Leichner, P.K., 1997. Patient-specific dosimetry using quantitative SPECT imaging and three-dimensional discrete Fourier transform convolution. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 38, 308-314.

Allison, J., Amako, K., Apostolakis, J., Araujo, H., Dubois, P.A., Asai, M., Barrand, G., Capra, R., Chauvie, S., Chytrcek, R., 2006. Geant4 developments and applications. *Nuclear Science, IEEE Transactions on* 53, 270-278.

Berger, M.J., Coursey, J.S., Zucker, M.A., Chang, J., 2005. ESTAR, PSTAR, and ASTAR: Computer Programs for Calculating Stopping-Power and Range Tables for Electrons, Protons, and Helium Ions (version 1.2.3). National Institute of Standards and Technology, Gaithersburg, MD.

Carlier, T., Eugene, T., Bodet-Milin, C., Garin, E., Ansquer, C., Rousseau, C., Ferrer, L., Barbet, J., Schoenahl, F., Kraeber-Bodere, F., 2013. Assessment of acquisition protocols for routine imaging of Y-90 using PET/CT. *EJNMMI research* 3, 11.

Chou, A.J., Geller, D.S., Gorlick, R., 2008. Therapy for osteosarcoma: where do we go from here? *Paediatr Drugs* 10, 315-327.

DeMarco, J.J., Solberg, T.D., Smathers, J.B., 1998. A CT-based Monte Carlo simulation tool for dosimetry planning and analysis. *Medical physics* 25, 1-11.

Dorfman, H.D., Czerniak, B., 1998. Bone tumors. Mosby, St. Louis.

du Plessis, F.C., Willemse, C.A., Lotter, M.G., Goedhals, L., 1998. The indirect use of CT numbers to establish material properties needed for Monte Carlo calculation of dose distributions in patients. *Medical physics* 25, 1195-1201.

Frank, R., McMillan, K., Simon, J., 2007. Liquid brachytherapy. Provisinal Patent 60/997873, USA.

Howlader N, N.A., Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). , 2011. SEER Cancer Statistics Review, 1975-2008. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

International Commission on Radiation Units and Measurements., 1992. Photon, electron, proton, and neutron interaction data for body tissues. International Commission on Radiation Units and Measurements, Bethesda, Md., U.S.A.

Jaffe, N., Bruland, Ø.S., Bielack, S.S., 2009. Pediatric and adolescent osteosarcoma. Springer, New York.

Legare, M.E., Bush, J., Ashley, A.K., Kato, T., Hanneman, W.H., 2011. Cellular and phenotypic characterization of canine osteosarcoma cell lines. J Cancer 2, 262-270.

Lhommel, R., Goffette, P., Van den Eynde, M., Jamar, F., Pauwels, S., Bilbao, J.I., Walrand, S., 2009. Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT. European journal of nuclear medicine and molecular imaging 36, 1696.

Mirabello, L., Troisi, R.J., Savage, S.A., 2009. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 115, 1531-1543.

Nickles, R.J., Roberts, A.D., Nye, J.A., Converse, A.K., Barnhart, T.E., Avila-Rodriguez, M.A., Sundaresan, R., Dick, D.W., Hammas, R.J., Thomadsen, B., 2004. Assaying and PET imaging of Yttrium-90: $1 \gg 34\text{ppm} > 0$. Ieee Nucl Sci Conf R, 3412-3414.

Parker, R.P., Hobday, P.A., Cassell, K.J., 1979. The direct use of CT numbers in radiotherapy dosage calculations for inhomogeneous media. Phys Med Biol 24, 802-809.

Rodriguez, C., Jr., 2014. Using Canine Osteosarcoma as a Model to Assess Efficacy of Novel Therapies: Can Old Dogs Teach Us New Tricks?, in: Kleinerman, M.D.E.S. (Ed.), Current Advances in Osteosarcoma. Springer International Publishing, pp. 237-256.

Schneider, W., Bortfeld, T., Schlegel, W., 2000. Correlation between CT numbers and tissue parameters needed for Monte Carlo simulations of clinical dose distributions. Phys Med Biol 45, 459-478.

Schwarz, R., Bruland, O., Cassoni, A., Schomberg, P., Bielack, S., 2009. The role of radiotherapy in osteosarcoma. Cancer Treat Res 152, 147-164.

Selwyn, R.G., Nickles, R.J., Thomadsen, B.R., DeWerd, L.A., Micka, J.A., 2007. A new internal pair production branching ratio of ^{90}Y : the development of a non-destructive assay for ^{90}Y and ^{90}Sr . Applied radiation and isotopes : including data, instrumentation and methods for use in agriculture, industry and medicine 65, 318-327.

Soppera, N., Bossant, M., Dupont, E., Henriksson, H., Rugama, Y., 2011. Recent Upgrades to the Nuclear Data Tool JANIS. J Korean Phys Soc 59, 1329-1332.

Yushkevich, P.A., Piven, J., Hazlett, H.C., Smith, R.G., Ho, S., Gee, J.C., Gerig, G., 2006. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. NeuroImage 31, 1116-1128.