Monte Carlo simulation on pre-clinical irradiation: 
A heterogeneous phantom study on monoenergetic kilovoltage photon beams

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Abstract. This study investigated radiation dose variations in pre-clinical irradiation due to the photon beam energy and presence of tissue heterogeneity. Based on the same mouse computed tomography image dataset, three phantoms namely, heterogeneous, homogeneous and bone homogeneous were used. These phantoms were generated by overriding the relative electron density of no voxel (heterogeneous), all voxel (homogeneous) and the bone voxel (bone homogeneous) to one. 360° photon arcs with beam energies of 50 - 1250 keV were used in mouse irradiations. Doses in the above phantoms were calculated using the EGSnrc-based DOSXYZnrc code through the DOSCTP. Monte Carlo simulations were carried out in parallel using multiple nodes in a high-performance computing cluster. It was found that the dose conformity increased with the increase of the photon beam energy from the keV to MeV range. For the heterogeneous mouse phantom, increasing the photon beam energy from 50 keV to 1250 keV increased seven times the dose deposited at the isocenter. For the bone dose enhancement, the mean dose was 2.7 times higher when the bone heterogeneity was not neglected using the 50 keV photon beams in the mouse irradiation. Bone dose enhancement affecting the mean dose was found in the photon beams with energy range of 50 – 200 keV and the dose enhancement decreased with an increase of the beam energy. Moreover, the MeV photon beam had a higher dose at the isocenter, and a better dose conformity compared to the keV beam.

1. Introduction
In radiotherapy, the external-beam treatment planning (clinical or pre-clinical) requires a calculation of radiation dose delivered to the tumour, while sparing the critical or normal tissues from harmful effect. Considering the high accuracy, Monte Carlo simulation is preferred to those semi-experimental or classic approaches in dose calculation [1]. However, Monte Carlo simulation is computation intensive, and usually takes days to finish the dose calculation of a treatment plan [2]. In this work, pre-clinical dosimetric study using Monte Carlo simulation was performed by a high-performance computing cluster to enhance the computing speed, so that a pre-clinical heterogeneous phantom study can be carried out efficiently.

Realistic pre-clinical models for the fractionation, normal tissue dose-volume and radiobiology studies are being developed to support the lack of clinical data in radiotherapy. Since the accuracy of the pre-clinical model depends on the similarity of the small-animal irradiation mimicking the radiotherapy process of the patient, many state-of-the-art radiation irradiators [3-5] with different photon beam energies, image-guided accessories [6], and treatment planning systems [7, 8] for the small animal were developed. The association of the above irradiation hardware and software for the advanced small-animal treatment procedure results in a highly conformal dose to the target volume, and a dose sparing the surrounding healthy tissue as much as possible.
Small-animal irradiation and imaging accessories such as the computed tomography (CT) [9-11], magnetic resonance [12-14] and position emission tomography [15-17] imaging are available in the mouse scale of millimeter. In order to further match the size of mouse compared to human, megavoltage (MV) photon beams (4 – 18 MV) generally used in the patient’s radiotherapy are replaced by kilovoltage (kV) beams because of the relatively higher beam attenuation. The use of kV photon beams in the mouse irradiation has dosimetric reasons of the beam attenuation and depth dose that fit the size of mouse. However, such kV photon beams in the small-animal irradiation produce extra bone dose, which is not present in the patient’s radiotherapy using MV beams. This unwanted bone dose enhancement from the mouse irradiation may lead to an uncertainty in the pre-clinical model. To date, patient dosimetry (e.g. mean and maximum imaging dose) due to heterogeneities such as bone regarding the popular imaging guidance procedures of kV cone-beam CT (kV-CBCT) in image-guided radiotherapy has been studied [18-22]. It is found that because of the increased photoelectric effect for the kV photon beams compared to the MV, a kV-CBCT procedure results in a bone dose enhancement up to a factor of 3 - 4 times than those in the surrounding soft tissue [19, 23]. This increased bone dose would affect the bone marrow which is a radiosensitive organ-at-risk [24-27]. However, there is a lack of studies concerning the bone dose enhancement for the small animal when using kV photon beams in the irradiation.

Although there are studies on dosimetric variations of pre-clinical irradiations using polyenergetic photon beams produced by different mouse irradiators [28, 29], there is no investigation concerning dosimetric variations using monoenergetic photon beams. In this study, a mouse phantom which is heterogeneous based on a mouse CT image dataset was used in Monte Carlo simulation and irradiated with monoenergetic kV photon beams with different energies. To study the effect of the bone dose enhancement due to the kV photon beam irradiation, the relative electron density of every bone voxel in the above phantom was overridden to one in order to generate another bone homogeneous mouse phantom without the bone heterogeneity. Monte Carlo simulations were performed by sampling variables of photon and electron energy depositions. Simulations on irradiations of the 360° photon arcs with energies of 50, 100, 150, 200, 250, 300 and 1250 keV were carried out in the above two phantoms together with a homogeneous mouse phantom with all relative electron densities in voxels overridden to one. The Electron Gamma Shower (EGSnrc)-based code was used to calculate doses in the three mouse phantoms [30, 31]. Monte Carlo simulation of particle transports in heterogeneous media is currently the most accurate dose calculation method for kV photon beams with different atomic numbers [5, 32]. The DOSCTP graphical user interface based on the DOSXYZnrc code was used to carry out the treatment plan and phantom edition [8, 33]. The aim of this study is to investigate dosimetric variations in the presence and absence of tissue heterogeneities, in particular the bone, in mouse irradiations using monoenergetic photon beams with different energies in the kV range. Doses at the interesting points (the isocenter and bone), mean doses, and maximum doses were calculated by Monte Carlo simulations using high-performance computing cluster.

2. Methods
A mouse CT image dataset obtained by a 225 kVp x-ray tube (GE Siefert 225, focal spot size = 0.4 mm) and flat-panel detector (Perkin Elmer, IRD1640) was converted to an EGSnrc-based Monte Carlo phantom using a modified CTcreate routine with the calibrated CT number and density conversion ramp specified for the mouse [7, 8]. The voxel size of the phantom was set to 0.1 × 0.1 × 0.18 cm³ for the x, y and z-axis, respectively. The z-axis of the phantom is parallel to the superior-inferior direction of the mouse. Figure 1(a) shows the x-y plane of the Monte Carlo heterogeneous mouse phantom with the isocenter, rib and spine. Each division in the ruler scale represents 1 cm in Fig. 1. Based on the heterogeneous mouse phantom in Fig. 1(a), a homogenous mouse phantom (Fig. 1(b)) was then generated by overriding the relative electron density in every voxel to one using the phantom editing feature in the DOSCTP code. In addition, a bone homogeneous mouse phantom as shown in Fig. 1(c) was generated by overriding the relative electron density of every bone voxel in the inhomogeneous mouse phantom to one. Through dosimetric comparisons among the heterogeneous, homogeneous and bone homogeneous mouse phantoms irradiated by different energies of photon beams, the effect of the presence of the heterogeneity such as bone in the dose distribution, which varies with the beam energy, can be investigated. To study the strength difference of the photoelectric effect in the bone between the kV and MV photon beams, a beam of 1250 keV was used to irradiate the three phantoms for comparison.

In radiation dose calculation using Monte Carlo simulation, paths of the individual particles (photons and electrons) are governed by random numbers distributed according to the known probabilities of the various scattering and energy deposition events. The energy deposition events are collected in cubical bins, and the energy deposited per unit mass is taken as a measure of dose that would be deposited under actual irradiation conditions. Since each particle is by definition statistically independent as well as governed by the same process, Monte Carlo simulations can be classified as “embarrassingly parallel” problem when implemented. As the accuracy of Monte Carlo simulation depends on the sampling size (histories), and the typical number of histories used for an accurate dose calculation (statistical uncertainty = ± 1%) is equal to couple hundred million, Monte Carlo simulation is recognized as a time-consuming but accurate method in dose calculation. Therefore, high-
performance computing is needed to improve the simulation speed. There are some studies concerning the speed enhancement in Monte Carlo simulation. Hissoiny et al [34] developed a new Monte Carlo dose calculation platform called “GPUMCD” using graphical processing unit (GPU). The GPUMCD can perform Monte Carlo radiation dose calculation for energies in the range of 0.01 – 20 MeV using the class II condensed history method. GPUMCD runs on a NVIDIA GTX480 graphical processor, and dosimetric results from GPUMCD were validated by the EGSnrc code that over 98% of voxels passed the gamma criteria of 2%/2mm. The computing speed of GPUMCD is more than 900 times faster than the EGSnrc running on a typical computing processor. Chow et al [35] investigated the probability to implement Monte Carlo simulation using the cell processor in the Playstation3 console. They found that the EGSnrc code could be parallelizable on the cell processor, provided that an architectural change of the EGSnrc was made so that the code was initiated on the powerPC processing element, and execution of the simulation loop within the program be split between the PowerPC processing and synergistic processing elements in the system. However, the performance of cell processor is worse than the GPU due to the limitation of the PowerPC processing element. In this study, the EGSnrc code version 4-r2-2-5 developed by the National Research Council Canada was used [30, 31]. The code was run in parallel using multiple nodes on the General Purpose Cluster at SciNet from the University of Toronto. The computing time was about 10 – 20 minutes per calculation, which is faster than a single PC CPU with computing time equal to 2 – 3 hours per calculation. The DOSXYZnrc associated with the EGSnrc was used to calculate the dose [33], and the DOSCTP running on the MATLAB platform was used to create the Monte Carlo mouse phantoms and irradiation plans [7].

Monoenergetic photon beams with energies of 50, 100, 150, 200, 250, 300 and 1250 keV were used in Monte Carlo simulations. The field size of the photon beam was 2.5 × 2.5 cm$^2$. The distance between the field and isocenter was equal to 5 cm as shown in Fig. 1(a). A 360$^\circ$ photon arc around the z-axis was used to irradiate the heterogeneous, homogeneous and bone homogeneous mouse phantom. The input file of the irradiation plan for Monte Carlo simulation was created by the DOSCTP, and the simulation was then automatically run on the DOSXYZnrc linked to the DOSCTP. Sampling histories of five hundred million of particle (photon and electron) tracks were used in each dose calculation. Under this number of history, the relative dose error (i.e. uncertainty as a fraction of the dose in the voxel) was on the order of $10^{-2}$ (1% - 3%) according to the Monte Carlo output file [33]. In dose calculations, the electron transport cut-off energy of 512 keV was used. The photon cut-off energy was set to 1 keV in the phantoms and the maximum fractional electron energy loss per step was set to 25%.

Based on the Monte Carlo results, point doses of interest such as the isocenter, rib and spine were determined from the heterogeneous, homogeneous and bone homogeneous mouse phantoms. Moreover, mean and maximum doses for each of the three phantoms were calculated with different photon beam energies. Although dose points in Fig. 1(a) are not shown in Figs. 1(b) and 1(c), the positions and coordinates of points for the homogeneous and bone homogeneous mouse phantom are the same as the heterogeneous phantom, because all mouse phantoms were generated from the same source of CT image dataset.

3. Results and discussion

Dose distribution of the homogeneous mouse phantom can be seen in Fig. 2 for photon beams with relatively low energy of 50 keV. The dose distribution in Fig. 2 shows the dose deposited by the 360$^\circ$ photon arc is conformed to the isocenter of the phantom, and all doses were normalized to that at the isocenter of the phantom. The diameter of the 100% dose contour in Fig. 2 is about 2.5 cm, which matched the field size of the photon beam. There is a dose gradient from the isocenter to the external contour of the mouse. This dose gradient was found to increase with the increase of photon beam energies from 50 keV to 1250 keV. It shows that higher photon beam energy can increase the dose conformity to the target at the isocenter.

Point doses of the isocenter, rib and spine for the heterogeneous, homogeneous and bone homogeneous mouse phantom irradiated by photon beams with energies in the range of 50 – 1250 keV are shown in Table 1. In the Table, the dose at the isocenter in the homogeneous mouse phantom is only slightly higher than that in the bone homogeneous phantom of about 1.5% for all photon beam energies. Comparing point doses of the rib and spine between the heterogeneous and bone homogeneous mouse phantom in Table 1, bone dose enhancements of 3.4 and 2.9 times are found in the rib and spine when using the 50 keV photon beams. These dose enhancements are due to the photoelectric effect occurring in the keV photon beam energy range in the bone, and are not seen in the 1.25 MeV photon beams. For this MeV photon beams, point doses of the rib and spine in the heterogeneous mouse phantom are 6.5% and 4.5% smaller than those in the bone homogeneous phantom. Moreover, the effect of the bone dose enhancement disappears when the photon beam energy is increased from 50 to 250 keV.
Figure 1. Computed Tomography images of the mouse with the relative electron density of (a) voxel unchanged (heterogeneous mouse), (b) all voxel overridden to 1 (homogeneous mouse), and (c) only the bone voxel overridden to 1 (bone homogeneous mouse). Dose points for the isocenter, rib and spine are shown in 1(a). The ruler scales show 1 cm division.

Figure 2. Dose distribution displayed as 2D contours in the homogeneous mouse phantom. Doses were calculated using Monte Carlo simulation with photon beam energy equal to 50 keV.
Table 1. Point doses of the isocenter, rib and spine, as shown in Fig. 1(a), in the heterogeneous, homogeneous and bone homogeneous mouse phantom for photon beam energies of 20, 100, 150, 200, 250, 300 and 1250 keV.

| Photon beam energy (keV) | Hetero mouse (Gy x10^{-13}) | Homo mouse (Gy x10^{-13}) | Bone homo mouse (Gy x10^{-13}) | Hetero mouse (Gy x10^{-13}) | Homo mouse (Gy x10^{-13}) | Bone homo mouse (Gy x10^{-13}) |
|--------------------------|---------------------------|---------------------------|-------------------------------|---------------------------|---------------------------|-------------------------------|
| 50                       | 7.34                      | 2.63                      | 2.43                          | 4.36                      | 1.22                      | 1.28                          |
| 100                      | 5.83                      | 3.23                      | 3.19                          | 2.72                      | 1.49                      | 1.51                          |
| 150                      | 6.54                      | 5.44                      | 5.27                          | 2.77                      | 2.25                      | 2.31                          |
| 200                      | 7.93                      | 7.69                      | 7.61                          | 3.41                      | 3.17                      | 3.28                          |
| 250                      | 10.21                     | 10.13                     | 10.03                         | 4.31                      | 4.27                      | 4.29                          |
| 300                      | 12.36                     | 12.46                     | 12.34                         | 5.12                      | 5.34                      | 5.18                          |
| 1250                     | 50.19                     | 53.09                     | 52.48                         | 20.38                     | 22.13                     | 21.79                         |

The variations of the mean and maximum doses in the mouse phantoms due to the heterogeneities for different photon beam energies are shown in Table 2. Comparing the mean doses in the heterogeneous and bone homogeneous mouse phantom, the mean dose in the heterogeneous mouse phantom is about 2.7 times higher than that in the bone homogeneous phantom using the 50 keV photon beams. This mean dose is increased from 50 to 250 keV and then slightly decreased, when the photon beam energy is higher than 250 keV. For the 300 keV photon beams, the mean dose in the heterogeneous phantom is slightly lower than that in the bone homogeneous phantom. This decrease of mean dose is more obvious for the 1250 keV photon beams in which the mean dose in the bone homogeneous mouse phantom is about 2.3% higher than that in the heterogeneous phantom. It is seen that the bone dose enhancement effect due to the keV photon beam is strongest at 50 keV up to 200 keV. Comparing mean and maximum doses of the heterogeneous and bone homogeneous mouse phantom as shown in Table 2, dose deviations are more significant in the low-energy photon beam (e.g. 50 keV) than the higher (e.g. 1250 keV). The deviations of mean and maximum dose between the heterogeneous and bone homogeneous mouse phantom due to the heterogeneities are 60.9% and 69.1% for the 50 keV photon beams, and only -1.25% and 1.07% for the 1250 keV photon beams, respectively. These large dose differences between the low- and high-energy photon beams reflect that the dependence of heterogeneities on the dose distribution is more significant in the mouse irradiation using photon beam with energy in the keV range. For photon beam energy in the range of 50 – 150 keV, the deviations of mean and maximum dose between the heterogeneous and bone homogeneous mouse phantom are smaller than those between the heterogeneous and bone homogeneous phantom. This shows that the bone dose enhancement due to the photoelectric effect is dominant in this photon beam energy range.

Table 2. Mean and maximum doses in the heterogeneous, homogeneous and bone homogeneous mouse phantom irradiated by the 360° photon arcs with beam energies of 20, 100, 150, 200, 250, 300 and 1250 keV.

| Photon beam energy (keV) | Heterogeneous Mouse | Homogeneous Mouse | Bone homogeneous Mouse |
|--------------------------|---------------------|-------------------|------------------------|
|                          | Mean dose (x10^{-13} Gy) | Maximum dose (x10^{-13} Gy) | Mean dose (x10^{-13} Gy) | Maximum dose (x10^{-13} Gy) | Mean dose (x10^{-13} Gy) | Maximum dose (x10^{-13} Gy) |
| 50                       | 2.61                | 8.73              | 1.02                   | 2.70                      | 0.97                      | 2.67                      |
| 100                      | 1.48                | 6.05              | 1.11                   | 3.37                      | 1.11                      | 3.33                      |
| 150                      | 1.52                | 6.58              | 1.42                   | 5.52                      | 1.42                      | 5.42                      |
| 200                      | 1.98                | 8.29              | 1.92                   | 7.96                      | 1.96                      | 7.89                      |
| 250                      | 2.52                | 10.39             | 2.49                   | 10.55                     | 2.54                      | 10.36                     |
| 300                      | 3.07                | 12.78             | 3.05                   | 13.14                     | 3.12                      | 13.00                     |
| 1250                     | 6.36                | 55.32             | 6.44                   | 54.73                     | 6.51                      | 53.94                     |

4. Conclusions
The dosimetric dependence on the photon beam energy and heterogeneity for the mouse irradiation was studied using Monte Carlo simulation. Monte Carlo mouse phantoms namely, heterogeneous, homogeneous and bone homogeneous based on the same mouse CT image dataset were generated by overriding the relative electron density of no voxel, all voxel and the bone voxel to one, respectively. Photon beam energies of 50, 100, 150,
200, 250, 300 and 1250 keV were used for the 360° photon arc in the mouse irradiations. Monte Carlo results showed that dose conformity increased when the photon beam energy increased from 50 keV to 1250 keV, showing that a greater dose gradient could be achieved in higher photon beam energy. In addition, point doses at the rib and spine were found to be 3.4 and 2.9 times higher when comparing the bone doses in the heterogeneous and bone homogeneous mouse phantoms using the 50 keV photon beam. The mean dose in the mouse irradiation was 2.7 times higher when the bone density was overridden to one using the 50 keV photon beam, and the increase of dose was decreased as the beam energy was increased. The dosimetry data in this study is useful when considering the options of photon beam energy in the small-animal treatment planning, or designing a mouse irradiator for pre-clinical model. Moreover, high-performance computing has been used to enhance the dose calculation speed from hours to minutes in Monte Carlo simulation, resulting in a more efficient preclinical study.

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