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Murine-specific internal dosimetry for preclinical investigations of imaging and therapeutic agents

Bryan Bednarz¹, Joseph Grudzinski¹, Ian Marsh¹, Abby Besemer^{1,2}, Dana Baiu³, Jamey Weichert⁴, and Mario Otto³

¹Department of Medical Physics, University of Wisconsin, Madison, WI 53705

²Department of Human Oncology, University of Wisconsin, Madison, WI 53705

³Department of Pediatrics, University of Wisconsin, Madison, WI 53705

⁴Department of Radiology, University of Wisconsin, Madison, WI 53705

Abstract

There is a growing need to estimate the absorbed dose to small animals from preclinical investigations involving diagnostic and therapeutic radiopharmaceuticals. This paper introduces a Monte Carlo-based dosimetry platform called RAPID, which is capable of calculating murine-specific three dimensional (3D) dose distributions. A comparison is performed between absorbed doses calculated with RAPID and absorbed doses calculated in a commonly used reference mouse phantom called MOBY. Four test mice containing different xenografts underwent serial PET/CT imaging using a novel theranostic agent NM404, which can be labeled with ¹²⁴I for imaging or ¹³¹I for therapy. Using the PET/CT data 3D dose distributions from ¹³¹I-NM404 were calculated in the mice using RAPID. Mean organ doses in these four test mice were compared to mean organ doses derived by using two previously published ¹³¹I S-values datasets in MOBY. In addition, mean tumor doses calculated in RAPID were compared to mean organ doses derived from unit density spheres. Large differences were identified between mean organ doses calculated in the test mice using RAPID and those derived in the MOBY phantom. Mean absorbed dose percent errors in organs ranged between 0.3% and 333%. Overall, mass scaling improved agreement between MOBY phantom calculations and RAPID where percent errors were all less than 26%, with the exception of the lung in which percent errors reached values of 48%. Percent errors in mean tumor doses in the test mice and unit density spheres were less pronounced, but still ranged between 8% and 23%. This work demonstrates the limitations of using pre-computed S-values in computational phantoms to predict organ doses in small animals from theranostic procedures. RAPID can generate accurate 3D dose distributions in small animals and in turn offer much greater insight on the ability of a given theranostic agents to image and treat diseases.

Keywords

internal dosimetry; nuclear medicine; theranostic; Monte Carlo

INTRODUCTION

Preclinical positron emission tomography (PET) enables the non-invasive characterization of biological processes in mice (e.g. metabolism, perfusion, and protein expression). It helps aid in drug discovery and development by providing useful information about the biodistribution, pharmacokinetics and pharmacodynamics (PKPD) and efficacy of new drugs. Typical preclinical PET studies require relatively large amounts of radioactivity to achieve a desired level of sensitivity and specificity. As a result, absorbed doses in mice can be quite large resulting in unintended effects such as change in gene expression, alteration of tumor characteristics and increased toxicity. Furthermore, the use of PET to characterize the biodistribution and dosimetry of novel theranostic agents is rapidly growing in the preclinical setting which has increased the need to estimate absorbed doses to mice during these studies.

A variety of investigators have attempted to estimate absorbed doses to mice from radioactive agents by coupling reference mouse phantoms with Monte Carlo simulations. Initially, stylized phantoms of mice containing organs with simplified geometries were used to perform Monte Carlo dose calculations (Hui et al. 1994, Flynn et al. 2001, Hindorf et al. 2004). It was eventually realized that voxel phantoms developed using high-resolution imaging information were much more anatomically realistic compared to stylized models. Voxel phantoms have been produced from CT (Stabin et al. 2006), MRI (Kolbert et al. 2003), and digital photographs of frozen cadaver slices (Bitar et al. 2007, Bitar et al. 2007). Significant dosimetric differences between using stylized and voxel phantoms in Monte Carlo simulations have been documented (Bitar et al. 2007). However, one of the biggest drawbacks associated with these different phantoms is that they still represent a single reference animal and fail to account for variation in shape, size, density and location of organs between mice.

Alternatively, a digital mouse phantom called MOBY was developed by Segars et al. (Segars et al. 2004) using non-uniform rational b-spline (NURBS) surfaces to define organ boundaries. Several groups have used the MOBY phantom to estimate absorbed doses to organs from radioactive agents (Larsson et al. 2007, Taschereau and Chatzioannou 2007, Keenan et al. 2010, Larsson et al. 2011, Xie and Zaidi 2013, Kostou et al. 2016). The NURBS method offers the ability to alter organ surfaces using affine or other transformation methods, which in theory, could be applied to conform the MOBY phantom to better match the specific mice under investigation. However, this process is laborious and requires familiarity with modeling tools that are generally not easily accessible to most users. Furthermore, Mauxion et al. (Mauxion et al. 2013) showed that a comparison between two similar digital mouse phantoms generated from the same software led to very different dose distributions in some organs demonstrating limitations of using digital mouse phantoms for performing Monte Carlo-based dosimetry for radioactive agents.

CT scans, which accompany most preclinical PET scans, provide an anatomical reference for the imaging agent in vivo and improve the accuracy of PET scans through attenuation and scatter correction methods. Since the voxel-based representation of a mouse anatomy and biodistribution of an imaging agent are acquired during a PET/CT scan, it seems logical

to utilize this murine-specific information for dosimetry calculations instead of relying on reference phantoms that may not accurately reflect the anatomy of the mouse being imaged. This work presents a Monte Carlo-based platform for murine-specific dosimetry called RAPID (Radionuclide Assessment Platform for Internal Dosimetry) (Besemer and Bednarz 2014, Besemer et al. 2015). A comparison between mean organ and tumor doses calculated using RAPID and those calculated using look-up tables produced in two standard mouse phantoms is provided. For all animals under consideration, organ and tumor doses were estimated following the delivery of the theranostic agent NM404. NM404 is an intravenously (IV) administered phospholipid ether analog that has shown universal tumor targeting properties in over 60 in vivo cancer and cancer stem cell models. NM404 can be labeled with ^{124}I for imaging or ^{131}I for therapy making it a powerful theranostic agent. Moreover, the imaging and therapy agents are chemically identical and administered at the same mass dose, this assuring the same in vivo biodistribution characteristics between the two molecules. This agent has been or is currently being evaluated clinically in multiple imaging and therapy trials (Grudzinski et al. 2014, Weichert et al. 2014, Lubner et al. 2015, Morris et al. 2015). This work highlights the advantages and disadvantages of performing murine-specific dosimetry when PET/CT imaging data is available.

MATERIALS AND METHODS

Xenograft tumor models

Four 6-8 week old male laboratory mice of the strain NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG, Jackson Laboratory, Bar Harbor, ME) were considered in this investigation. Human tumor xenografts were established by the subcutaneous inoculation of 4×10^6 tumor cells (100 μl cell suspension in 2% FBS) in the hind limb/flank. Four different xenografts were investigated including two neuroblastoma cell lines CHLA20 and NB1691 (courtesy of A. Davidoff, St. Jude Children's Research Hospital, Memphis, TN), a Ewings sarcoma cell line Tc-71, and a Rhabdomyosarcoma cell line Rh-30 (both obtained from COG Cell Repository, Lubbock, TX). Mice were housed in aseptic conditions in a vivarium situated in the same building with open access to food and water and placed on a 12-hour light/dark cycle. All procedures were in agreement with current institutional animal protocols approved by the UW School of Medicine and Public Health Institutional Animal Care and Use Committee and following the National Research Council Guide for the Care and Use of Laboratory Animals.

PET/CT image acquisition

PET/CT imaging was performed using the Inveon microPET/CT (Siemens, Nashville, TN). Each of the four mice were administered 8.4-10.1 MBq ^{124}I -NM404 by tail vein injection. During scanning, mice were anesthetized with 2% isoflurane. Each PET scan was terminated after 40 million counts were collected and followed by a CT scan without removing the animals from the scanner. The counts were binned in 3D histograms and the resulting images were reconstructed using ordered-subset expectation maximization (OSEM) followed by maximum a posteriori (MAP) algorithm. Important information about the mice and imaging time points is show in Table 1.

Dosimetry Workflow

Following acquisition, PET/CT data at each time point was coregistered and then resampled to match the CT voxel resolution. A CT mask was created at each time point to remove background activity that persists outside of the mouse volume. The image pre-processing and ROI contouring were performed using the AMIRA software (AMIRA, Mercury Computer Systems, Berlin, Germany). For this work, dose distributions in mice from ^{131}I -NM404 were estimated using the pre-treatment PET images of ^{124}I -NM404. Therefore, the radioactivity concentration of the imaging/tracer radionuclide was converted to that of the therapeutic radionuclide at each time point by accounting for the difference in physical decay rates. The tumor and normal tissue ROIs were contoured manually based on both anatomical and functional images.

All simulations in this work were performed using the MC code Geant4 version 9.630 (Agostinelli 2003). Geant4 is a versatile object-oriented simulation toolkit that allows for the modeling of complex geometries, radiation sources, and detectors. Geant4 has been benchmarked for a variety of different medical physics applications (Faddegon et al. 2009, Bednarz et al. 2010, Titt et al. 2012, Besemer et al. 2013, Yang and Bednarz 2013, Yang et al. 2016). The CT and PET images were used in the MC simulation to define the geometry and source distribution, respectively. The CT images were also used to define the material composition and mass density of the simulation geometry. Mouse tissue compositions were defined by segmenting the entire range of units (HUs) into 27 materials based on tissue compositions defined by Schneider et al. (Schneider et al. 2000). Each HU was given a unique mass density according to the CT scanner specific calibration. The PET images were used to define the source distribution of ^{131}I activity in the mice. The decay is simulated using the G4RadioactiveDecay module (S. Hauf 2013), which allows the simulation of the decay of more than 2000 radioactive nuclei using the decay information from the ENSDF database (Bhat 1992). The decay point is sampled uniformly throughout each voxel.

Absorbed dose rates in each voxel were calculated for each time point. A total of 4,000 ^{131}I decays were simulated per voxel. Enough decays were simulated so that the relative error in each voxel was less than 1%. Simulations were performed on a 16-node cluster (64 Intel® Xeon™ 2.8 GHz processors). The cluster has been uniquely constructed to perform direct or parallel Monte Carlo simulations. Following the simulations, each ROI volume segmented in the CT was co-registered to a corresponding ROI volume at a reference time point using normalized mutual information based affine co-registration. Each respective CT transformation matrix was then applied to each corresponding dose-rate volume. A time-integral was performed on the co-registered dose rate distributions to calculate total absorbed doses in each voxel using Matlab (Mathworks, Natick, MA).

Reference Phantom Data

Murine-specific organ doses were compared to reference data calculated in the MOBY phantom. Reference phantom data in the form of S-values were taken from Keenan et al. (2010) and Koustou et al. (2016) for a 25-g and 28-g MOBY mouse reference phantom, respectively. Both groups calculated S-values in the MOBY for ^{131}I using the Monte Carlo code Geant4. The S-value is defined as the product of the emitted energy per disintegration

and the absorbed fraction for a given combination of source and target regions and type of radiation emitted, divided by the mass of the target organ. The S-values for the MOBY phantoms and several source/target organs used in this study are provided in Table 2.

Two different methods were used to derive absorbed doses to organs in the MOBY phantom reflecting the availability of S-values provided in the literature. In Method 1 organ-specific S-values were used to calculate the self-absorbed dose to each organ, which is typically designated $S(\text{target} \leftarrow \text{target})$. Of course, this method neglects any dose contribution to the organ from the rest of the body or ‘cross-fire’. Method 2 sums the contributions of all the source organs listed in Table 2 (including the target organ) to determine the mean organ doses. Therefore, both $S(\text{target} \leftarrow \text{target})$ and $S(\text{target} \leftarrow \text{source})$ were used. Tabulated S-values were multiplied by the cumulative activities in representative organs in both methods.

Furthermore, it is often customary when performing human patient dosimetry calculations to scale S-values calculated on a reference model in order to account for differences in tissue masses between the model and the patient. For this work, we used a similar scaling approach for each individual mouse organ that is often used for human patients. If the source and target are the same, the scaling factor is simply,

$$S_{\text{mouse}}(\text{target} \leftarrow \text{target}) = S_{\text{ref}}(\text{target} \leftarrow \text{target}) \times \frac{m_{\text{ref}}}{m_{\text{mouse}}} \quad (1)$$

where $S_{\text{mouse}}(\text{target} \leftarrow \text{target})$ and $S_{\text{ref}}(\text{target} \leftarrow \text{target})$ are the S-values for the patient and standard model, and m_{mouse} and m_{ref} are the tissue masses for the patient and reference model, respectively. Note that the $1/m$ scaling corrects for energy deposition under the assumption that no electron escapes the source region. Scaling for γ -rays in human patients is also performed, but is neglected in this work because it is assumed that almost all γ -rays escape the smaller organs in the mice. Mass corrections for cross-fire S-values were also not used in this work.

Cumulative organ activities were calculated for each mouse imaged in this investigation by integrating the organ-specific time activity curves that are derived from the longitudinal PET/CT imaging scans. In particular, a trapezoidal integration was used where the initial time point was determined by linearly extrapolating back to the ordinate and assuming only exponential physical decay after the last imaging time point.

Unit Density Sphere Data

Finally, tumor doses in the test mice were compared to representative tumor doses calculated using unit density sphere S-values. S-values for ^{131}I were taken from OLINDA (Stabin et al. 2005). Following the same method as above, the S-values were multiplied by the cumulative activities in each tumor volume, which were derived by integrating the time activity curve for the tumor volume in each mouse. Given the dependency of S-values on mass, the corresponding S-values for each tumor volume had to be interpolated from the OLINDA S-value data. For this data, it was determined that a reasonable fit ($R^2 = 0.9998$) was produced using a simple power regression of the form ax^b where x is the mass of the sphere and both a

and b are coefficients with values 0.0302 and -0.958, respectively. Also as a benchmark S -values were calculated using RAPID for spheres with masses of 1, 10, 100, 1000 g. For the four masses considered, the percent difference from OLINDA S -values based on the aforementioned fit were 0.1%, 0.6%, 0.3% and 0.5%, respectively. In addition to mean doses, dose volume histograms (DVH) were also calculated in the tumors using RAPID to determine the amount of dose heterogeneity in these tumors.

RESULTS

Organ Masses

A comparison between organ masses of the test mice investigated in this study and the two reference phantoms are provided in Table 3. As expected, there are appreciable differences between the estimated organ masses of the test mice and those used in the reference phantoms. In most cases, organ masses of the test mice were smaller than organ masses in the reference phantom except in the lungs where the test mice lung masses were significantly larger than the reference lung masses. Table 3 highlights the discrepancies between the CT-based anatomies and reference anatomies used in mice phantoms, which will ultimately impact the final dose calculation.

Imaging and pharmacokinetics

Figure 1 presents time activity curves (TAC) of NM404 (%ID/g) in organs of interest. TACs are produced by decay correcting the longitudinal ^{124}I -NM404 PET data representing the actual amount of NM404 present at a given time point. Although the absolute concentrations in each mouse are comparable, it is evident from the images that the biodistribution of radiopharmaceutical concentration is noticeably different. For example, the peak concentration in the heart ranged between 11 and 15% ID/g and the minimum concentration ranged between 2 and 5% ID/g in the four mice considered, reflecting mouse-specific variations in uptake and clearance from the blood.

Absorbed dose distributions and comparison to reference phantom data

The Monte Carlo derived absorbed dose rate distributions per injected activity as a function of time are illustrated for each mouse as 3D colorwashes in Figure 2 (a-d). Figure 3 (a-d) provides the mean absorbed doses in each organ for the four mice evaluated using RAPID, along with those derived using mass scaled S -values in the two MOBY phantoms for the two methods considered. Similar to the activity distributions, it is evident that the absorbed dose distributions vary between the different mice. The largest absolute percent difference between the maximum and minimum mean absorbed dose calculated using RAPID was in the liver with a value of 64%. The heart, liver, kidneys and lungs typically received the highest absorbed dose per injected activity whereas the brain received the lowest absorbed dose per injected activity. The relatively high dose to the heart, liver, kidney and lung can be attributed to the fact that NM404 slowly clears from the blood. It should be noted that the entire heart contour contains both the heart wall and blood pool. We expect that the absorbed dose to the heart wall would be less than the dose to the entire heart.

Table 4 provides the percent error between the absorbed dose to each organ derived using S-values in the two MOBY phantoms for the two methods considered and the absorbed dose calculated with RAPID. It is clear that absorbed dose differences between organs in the test mice and organs in the MOBY phantoms were significant. In general, the agreement between RAPID organ doses and MOBY organ doses calculated using S-values provided by Keenan et al. (2010) was better than MOBY organ doses calculated using S-values provided by Kostou et al. (2016). In all but four organs, the agreement improved when mass scaling was performed using the S-values of Keenan et al. (2010). Mass scaling only led to improvement in 10 out of 20 organs when RAPID organ doses were compared to those calculated using the S-values of Kostou et al. (2016). The better agreement observed when using the S-values of Keenan et al. (2010) is likely due to the fact that organ masses in the 25-g MOBY phantom better matched organ masses in the test mice compared to the 28-g MOBY phantom as shown in Table 3. As depicted in Figure 3, accounting for organ ‘cross-fire’ in Method 2 only slightly increased the absorbed doses to the target organs when compared to Method 1. However, in most cases the increase in absorbed dose did not lead to better agreement with RAPID.

Likely, multiple factors led to the discrepancies reported between RAPID and MOBY. Firstly, as shown by Mauxion et al. (2013), minor geometric variations between mice may lead to significantly different S-values representing self-absorbed dose and “cross-fire” dose in organs. Such differences will be further exacerbated by utilizing microCT images to characterize organ sizes and tissue densities. Also, motion artifacts will influence the ability of microCT scanners to characterize tissue densities accurately. This issue is especially problematic in the lung, which likely led to the major discrepancies between RAPID and both MOBY phantoms reported in our investigation. The average measured density of tissues in the lung across all test mice was ~0.6 g/cc, which is much higher than the uniform density generally assumed for the MOBY lung of ~0.3 g/cc. The larger, and likely erroneous, lung densities used by RAPID significantly impacted the final absorbed dose estimation in this organ. Finally, the microPET images used in for the dose calculations in RAPID are also subject to uncertainty. The limited resolution of the microPET scanner leads to partial volume effects, which will be exacerbated in small volumes. Partial volume effects will influence both RAPID and MOBY calculations, but may be more significant in RAPID where heterogeneous activity distributions are utilized.

Tumor Absorbed Dose versus Unit Density Sphere Models

Table 5 provides a comparison between the mean absorbed doses to the tumor calculated in the test mice and the mean absorbed doses calculated assuming the tumor is a unit density sphere based on OLINDA S-value estimates (Stabin et al. 2005). All of the percent errors in absorbed doses were less than 23%. The OLINDA sphere dose was consistently larger than the MC dose, which is opposite of the trend detected when comparing absorbed doses in most organs between the test mice and MOBY phantom. It is believed that the shape of the tumor impacted the ability of unit density spheres to accurately predict absorbed dose to the tumor. The tumor volumes in the test mice were more ellipsoidal than spherical as illustrated in Figure 4. Amato et al. (Amato et al. 2009) showed that specific absorbed fractions in spheres and ellipsoids depend on the volume to surface area ratio. The specific absorbed

fraction for prolated ellipsoids tend to be smaller than spheres with equivalent volumes. The OLINDA sphere dose likely overestimated the tumor doses because of the oblong nature of the tumor volumes. It is interesting to note that the two tumor volumes that were less oblong, Mouse 2 and 4, had smaller differences when compared to the OLINDA sphere absorbed doses. Furthermore, unlike healthy organs, tumors in the test mice were each inoculated on the side flank making them much less susceptible to ‘cross-fire’ dose from adjacent organs and tissues.

DISCUSSION

There is a compelling need to estimate absorbed doses to mice from radionuclides used in preclinical studies, which has increased recently due in large part to the development of novel theranostic agents. PET imaging is often used to characterize the biodistribution of theranostic agents, thus providing useful information in the early stages of drug development. These PET images can then be used to estimate absorbed doses to organs or tumors to help evaluate the potential efficacy of molecular radiotherapy treatments prior to being used on patients. Reference phantoms, such as MOBY, have been commonly used to represent the anatomy of the animals during the preclinical dosimetry process. However, it seems appropriate to utilize CT scans that are acquired during most preclinical PET studies to perform dosimetry on the actual anatomy of the animals under investigation. In this work a murine-specific dosimetry platform called RAPID was introduced and a comparison between mean organ and tumor absorbed doses in four different test mice was done using either RAPID or reference phantoms.

In general, significant discrepancies were found between mean organ doses calculated with RAPID and the two MOBY phantoms. These discrepancies can be attributed to differences in organ sizes, tissue densities and the characterization of the pharmacokinetic behavior of the agent in the mice. Mean absorbed dose percent errors ranged between 0.5% and 48%, even when a scaling approach was applied to account for the large differences in organ masses between the test mice and the MOBY phantom. These discrepancies are likely due to multiple factors including the sensitivity of S-values on even small variations in mice anatomy, motion artifacts in the CT data, and partial volume effects in the PET data. Furthermore, it is clear from this study that improved scaling methods for murine dosimetry need to be devised for murine animals.

Alternatively, organ masses can be deformed in the MOBY phantom to better match the mouse it is attempting to model, but the deformable registration process can be laborious and a unique dose calculation for the each individual mouse would still be required. S-value tables can be produced for a range of mouse sizes by scaling the MOBY phantom (Xie and Zaidi 2013), but even improved models may not be able to accurately characterize dose distributions for some radioactive agents since the particle ranges of decay products involved in small animal imaging are of the same order of magnitude as organ dimensions as pointed out by Mauxion et al. (Mauxion et al. 2013). Uniform organ densities are also used in the MOBY phantom, albeit most organs in mice contain a distribution of tissue densities. Differences in tissue densities between the test mice and the MOBY phantoms also contributed to the dose discrepancies observed in this study.

The RAPID platform has clear advantages over reference models. One such advantage is that the specific heterogeneous distribution of an agent that is captured on a voxel level with PET/CT can be directly translated into 3D absorbed dose distributions using Monte Carlo simulations. This means that the heterogeneity of the absorbed dose in organs and tumors can be assessed, as exemplified for tumor volumes in Figure 5. Conversely, absorbed doses calculated using reference phantoms are commonly averaged over the entire organ or tumor. Furthermore, the voxel level heterogeneity of the absorbed dose afforded by RAPID leads to implementation of better predictors of radiation-induced effects for radionuclide therapy such as the biological effective dose (BED) (Grudzinski et al. 2010). Despite being out of the scope of this paper, RAPID is currently configured to perform voxel-level BED calculations. In addition, there has been recent attention to investigate the combination of radionuclide therapy and external beam radiotherapy. Small animal irradiators with 3D treatment planning capabilities are currently available affording the ability to deliver conformal dose distributions in mice. Understanding the total 3D dose distribution from radionuclide therapy and EBRT seems imperative when assessing the treatment efficacy of this combination approach (Morris et al. 2015). Finally, quantitative 3D data can prove very important when designing maximum tolerable dose studies because starting doses can be better optimized with respect to the actual mouse. This has the potential to save both time and money during the drug development process.

Despite these advantages, the approach presented in this paper also has drawbacks. Respiratory and cardiac motion led to blurring in the microCT images impacting our ability to accurately characterize material properties in these organs. This was most impactful in the lung where average density of tissues in the lung across all test mice was ~0.6 g/cc, which is much higher than the uniform density generally assumed for the lung of ~0.3 g/cc. These likely erroneous lung densities used by RAPID significantly impacted the final absorbed dose estimation in this organ. Lung dosimetry can be improved by using respiratory gating approaches during microCT scanning or by assuming a uniform density in the lung during the Monte Carlo simulations. In addition, peristalsis along with respiratory and cardiac motion make imaging the bowel difficult (Jelicks 2010). Typically, differentiation of vital organs in the bowel cannot be done without suitable oral contrast agents, but the impact of these agents on drug pharmacokinetics and dosimetry has never been investigated. Finally, a significant amount of effort is required for organ and tumor volume segmentation at each time point for each mouse. Automated segmentation would significantly improve the workflow of murine-specific dosimetry, which for some pre-clinical trials could involve a large number of mice. It seems reasonable to suggest the use of the MOBY phantom as an atlas to help guide the automated segmentation process (Scheenstra et al. 2009, Nie and Shen 2013).

CONCLUSION

This work demonstrates the limitations of using S-values computed in digital mouse phantoms for preclinical dosimetry with focus on theranostic agents. If S-values are to be used for preclinical dosimetry then improved scaling methods that adequately reflect electron transport in small organs need to be developed. The most accurate representation of the geometry and material composition of a mouse along with the biodistribution of a

radiolabeled theranostic agent within is obtained with PET/CT scanning. These images coupled with Monte Carlo simulations can generate accurate 3D dose distributions in small animals and in turn offer useful insight on the ability of a given theranostic agent to treat diseases. Given the increased use of novel theranostic agents clinically, either alone or in combination with another treatment approach, we envision a greater need to perform murine-specific dosimetry in the future.

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References

- Agostinelli, Sea. Geant4 - A simulation toolkit. Nucl Instrum Methods Phys Res A. 2003; 506:250.
- Amato E, Lizio D, Baldari S. Absorbed fractions in ellipsoidal volumes for beta(-) radionuclides employed in internal radiotherapy. Phys Med Biol. 2009; 54:4171–80. [PubMed: 19521004]
- Bednarz B, Daartz J, Paganetti H. Dosimetric accuracy of planning and delivering small proton therapy fields. Phys Med Biol. 2010; 55:7425–38. [PubMed: 21098920]
- Besemer A, Grudzinski J, Titz B, Bednarz B. Evaluation of dosimetric uncertainties in individualized targeted radionuclide therapy (TRT) treatment planning using pre-clinical data. Medical Physics. 2015; 42:3675–3675.
- Besemer A, Bednarz B. Validation of a patient-specific Monte Carlo targeted radionuclide therapy dosimetry platform. Medical Physics. 2014; 41:303–304.
- Besemer A, Paganetti H, Bednarz B. The clinical impact of uncertainties in the mean excitation energy of human tissues during proton therapy. Phys Med Biol. 2013; 58:887–902. [PubMed: 23337713]
- Bhat MR. Evaluated nuclear structure data file (ENSDF). Nuclear Data for Science and Technology. 1992
- Bitar A, Lisbona A, Bardiès M. S-factor calculations for mouse models using monte-carlo simulations. Q J Nucl Med Mol Imaging. 2007; 51:343–51. [PubMed: 17538523]
- Bitar A, Lisbona A, Thedrez P, Sai Maurel C, Le Forestier D, Barbet J, Bardiès M. A voxel-based mouse for internal dose calculations using monte carlo simulations (MCNP). Phys Med Biol. 2007; 52:1013–25. [PubMed: 17264367]
- Faddegon BA, Kawrakow I, Kubyshev Y, Perl J, Sempau J, Urban L. The accuracy of egsnrc, geant4 and penelope monte carlo systems for the simulation of electron scatter in external beam radiotherapy. Phys Med Biol. 2009; 54:6151–63. [PubMed: 19779217]
- Flynn AA, Green AJ, Pedley RB, Boxer GM, Boden R, Begent RH. A mouse model for calculating the absorbed beta-particle dose from (131)I- and (90)Y-labeled immunoconjugates, including a method for dealing with heterogeneity in kidney and tumor. Radiat Res. 2001; 156:28–35. [PubMed: 11418070]
- Grudzinski JJ, Titz B, Kozak K, Clarke W, Allen E, Trembath L, Stabin M, Marshall J, Cho SY, Wong TZ, Mortimer J, Weichert JP. A phase 1 study of 131I-NM404 in patients with relapsed or refractory advanced solid tumors: Dosimetry, biodistribution, pharmacokinetics, and safety. PLoS One. 2014; 9:e111652. [PubMed: 25402488]
- Grudzinski JJ, Tomé W, Weichert JP, Jeraj R. The biological effectiveness of targeted radionuclide therapy based on a whole-body pharmacokinetic model. Phys Med Biol. 2010; 55:5723–34. [PubMed: 20826898]
- Hindorf C, Ljungberg M, Strand SE. Evaluation of parameters influencing s values in mouse dosimetry. J Nucl Med. 2004; 45:1960–5. [PubMed: 15534069]

- Hui TE, Fisher DR, Kuhn JA, Williams LE, Nourigat C, Badger CC, Beatty BG, Beatty JD. A mouse model for calculating cross-organ beta doses from yttrium-90-labeled immunoconjugates. *Cancer*. 1994; 73:951–7. [PubMed: 8306284]
- Jelicks LA. Imaging the gastrointestinal tract of small animals. *J Neuroparasitology*. 2010; 1
- Keenan MA, Stabin MG, Segars WP, Fernald MJ. Radar realistic animal model series for dose assessment. *J Nucl Med*. 2010; 51:471–6. [PubMed: 20197451]
- Kolbert KS, Watson T, Matei C, Xu S, Koutcher JA, Sgouros G. Murine s factors for liver, spleen, and kidney. *J Nucl Med*. 2003; 44:784–91. [PubMed: 12732681]
- Kostou T, Papadimitroulas P, Loudos G, Kagadis GC. A preclinical simulated dataset of S-values and investigation of the impact of rescaled organ masses using the moby phantom. *Phys Med Biol*. 2016; 61:2333–55. [PubMed: 26930000]
- Larsson E, Ljungberg M, Strand SE, Jönsson BA. Monte Carlo calculations of absorbed doses in tumours using a modified moby mouse phantom for pre-clinical dosimetry studies. *Acta Oncol*. 2011; 50:973–80. [PubMed: 21767199]
- Larsson E, Strand SE, Ljungberg M, Jönsson BA. Mouse s-factors based on Monte Carlo simulations in the anatomical realistic moby phantom for internal dosimetry. *Cancer Biother Radiopharm*. 2007; 22:438–42. [PubMed: 17651052]
- Lubner SJ, Mullvain J, Perlman S, Pishvaian M, Mortimer J, Oliver K, Heideman J, Hall L, Weichert J, Liu G. A phase 1, multi-center, open-label, dose-escalation study of ¹³¹I-NM404 in subjects with relapsed or refractory advanced solid malignancies. *Cancer Invest*. 2015; 33:483–9. [PubMed: 26536061]
- Mauxion T, Barbet J, Suhard J, Pouget JP, Poirot M, Bardiès M. Improved realism of hybrid mouse models may not be sufficient to generate reference dosimetric data. *Med Phys*. 2013; 40:052501. [PubMed: 23635291]
- Morris ZS, Weichert JP, Saker J, Armstrong EA, Besemer A, Bednarz B, Kimple RJ, Harari PM. Therapeutic combination of radiolabeled NM404 with external beam radiation in head and neck cancer model systems. *Radiother Oncol*. 2015; 116:504–9. [PubMed: 26123834]
- Nie J, Shen D. Automated segmentation of mouse brain images using multi-atlas multi-roI deformation and label fusion. *Neuroinformatics*. 2013; 11:35–45. [PubMed: 23055043]
- Hauf S, K M, Batic M, Bell ZW, Hoffmann DH, Lang PM, Neff S, Pia MG, Weidenspointner G, Zoglauer A. Radioactive decays in Geant4. *Nuclear Science IEEE Transactions*. 2013; 60:2966–2983.
- Scheenstra AE, van de Ven RC, van der Weerd L, van den Maagdenberg AM, Dijkstra J, Reiber JH. Automated segmentation of in vivo and ex vivo mouse brain magnetic resonance images. *Mol Imaging*. 2009; 8:35–44. [PubMed: 19344574]
- Schneider W, Bortfeld T, Schlegel W. Correlation between ct numbers and tissue parameters needed for monte carlo simulations of clinical dose distributions. *Phys Med Biol*. 2000; 45:459–78. [PubMed: 10701515]
- Segars WP, Tsui BM, Frey EC, Johnson GA, Berr SS. Development of a 4-d digital mouse phantom for molecular imaging research. *Mol Imaging Biol*. 2004; 6:149–59. [PubMed: 15193249]
- Stabin MG, Peterson TE, Holburn GE, Emmons MA. Voxel-based mouse and rat models for internal dose calculations. *J Nucl Med*. 2006; 47:655–9. [PubMed: 16595500]
- Stabin MG, Sparks RB, Crowe E. Olinda/exm: The second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*. 2005; 46:1023–7. [PubMed: 15937315]
- Taschereau R, Chatziioannou AF. Monte carlo simulations of absorbed dose in a mouse phantom from 18-fluorine compounds. *Med Phys*. 2007; 34:1026–36. [PubMed: 17441249]
- Titt U, Bednarz B, Paganetti H. Comparison of mcnpX and geant4 proton energy deposition predictions for clinical use. *Phys Med Biol*. 2012; 57:6381–93. [PubMed: 22996039]
- Weichert JP, Clark PA, Kandela IK, Vaccaro AM, Clarke W, Longino MA, Pinchuk AN, Farhoud M, Swanson KI, Floberg JM, Grudzinski J, Titz B, Traynor AM, Chen HE, Hall LT, Pazoles CJ, Pickhardt PJ, Kuo JS. Alkylphosphocholine analogs for broad-spectrum cancer imaging and therapy. *Sci Transl Med*. 2014; 6:240ra75.
- Xie T, Zaidi H. Monte carlo-based evaluation of S-values in mouse models for positron-emitting radionuclides. *Phys Med Biol*. 2013; 58:169–82. [PubMed: 23221270]

- Yang YM, Bednarz B. Consistency evaluation between egsrc and Geant4 charged particle transport in an equilibrium magnetic field. *Phys Med Biol*. 2013; 58:N47–58. [PubMed: 23370042]
- Yang YM, Svatos M, Zankowski C, Bednarz B. Concurrent monte carlo transport and fluence optimization with fluence adjusting scalable transport Monte Carlo. *Med Phys*. 2016; 43:3034. [PubMed: 27277051]

Figure 1. Concentration of NM404 over time for normal organs in test mice 1-4 (a-d). Imaging time points for each mouse are provided in Table 1.

Figure 2.
3D colorwashes of absorbed dose rate distributions calculated in the test mice. Each row represents a different xenograft including NB1691 (top row), CHLA20 (2nd row), Rh30 (3rd row), and Tc71 (bottom row).

Figure 3.

Mean absorbed doses in several organs of interest calculated in test mice 1-4 (a-d) using RAPID or mass scaled S-values in the MOBY phantoms for the two methods considered.

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Figure 4.
3D representation of the tumor volumes in the test mice.

Figure 5.
Dose volume histograms for the tumors in the four different test mice.

Table 1

Animal imaging data for the four mice used in this work.

Mouse ID	Cell Line	Imaging Time Points (hrs)	Initial Body Weight (g)	Injected Activity (MBq)
1	NB1691	3, 24, 45, 70, 96	20.0	9.92
2	CHLA20	2, 24, 45, 70, 96	22.9	10.0
3	Rh30	1, 24, 48, 72, 170	26.6	8.40
4	Tc71	1, 24, 48, 72, 170	27.2	8.44

S-values for ^{131}I calculated using the 25-g MOBY phantom (Keenan et al. 2010) and 28-g MOBY digital phantom (Kostou et al. 2016).

Table 2

Source	S-value (Gy/Bq-s)									
	Brain		Lungs		Heart		Kidneys		Liver	
	Keenan et al	Kostou et al	Keenan et al	Kostou et al	Keenan et al	Kostou et al	Keenan et al	Kostou et al	Keenan et al	Kostou et al
Brain	6.42×10^{-11}	4.91×10^{-11}	5.22×10^{-14}	3.37×10^{-14}	4.05×10^{-14}	1.14×10^{-14}	1.28×10^{-14}	1.89×10^{-14}	2.22×10^{-14}	1.65×10^{-14}
Lungs	5.04×10^{-14}	3.87×10^{-14}	2.30×10^{-10}	1.05×10^{-10}	6.69×10^{-12}	1.40×10^{-12}	5.45×10^{-14}	8.85×10^{-14}	1.43×10^{-12}	7.48×10^{-13}
Kidneys	1.09×10^{-14}	9.79×10^{-15}	5.50×10^{-15}	3.94×10^{-14}	4.63×10^{-14}	1.33×10^{-14}	9.60×10^{-11}	1.39×10^{-10}	2.21×10^{-13}	3.25×10^{-13}
Liver	2.23×10^{-14}	1.73×10^{-14}	1.37×10^{-12}	6.73×10^{-13}	5.15×10^{-13}	1.34×10^{-13}	2.18×10^{-13}	6.61×10^{-13}	1.75×10^{-11}	1.38×10^{-11}
Heart	4.46×10^{-14}	3.29×10^{-14}	6.43×10^{-12}	3.41×10^{-12}	1.33×10^{-10}	1.11×10^{-10}	4.47×10^{-14}	7.21×10^{-14}	2.21×10^{-13}	3.64×10^{-13}

Organ mass (g) comparison between the test mice, the 25-g MOBY phantom (Keenan et al. 2010) and the 28-g MOBY phantom (Kostou et al. 2016).

Table 3

<u>Organ</u>	Mouse 1	Mouse 2	Mouse 3	Mouse 4	MOBY	
					Keenan et al	Kostou et al
Brain	0.47	0.58	0.42	0.34	0.47	0.67
Lungs	0.18	0.47	0.26	0.26	0.087	0.14
Heart	0.26	0.26	0.25	0.26	0.24	0.22
Kidneys	0.24	0.26	0.26	0.27	0.30	0.39
Liver	1.26	1.34	1.17	1.16	1.74	2.16
Tumor	0.25	0.18	0.54	0.45	-	-
Whole Body	21.5	23.3	25.5	26.5	25.0	28.0

Table 4

Percent error (DMOBY-DRAPID/DRAPID) between the absorbed dose to each organ calculated with RAPID and those derived using S-values in the MOBY phantom for the three methods considered. S-values for a whole body source to a heart target and S-values for a marrow target from several source organs were not available.

	Method 1				Method 2				
	Unscaled		Scaled		Unscaled		Scaled		
	Keenan at al.	Kostou et al.	Keenan at al.	Kostou et al.	Keenan at al.	Kostou et al.	Keenan at al.	Kostou et al.	
Mouse 1	Brain	13.4%	-13.4%	11.4%	23.0%	14.1%	-12.9%	12.1%	23.6%
	Lungs	52.2%	-30.5%	-25.4%	-44.4%	66.1%	-23.3%	-11.4%	-37.2%
	Heart	27.7%	6.5%	17.4%	-9.6%	33.0%	7.8%	22.7%	-8.4%
	Kidneys	-11.0%	-35.5%	12.1%	5.1%	-8.3%	-31.6%	14.8%	9.0%
	Liver	-13.3%	-31.7%	19.3%	16.8%	-11.8%	-30.4%	20.8%	18.1%
Mouse 2	Brain	39.2%	6.3%	12.3%	24.0%	39.2%	6.9%	13.2%	24.7%
	Lungs	333.0%	97.5%	-20.3%	-40.6%	332.7%	104.3%	-7.3%	-33.9%
	Heart	27.9%	6.7%	13.5%	-12.6%	27.9%	9.4%	25.9%	-9.9%
	Kidneys	-1.6%	-28.8%	13.4%	6.3%	-1.6%	-24.9%	14.8%	10.2%
	Liver	-18.3%	-35.6%	6.0%	3.7%	-18.3%	-33.2%	9.5%	6.1%
Mouse 3	Brain	2.5%	-21.8%	11.7%	23.3%	3.1%	-21.3%	12.3%	23.8%
	Lungs	112%	-3.2%	-30.1%	-47.9%	122.2%	2.0%	-20.0%	-42.7%
	Heart	14.4%	-4.5%	6.2%	-18.3%	21.6%	-2.9%	13.3%	-16.7%
	Kidneys	-10.1%	-34.9%	2.8%	-3.6%	-7.9%	-31.8%	5.0%	-0.5%
	Liver	-30.0%	-44.8%	4.4%	2.2%	-27.8%	-43.2%	6.7%	3.9%
Mouse 4	Brain	-24.0%	-42.0%	4.2%	15.1%	-23.3%	-41.4%	4.9%	15.6%
	Lungs	118.0%	-0.3%	-28.2%	-46.5%	128%	4.7%	-18.4%	-41.4%
	Heart	14.7%	-4.3%	5.4%	-18.8%	22.5%	-2.6%	13.2%	-17.1%
	Kidneys	-14.2%	-38.0%	-2.5%	-8.6%	-11.9%	-34.6%	-0.2%	-5.3%
	Liver	-30.3%	-45.0%	4.8%	2.6%	-28.1%	-43.4%	7.1%	4.2%

Table 5

Percent error ($(D_{\text{SPHERE}} - D_{\text{RAPID}}) / D_{\text{RAPID}}$) between the absorbed dose to each organ calculated with RAPID and those derived using assuming the tumor is a unit density sphere based on OLINDA S-value estimates (Stabin et al. 2005).

	Mean MC Dose (Gy)	Mean OLINDA Sphere Dose (Gy)	% Diff
Mouse 1	13.6	15.9	17.4%
Mouse 2	11.0	12.3	11.7%
Mouse 3	15.9	19.4	22.5%
Mouse 4	7.05	7.64	8.35%