Toward an organ based dose prescription method for the improved accuracy of murine dose in orthovoltage x-ray irradiators

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Purpose: Accurate dosimetry is essential when irradiating mice to ensure that functional and molecular endpoints are well understood for the radiation dose delivered. Conventional methods of prescribing dose in mice involve the use of a single dose rate measurement and assume a uniform average dose throughout all organs of the entire mouse. Here, the authors report the individual average organ dose values for the irradiation of a 12, 23, and 33 g mouse on a 320 kVp x-ray irradiator and calculate the resulting error from using conventional dose prescription methods.

Methods: Organ doses were simulated in the Geant4 application for tomographic emission toolkit using the MOBY mouse whole-body phantom. Dosimetry was performed for three beams utilizing filters A (1.65 mm Al), B (2.0 mm Al), and C (0.1 mm Cu + 2.5 mm Al), respectively. In addition, simulated x-ray spectra were validated with physical half-value layer measurements.

Results: Average doses in soft-tissue organs were found to vary by as much as 23%–32% depending on the filter. Compared to filters A and B, filter C provided the hardest beam and had the lowest variation in soft-tissue average organ doses across all mouse sizes, with a difference of 23% for the median mouse size of 23 g.

Conclusions: This work suggests a new dose prescription method in small animal dosimetry: it presents a departure from the conventional approach of assigning a *single dose value* for irradiation of mice to a more comprehensive approach of characterizing individual organ doses to minimize the error and uncertainty. In human radiation therapy, clinical treatment planning establishes the target dose as well as the dose distribution, however, this has generally not been done in small animal research. These results suggest that organ dose errors will be minimized by calibrating the dose rates for all filters, and using different dose rates for different organs.

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1. INTRODUCTION

Small animals are an important component of preclinical medical research, typically being used to test safety and efficacy before studies begin in human subjects.¹ Murine models allow researchers to work with large sample sizes at relatively low cost, and as such, it is not surprising that murine models are popular for both radiation countermeasure and radiation therapy studies.

In order to achieve consistent results in small animal radiation studies, great emphasis is given to minimize the uncertainty that results from factors that can be controlled and monitored, such as the radiation dosimetry.² In an ideal world, image guided therapy (IGT), such as is available on the 225Cx (Precision X-ray, North Branford, CT), would be used for each individual mouse to ensure accurate doses were delivered to the target location. However, for experiments that require multiple irradiations due the large number of

mice involved, it is not feasible to use image guided treatment machines to individually image, plan, and treat the animals one at a time.

For experiments that seek to estimate risk thresholds or functional endpoints in steep dose response curves, it is imperative to accurately know the dose that was delivered to the target organ. However, with current dosimetry methods used for irradiation, the researcher often assumes a uniform and homogenous dose profile throughout the entire mouse. This drives the need for new methods of dose prescription to provide accurate dosimetry where irradiation is performed by small animal orthovoltage x-ray irradiators.

Recently, due to concerns of national security, more researchers have considered the use of orthovoltage irradiators instead of the use of Cs-137 irradiators.²⁹ One popular orthovoltage machine used for whole body irradiation of mice is the Xrad-320 (Precision X-ray).³⁰ Currently, most researchers prescribe dose based upon a single dose rate value that is provided to them. Using this conventional prescription method, the exposure time for an animal is calculated by dividing the final target dose by the provided dose rate value.

Low kV studies on small animal x-ray irradiators at 120 and 225 kVp have been performed that describe dose distributions in small animals.^{3–6} In addition, studies have been performed assuming monoenergetic photon fluences; however, polyenergetic Xrad-320 spectra have not been investigated.⁷ While others have studied the radiobiological effects of irradiation on an Xrad-320, to date, no realistic whole-body mouse simulation of dose from a 320 kVp machine has been performed.⁸

Here we calculate the Monte Carlo simulated doses in multiple organs using the MOBY mouse phantom.⁹ This work quantifies the dosimetry error that can arise by neglecting to calculate specific organ doses in mice when using the Xrad-320. The results presented here are not meant to be used as a look-up table, since they are dependent on the experimental geometry and setup.

2. MATERIALS AND METHODS

2.A. Geant4 application for tomographic emission (GATE)

The GATE is a toolkit that interfaces to Geant4 and allows for an easy way to setup medical physics dosimetry simulations.^{10–13} GATE has been validated for low energy electromagnetic simulations, and it is commonly used for PET/SPECT studies.^{14–16} In addition, GATE has previously been used to study the dose in mice from imaging at 80 kVp.¹⁴ GATE v6.2 was used as an interface to Geant4 to determine the doses delivered to mice. Geant4 is a Monte Carlo physics simulation software developed at CERN originally for high energy physics applications.¹⁷ The physics settings for the GATE simulations are shown in Table I. In order to achieve high resolution dose output, several default parameters were modified to allow for the production of lower energy particles. One such change was the electron cut value; modified to 0.01 mm from the default value of 1 mm. In muscle tissue, an

TABLE I. Physics settings in GATE.

Process	Model
Photoelectric	Livermore
Electron ionization	Standard
Bremsstrahlung	Standard
Compton scatter	Livermore
Rayleigh scatter	Livermore
e [−] e ⁺ Multiple scatter	Urban93

electron cut of 0.01 mm corresponds to a production threshold energy of about 15 keV. Due to the submillimeter voxel size used in this simulation, particles with track lengths less than 1 mm were considered to ensure accuracy of dose deposition to the ~ 0.1 mm voxel size resolution. However, since there was a trade-off between the dose accuracy and simulation time, the cut values were not set to an arbitrarily small value. An electron cut value of 0.01 mm was experimentally found to provide a reasonable compromise between efficiency and accuracy. In addition, low energy physics models, such as the Livermore model (valid 250 eV to 100 GeV), were used in place of the standard model (valid 1 keV to 100 TeV) where possible (GATE User's Guide V6.2).

2.B. Xrad-320

The small animal irradiator studied here was the Xrad-320, capable of providing a maximum treatment beam of 320 kVp. For this machine, there were four filters available as shown in Table II. The most commonly used filters are B (2 mm Al) and C (0.1 mm Cu + 2.5 mm Al) since they provide moderate beam hardening without severe detriment to dose rate. The field size was 20×20 cm² at the location of the 3 mm thick stainless steel shelf. The removable shelf was 50 cm from the anode focal spot, and can be used to hold the mouse specimen during irradiation.

2.C. Phantom

The MOBY realistic mouse phantom, a whole body murine computer model, was used as the input to GATE for the spatial map of the atomic composition and density of materials in the body.⁹ A 33 g mouse (the default size) was voxelized into $256 \times 256 \times 800$ voxels of size $0.145 \times 0.145 \times 0.145$ mm³. Since the default 33 g mouse was larger than the young mice that researchers commonly work with, additional 12 and 23 g mouse models were created by scaling

TABLE II. Available filters for the Xrad-320 machine.

Filter name	Filtration amount
A	1.65 mm Al
B	2 mm Al
C	0.1 mm Cu + 2.5 mm Al
D	0.8 mm Sn + 0.25 mm Cu + 1.5 mm Al

FIG. 1. The MOBY phantom was used to define the (a) material definition for dosimetry derived from photon attenuation data, (b) anatomical definitions of organs derived from the source activity output, and (c) corresponding organ masks such as the lung mask.

the voxel size, resulting in $256 \times 256 \times 800$ voxels of size $0.1036 \times 0.1036 \times 0.1036 \text{ mm}^3$ and $0.1286 \times 0.1286 \times 0.1286 \text{ mm}^3$, respectively.

The MOBY phantom was chosen for these experiments since it has been used extensively in GATE simulations.^{18–20} In addition, voxelized mouse models have previously been used for other dosimetry studies, such as for the use of calculating organ dose conversion values (S-factors) in mice for injected radionuclides.^{21–23} The MOBY software provided two outputs as shown in Fig. 1: (a) a photon attenuation map that was used as the material information for the photon dosimetry, and (b) an output (radioactive nuclide source activity) file that allowed for each individual organ to be assigned a unique integer value. These unique integer values allowed for binary-mask segmentation and tallying of the dose in all of the individual organs.

2.D. X-ray spectra

The x-ray tube used in the Xrad-320 was simulated in Geant4 v9.4p02 according to specifications provided by the manufacturer. The bremsstrahlung energy spectrum was obtained by simulating physical interactions of a monoenergetic 320 keV electron beam in a tungsten anode target. The emitted bremsstrahlung photons were measured with a simulated detector placed at 50 cm SOD, and binned by energy. Three filters (A, B, and C), as shown in Table II, were separately placed in the simulation to harden the beam.

2.E. Monte Carlo dose

By utilizing GATE radiation therapy dose actors, the dose output was stored in voxels (dosels) with the same resolution as the input phantom anatomy. Binary masks were used to tally the dose in each individual organ, as shown in

Fig. 1(c). The red bone marrow dose was calculated by using the homogenous bone approximation, in which the dose delivered to homogenous skeletal tissue was used as the estimate of red bone marrow dose.²⁴ Once the filtered energy spectra were obtained from Geant4, the relative emission frequency at each energy bin was then used as the beam input for the GATE dose simulations. The dose output for each individual x-ray spectrum utilized 4×10^9 source particles and required ~ 35 days of simulation time on an Intel i7-3820 CPU running at 3.6 GHz (this was cut down to ~ 9 days by running simultaneously on all four cores).

2.F. Simulation geometry

A single mouse was centered at a position that was 50 cm from the focal spot of the x-ray tube, representative of the Xrad-320 geometry. The mouse was prone so that the $20 \times 20 \text{ cm}^2$ beam entered the mouse from the dorsal side. No machine shielding was included in the simulations. GATE simulations were also performed to measure the dose difference due to the inclusion of a 3 mm stainless steel shelf placed on the ventral side of the MOBY phantom. The simulation results reported here did not include the 3 mm stainless steel shelf in the simulation, since it was determined that the steel shelf did not lead to substantial changes in calculated organ dose values.

2.G. Experimental verification of Monte Carlo results

Validation of the Monte Carlo simulations was performed by comparing the beam quality of Geant4 x-ray spectra to the measured beam quality of the Xrad-320. The half-value layers (HVLs) were experimentally obtained on the Xrad-320 by measuring the change in exposure as high-purity copper filters were added at the output window of the tube. The exposure was measured free-in-air by placing a 6 cm^3 ion chamber (RadCal) in the irradiator, at a distance of 50 cm from the anode focal spot.

Measurements of the 3 mm shelf backscatter were also performed for further validation of the Monte Carlo simulations. A GATE simulation that calculated the backscatter dose in a $1 \times 1 \times 1 \text{ cm}^3$ volume of water was compared to a physical experiment, in which a 0.18 cm^3 ion chamber (RadCal, Monrovia, CA) was used to record the exposure with the 3 mm stainless steel shelf in place versus removed. For the free-in-air geometry with the shelf removed, the ion chamber was positioned on top of Styrofoam to achieve the same 50 cm SOD.

For the Monte Carlo HVL simulations, an amount of copper corresponding to the experimentally measured HVL was added in front of the simulated x-ray beam and the dose deposited in a volume of water was recorded at a distance of 50 cm away from the x-ray tube. The ratio of the dose for the beam with added copper to the dose from the beam without added copper was calculated, and compared against the expected value of 0.5. This simulation was performed without a shelf. Due to the similarity of filter A and B beams, only the filter B and C HVLs were calculated.

FIG. 2. Relative energy spectra, showing relative beam hardening as more filtration is used. Data were obtained from simulations performed using Geant4. Data were rebinned in groups of five to create this figure.

3. RESULTS

The obtained Xrad-320 spectra for filters A, B, and C are shown in Fig. 2, compared to the “open” (no-filter) spectrum. The mean photon energy was found to be 71, 81, 85, and 94 keV for the open beam and filters A, B, and C, respectively.

Experimentally measured HVL data are shown in Fig. 3, where the HVL's were found to be 1.04, 1.06, and 1.43 mm Cu for the filters A, B, and C, respectively. For the Monte Carlo HVL simulations, the addition of 1 mm Cu for filter B was found to decrease the dose to a ratio of 0.453 ± 0.001 , and the addition of 1.4 mm Cu for filter C was found to decrease the dose to a ratio of 0.477 ± 0.003 .

In the MOBY phantom, there was an increase in absolute dose due to the 3 mm stainless steel shelf, but after normalization, the effect of backscatter on relative organ doses was

FIG. 3. Physical measurements of Xrad-320 beam attenuation with the addition of high purity copper filters. The black dotted line intersects the curves at the beam HVL. Filters A, B, and C are shown.

FIG. 4. Spatial dose distribution in the central coronal slice of the 33 g MOBY phantom for filter B. Doses are normalized per 1×10^9 source particles (photons emitted by x-ray tube).

found to be negligible. For filter B, the increase in absolute dose resulting from shelf backscatter averaged 1.8% over all the organs [min organ = 1.1%, max organ = 2.7%]. For filter B, after normalization, the increase in relative dose resulting from backscatter averaged 0.12% over all the organs [min organ = -0.1%, max organ = 0.4%]. Since the 3 mm shelf was found to have a negligible effect on the relative organ dose values, all of the results presented here are for simulations that were performed with the shelf removed and with the dose values normalized.

The physical ion chamber measurements of the increased exposure due to the backscatter from the 3 mm shelf with filter B was found to be $6.4\% \pm 2\%$. Similarly, the simulated absolute dose increase from backscatter to the $1 \times 1 \times 1 \text{ cm}^3$ water volume was $3.47\% \pm 0.01\%$ and $4.31\% \pm 0.01\%$ for filters B and C, respectively.

A sample dose distribution from the Monte Carlo simulations in the 33 g MOBY phantom is shown in Fig. 4. The dose distribution displayed in the soft tissue structures was relatively uniform, with apparent dose increases in the cortical bone structures. The stomach, CSF, and colon cavity doses were not displayed since the contents of these organs are usually not of radiological concern.

The simulated dose results for filters A, B, and C are shown in Fig. 5. In soft tissue, the ratio of the largest to the smallest relative organ dose value was found to be 1.34, 1.30, and 1.26 for the filters A, B, and C, respectively, in the 33 g mouse; 1.34, 1.29, and 1.24 for the filters A, B, and C, respectively, in the 23 g mouse; and 1.32, 1.27, and 1.23, respectively, in the 12 g mouse.

4. DISCUSSION

4.A. Experimental verification

For perfect agreement between simulated and measured spectra, the dose ratio should be 0.5 after adding one HVL of additional copper filtration. Since the simulated dose ratios were less than 0.5 after adding the HVL thickness of copper determined from physical measurement, the variation of organ doses reported here may be slightly overestimated due to the softer beams. However, it should be noted that the HVL does not uniquely characterize an x-ray beam, and two separate x-ray beams may have the same HVL, but different overall energy spectra.

FIG. 5. Monte Carlo simulated relative organ doses were found to be nearly identical for the (a) 33 g, (b) 23 g, and (c) 12 g mouse phantoms. These results show the dose to ten organs for three different filters on the Xrad-320. All doses were normalized to the dose to skeletal bone.

4.B. Organ dose errors

The results presented here are not meant to be used as a look-up table for researchers to prescribe dose to mice; they are meant to demonstrate the magnitude of differences that can arise between individual organ doses. When dose accuracy is essential to experimental outcomes, researchers irradiating mice should consult a physicist, in order to have dosimetry performed for their unique geometry and setup. The dose errors that result from using the conventional dose prescription method are shown in Table III.

TABLE III. Simulation results of the calculated dose prescription percent errors for comparing the resulting dose error in each organ if a uniform dose distribution is assumed according to the conventional dose prescription method. All dose errors are relative to the dose in the liver. Absolute standard error of the mean is shown in parentheses.

	12 g						23 g						33 g					
	A		B		C		A		B		C		A		B		C	
Gonads	-1.9%	$\pm(0.0\%)$	-1.9%	$\pm(0.0\%)$	-1.7%	$\pm(0.0\%)$	-3.0%	$\pm(0.0\%)$	-2.7%	$\pm(0.0\%)$	-2.3%	$\pm(0.0\%)$	-3.2%	$\pm(0.0\%)$	-3.0%	$\pm(0.0\%)$	-2.8%	$\pm(0.0\%)$
Bladder	-2.8%	$\pm(0.0\%)$	-2.2%	$\pm(0.0\%)$	-2.3%	$\pm(0.0\%)$	-4.2%	$\pm(0.0\%)$	-3.0%	$\pm(0.0\%)$	-2.2%	$\pm(0.0\%)$	-3.9%	$\pm(0.0\%)$	-3.5%	$\pm(0.0\%)$	-3.8%	$\pm(0.0\%)$
Liver	...		...		...		...		...		...		...		...		...	
Thyroid	-1.7%	$\pm(0.0\%)$	-0.8%	$\pm(0.0\%)$	-0.3%	$\pm(0.0\%)$	-1.7%	$\pm(0.0\%)$	-0.9%	$\pm(0.0\%)$	-0.1%	$\pm(0.0\%)$	-2.1%	$\pm(0.0\%)$	-1.0%	$\pm(0.0\%)$	-0.2%	$\pm(0.0\%)$
Bone	267.4%	$\pm(0.5\%)$	236.2%	$\pm(0.5\%)$	176.8%	$\pm(0.3\%)$	267.7%	$\pm(0.5\%)$	238.5%	$\pm(0.5\%)$	180.4%	$\pm(0.3\%)$	267.7%	$\pm(0.5\%)$	239.5%	$\pm(0.5\%)$	182.2%	$\pm(0.4\%)$
Brain	15.3%	$\pm(0.0\%)$	12.5%	$\pm(0.0\%)$	10.6%	$\pm(0.0\%)$	18.0%	$\pm(0.0\%)$	15.3%	$\pm(0.0\%)$	12.3%	$\pm(0.0\%)$	19.8%	$\pm(0.0\%)$	16.7%	$\pm(0.0\%)$	13.7%	$\pm(0.0\%)$
Red bone marrow	27.8%	$\pm(0.1\%)$	24.4%	$\pm(0.1\%)$	20.3%	$\pm(0.0\%)$	28.1%	$\pm(0.1\%)$	25.0%	$\pm(0.1\%)$	21.0%	$\pm(0.0\%)$	28.4%	$\pm(0.1\%)$	25.4%	$\pm(0.1\%)$	21.1%	$\pm(0.0\%)$
Colon	2.0%	$\pm(0.0\%)$	1.7%	$\pm(0.0\%)$	1.1%	$\pm(0.0\%)$	2.1%	$\pm(0.0\%)$	1.8%	$\pm(0.0\%)$	1.6%	$\pm(0.0\%)$	2.3%	$\pm(0.0\%)$	2.2%	$\pm(0.0\%)$	1.7%	$\pm(0.0\%)$
Lung	8.8%	$\pm(0.0\%)$	6.8%	$\pm(0.0\%)$	6.8%	$\pm(0.0\%)$	9.4%	$\pm(0.0\%)$	8.2%	$\pm(0.0\%)$	7.4%	$\pm(0.0\%)$	9.9%	$\pm(0.0\%)$	8.8%	$\pm(0.0\%)$	7.4%	$\pm(0.0\%)$
Stomach	9.3%	$\pm(0.1\%)$	7.3%	$\pm(0.0\%)$	6.6%	$\pm(0.0\%)$	10.6%	$\pm(0.1\%)$	8.8%	$\pm(0.1\%)$	8.0%	$\pm(0.0\%)$	11.9%	$\pm(0.1\%)$	10.5%	$\pm(0.1\%)$	8.7%	$\pm(0.1\%)$
Range (excluding bone)	31%		27%		23%		32%		28%		23%		32%		29%		25%	

Since softer beams exhibit more hardening and a greater attenuation with depth, the dose distribution for filter A was found to be more inhomogeneous than the dose distributions from the spectra that utilized more filtration such as for filter C. Assuming organ dose normalization to the liver, and by increasing the filtration from filter A to filter C, the range of soft-tissue organ dose percent differences was found to decrease from 32% to 25% for the 33 g mouse, 32% to 23% for the 23 g mouse, and from 31% to 23% for the 12 g mouse. Using a single dose rate measurement to prescribe dose can thus result in up to a 23%–32% error in the calculated organ dose values depending on filter choice, the size of the mouse, and the target organ.

Aside from the bone dose, the maximum soft-tissue dose always occurred in the red bone marrow, with the second highest organ dose in the brain. The minimum dose values occurred in either the gonads or the bladder, with the dose values being very similar in these two organs for all filters. The variation between these maxima and minima is likely due to anatomical variation such as differences in proximity to cortical bone structures, and attenuation effects caused by differences in depth from the beam entrance.

A method of calibration to accurately calculate organ based doses in mice can be performed with a dosimeter such as a thermoluminescent dosimeter (TLD) or a metal oxide semiconductor field effect transistor (MOSFET).^{25,26} One of these point dosimeters can be placed in a mouse phantom, as shown in Fig. 6. The mouse phantom, ideally a tissue-equivalent cylinder that approximates the shape and size of the mouse, serves to provide a realistic model of the mouse placement, irradiation geometry, and also offers a known location of the point of measurement. A hole can be drilled along the axis of the cylinder in order to insert the point dosimeter, to obtain an in-tissue dose reading. The estimated dose in the mouse phantom is then calculated by cross-calibrating the detector to a free-in-air ion chamber reading and then applying an f-factor correction to convert to a tissue dose. This single point dose value provides an estimate

FIG. 6. Cylindrical mouse phantom (made of tissue equivalent plastic) shown here with a micro-MOSFET inserted along the central axis. The laser shows the central location of the Xrad-320 field.

of the dose to the center of the mouse—neglecting attenuation effects, beam hardening effects, and tissue inhomogeneity. However, by using the relative organ doses, as shown in Fig. 5, one can use this reference point dose to scale to the calculated dose in other organ locations. Likewise, if a reference point dose *rate* is known for a specific geometry, all other organ specific dose rates can then be calculated. When using this method researchers can deliver radiation to animals based on an organ specific dose prescription and theoretically avoid the aforementioned dose errors that can arise from the conventional prescription method.

Others have demonstrated good beam uniformity over the field size for the Xrad-320, with 4.4% standard deviation of film pixel values in the x-ray field.²⁷ However, the authors suggest centering the mouse under the x-ray window (via laser alignment), since this is likely the same location where calibration was performed to measure the dose rate.

For beams utilizing filters A, B, and C on the Xrad-320, the average dose to skeletal bone tissue was found to be several times larger than the average dose to soft-tissue organs. This occurred from the higher f-factor of bone for low energy x rays which arises due to an increased probability of photoelectric absorption.²⁸ In order to calculate the dose to bone, researchers must apply the bone specific f-factor. From simulation, the bone dose was found to be ~270%, ~240%, and ~180% higher than the dose to the liver for the filters A, B, and C, respectively (liver was chosen for comparison since it is a large, and central soft-tissue organ). Therefore, to achieve a given dose in bone, the exposure time will be a factor of roughly three times less than the calculated exposure time using the conventional prescription method.

5. CONCLUSION

In the 12, 23, and 33 g MOBY mouse phantoms, soft tissue organ-dose errors using the current method of a single point dose rate measurement may reach 23%–32%; the minimum of 23% error corresponded to filter C and the 12 g mouse, and the maximum of 32% error corresponded to filter A and the 33 g mouse. It was found that more uniform organ doses among soft tissue organs were a result of higher filtered beams. In 12, 23, and 33 g MOBY mouse phantoms, the bone dose was found to range from 2.8 to 3.7 times larger than the dose to soft tissue organs such as the liver, for filter C and A, respectively. The results presented here suggest that organ dose errors will be minimized by calibrating the dose rates for all filters, and using different dose rates for different organs.

Future work will consider new geometry to model unsedated mice during irradiation. When considering the irradiation of live mice, the beam does not necessarily enter the dorsal side of the mouse, and changes in the mouse posture such as standing, sitting, or moving around can impact the dosimetry. In addition, 4D motion due to breathing can be included in the simulation to increase the accuracy of this dosimetry model.

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