Investigation of the effects of treatment planning variables in small animal radiotherapy dose distributions

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Purpose: Methods used for small animal radiation treatment have yet to achieve the same dose targeting as in clinical radiation therapy. Toward understanding how to better plan small animal radiation using a system recently developed for this purpose, the authors characterized dose distributions produced from conformal radiotherapy of small animals in a microCT scanner equipped with a variable-aperture collimator.

Methods: Dose distributions delivered to a cylindrical solid water phantom were simulated using a Monte Carlo algorithm. Phase-space files for 120 kVp x-ray beams and collimator widths of 1–10 mm at isocenter were generated using BEAMnrc software, and dose distributions for evenly spaced beams numbered from 5 to 80 were generated in DOSXYZnrc for a variety of targets, including centered spherical targets in a range of sizes, spherical targets offset from centered by various distances, and various ellipsoidal targets. Dose distributions were analyzed using dose volume histograms. The dose delivered to a mouse bearing a spontaneous lung tumor was also simulated, and dose volume histograms were generated for the tumor, heart, left lung, right lung, and spinal cord.

Results: Results indicated that for centered, symmetric targets, the number of beams required to achieve a smooth dose volume histogram decreased with increased target size. Dose distributions for noncentered, symmetric targets did not exhibit any significant loss of conformality with increasing offset from the phantom center, indicating sufficient beam penetration through the phantom for targeting superficial targets from all angles. Even with variable collimator widths, targeting of asymmetric targets was found to have less conformality than that of spherical targets. Irradiation of a mouse lung tumor with multiple beam widths was found to effectively deliver dose to the tumor volume while minimizing dose to other critical structures.

Conclusions: Overall, this method of generating and analyzing dose distributions provides a quantitative method for developing practical guidelines for small animal radiotherapy treatment planning. Future work should address methods to improve conformality in asymmetric targets. © 2010 American Association of Physicists in Medicine. [DOI: [10.1118/1.3276738](https://doi.org/10.1118/1.3276738)]

Key words: Monte Carlo, small animal radiotherapy, treatment planning

I. INTRODUCTION

Advances in radiation therapy for cancer patients have dramatically increased our ability to effectively target radiation treatment. Techniques such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy allow dose to be effectively shaped to maximize radiation delivered to the target, while minimizing radiation delivered to the surrounding tissues. These advances, however, have manifested only in the clinical setting, and have not been translated back for use in small animal cancer research.

In the laboratory, small animal radiation therapy often still relies on crude methods using broad-field irradiation generators, generally with lead shields to shape the beam approximately to the volume of interest.^{1–3} These methods may be sufficient for delivering doses to large target regions and subcutaneous tumors. However, they do not allow for three-dimensional shaping of the radiation dose to the target, and

therefore are poor for treating spontaneous and orthotopic tumors. The differences between small animal and clinical therapy methods limit our ability to conduct small animal radiotherapy research that approximates the treatments available to humans. This is unfortunate, given the significant effort that has been put into developing small animal cancer models for research.

Several laboratories are addressing this issue by developing methods for more precise small animal radiation therapy, including groups at Johns Hopkins University,^{4–10} Princess Margaret Hospital,¹¹ and Washington University.^{12–16} Our group has previously developed a method for precision irradiation of small animals by adapting an existing small animal microCT scanner with an x-ray tube operating at 70–120 kVp using a variable-aperture collimator with an aperture range of 1–102 mm at isocenter.¹⁷ Using this microCT/RT system, we can deliver several narrow beams from different angles, allowing the dose to be focused on a target. However,

FIG. 1. A sample treatment plan shown in RT_IMAGE. A cross-sectional view of the phantom with a central spherical 5 mm target region and five treatment beams is shown in (a); a cross-sectional view of the phantom with an ellipsoidal $2 \times 8 \times 2$ mm³ target region and five treatment beams is shown in (b); a 3D view of the phantom and treatment beams for the spherical target is shown in (c).

the ideal way to utilize our system to achieve optimal dose conformity in murine subjects is unclear, as are the limitations of our current treatment planning methods. To address these uncertainties, in this study we use Monte Carlo simulations to understand how well we can deliver dose to targets, both spherical and ellipsoidal, located centrally and superficially, in a small animal subject. We also address how dose conformity is affected by the number of beams in the treatment plan. Specifically, we first discuss the effects of beam numbers, target locations, and target shape, found using solid water phantoms. Finally, to assess our ability to target tumors in real murine subjects, we analyze the dose distributions generated for an actual tumor-bearing mouse using microCT imaging data produced by our system.

FIG. 2. Depth dose curves before (thin lines) and after (thick lines) adjustment of the inherent filtration for 20, 10, 5, and 2 mm beams. Film measurements are represented by markers.

II. METHODS AND MATERIALS

II.A. Generation of a solid water phantom

A cylindrical solid water phantom with a diameter of 25 mm and a length 40 mm was generated using the RT_IMAGE software package.¹⁸ These dimensions were chosen to crudely approximate those of a typical murine subject. The pixel resolution was 194 μ m.

II.B. Treatment planning

For all targets, plans with 5, 10, 20, 30, 40, 50, 60, 70, and 80 evenly spaced 120 kVp beams were simulated using RT_IMAGE. Targets included 1, 2, 3, 5, 7, and 10 mm spherical targets located at the center of the phantom, 2 mm targets offset from the phantom center by 10%, 20%, 30%, and 40% of the phantom diameter, and ellipsoidal targets with diameter dimensions of $2 \times 4 \times 2$, $2 \times 6 \times 2$, and $2 \times 8 \times 2$ mm³, with the long dimension oriented in the plane of the gantry rotation. The size of offset targets, 2 mm, was chosen in order to allow for greater offset within the phantom diameter. For ellipsoidal targets, beam widths were allowed to vary within the treatment plan and were based on the width of the projected image of the target at the beam angle. All beams were considered to be collimated to dodecagonal profiles in accordance with the variable-aperture collimator in the microCT/RT system.^{19,20} A sample treatment plan is shown in Fig. 1.

II.C. Generation of phase-space files

Phase-space files were generated using BEAMnrc software. The x-ray tube model was built using the XTUBE component module on the basis of manufacturer's specifications. The inherent filtration was adjusted²¹ to take into account changes over the lifetime of the x-ray tube by fitting simulated depth dose curves to EBT Gafchromic film measurements.²² EBT Gafchromic films were calibrated in the 120 kVp microCT beam using an ionization chamber. Eleven (6×6 cm² films were sandwiched between twelve 3 mm thick solid water slabs, and the central axis depth dose curves and beam profiles for various beam sizes were mea-

TABLE I. Approximate simulation run times for beam diameters of 1–10 mm.

Beam diameter (mm)	Approximate CPU time (hr)
1	0.2
2	0.3
3	0.6
4	1.0
5	1.4
6	2.0
7	2.9
8	3.9
9	4.6
10	5.1

FIG. 3. Dose distributions and DVH for [(a) and (d)] 10, [(b) and (e)] 30, and [(c) and (f)] 50 beams for a 5 mm centered spherical target.

sured. Depth dose curves before and after adjustment are shown in Fig. 2.

A two-stage simulation was used for phase-space file generation. The first phase-space file, scored just outside the x-ray tube, was used as the source for the second stage of the simulation, where particle transport through the variable-aperture collimator was modeled. The collimator apparatus has been described previously.^{17,19,20} Directional Bremsstrahlung splitting was used in the first BEAMnrc simulation. The electron energy cutoff and photon energy cutoff (PCUT), below which particle histories are terminated, and the energy is deposited locally, were set to 0.516 and 0.005 MeV, respec-

tively. Rayleigh scattering, bound Compton scattering, and electron impact ionization were included in the simulations. The particle density below the collimator was above 5.6×10^9 photons/cm² for all beam sizes.

II.D. Generation of dose distributions

Dose distributions were generated using DOSXYZnrc software. Phase-space files produced in the BEAMnrc simulations were incident on the voxelized phantom described above from the planned treatment angles. Unlike in the BEAMnrc simulations, the electrons were not transported,

since their effect on dose distributions would be negligible. Dose distributions simulated with and without electron transport agreed within the statistical uncertainties of the simulations, except for in the surface layer of voxels. The differences in the surface layer of voxels were below 5%.²⁰ PCUT was set to 0.005 MeV. A photon splitting number, N_{split} , of 175 was used to increase the efficiency of the simulation. This value for N_{split} yields close to the optimal calculation efficiency.²⁰ Simulations were conducted on a 2×3 GHz Quad-Core Intel Xeon machine. The number of particles simulated was chosen to achieve less than 1% statistical uncertainty for the highest 20 doses in each simulation. The number of particles ranged from 1 million for a 1 mm beam diameter to 8×10^7 for a 10 mm beam diameter.

II.E. Data analysis

Data were analyzed using RT_IMAGE software. For spherical targets, the nontarget region was defined as the cylindrical slice through the full diameter of the phantom of height equal to the target diameter, and not including the target region itself. For ellipsoidal targets, the in-plane nontarget region was defined similarly as the cylindrical slice through the full diameter of the phantom of height equal to the height of the target in the direction perpendicular to the plane of gantry rotation, and not including the target region itself; the out-of-plane nontarget region was defined as the two cylindrical slices above and below the in-plane nontarget region to the height of the largest beam width.

Dose volume histograms (DVHs) were created in RT_IMAGE by defining regions of interest corresponding to the target and nontarget regions. To yield a quantitative measure of the difference between the two DVHs, the difference was defined as the sum over all doses (x -axis) of the absolute value of the difference in voxel percentages (y -axis).

To determine the total energy delivered to a region, the dose in Gray at each voxel was multiplied by the voxel mass, assuming a density of water of 1 g/cc, and the energy was summed across all voxels in the region.

II.F. Dose distributions in mouse CT data

RT_IMAGE was used to identify a tumor target region in a 70 kV microCT image of a mouse bearing a spontaneous lung tumor generated using our microCT system.²³ A phantom file with material and density information for use in the Monte Carlo simulation was generated in RT_IMAGE. The image was segmented into four materials: air, lung, muscle, and bone. A calibration curve with two linear segments was created based on a 70 kV scan of a phantom with tissue equivalent materials. The HU limits for tissue segmentation were -900, -400, and 300 between air, lung, soft tissue, and bone. A treatment plan with 30 evenly spaced beams with variable beam widths was constructed, and the dose distribution was simulated using methods identical to those used for the homogeneous cylindrical phantom described above. The

FIG. 4. Smoothness effect as a function of beam number. Smoothness effect is defined as the sum over all doses of the absolute value of the difference in voxel percentages between the given number of beams and 360 beams. 360 beams were sufficiently smooth to accurately approximate the DVH using an infinite number of beams.

tumor, heart, right and left lungs, and spinal cord were contoured, and dose volume histograms for these regions as well as the tumor were generated in RT_IMAGE.

III. RESULTS

The approximate simulation run times are shown in Table I.

III.A. Effect of beam number

As the number of beams increased, the dose distribution throughout the nontarget region became increasingly uniform. The dose distributions within the target region remained relatively uniform across different beam numbers. This can be seen in visualizations of cross-sectional slices through the phantom [Figs. 3(a)–3(c)], as well as in DVH for the target and nontarget regions [Figs. 3(d)–3(f)].

The increasing uniformity of dose distributions was quantified by comparing the DVH for a given number of beams with the DVH for 360 beams. For the phantom and target sizes used in this study, 360 beams were found to yield a sufficiently smooth DVH to approximate the DVH for an infinite number of beams, at which a maximally smooth DVH could be expected. The smoothness effect for all six spherical target sizes are shown in Fig. 4 as a function of beam number. It is evident that as the number of beams increased, the smoothness effect decreased. However, the marginal decrease in smoothness effect caused by the addition of each beam decreased with higher total beam numbers.

III.B. Effect of target location

Location of the target away from the center of the phantom did not introduce any significant changes in dose distribution or effect of beam number. Figure 5 shows the increasing smoothness of nontarget dose distribution and DVH with increasing beam number. As the offset increased, the DVH for the nontarget regions shifted slightly leftward, and the

FIG. 5. Dose distributions and DVH for [(a) and (d)] 10, [(b) and (e)] 30, and [(c) and (f)] 50 beams for a 2 mm spherical target offset by 40% of the phantom diameter (1 cm).

FIG. 6. DVH for the target and nontarget regions for a 2 mm target with 0%–40% offset for (a) 10, (b) 40, (c) 80, and (d) 360 beams; and (e) total energy delivered to the target and nontarget regions for 10, 40, 80, and 360 beams for each offset.

DVH for the target regions shifted slightly rightward [Fig. 6(a)–6(d)]. Correspondingly, the total nontarget dose decreased with increasing offset, while the total dose to the target region remained relatively constant. This effect was independent of beam number [Fig. 6(e)].

III.C. Effect of target shape

For nonspherical targets, the dose conformity increased with increasing numbers of beams, similar to the results for spherical targets (Fig. 7). However, because beam diameters

a

d

b

e

c

f

FIG. 7. Dose distributions and DVH for [(a) and (d)] 10, [(b) and (e)] 30, and [(c) and (f)] 50 beams for a $2 \times 8 \times 2$ mm³ ellipsoidal target. The in-plane nontarget region is defined as the cylindrical slice with height equal to the target region height parallel to the gantry rotation (2 mm). The out-of-plane nontarget region is defined as the two cylindrical slices above and below the in-plane nontarget region, extending to the height of the largest beam width (8 mm), i.e., from -4 to -1 mm below the center of the target and 1–4 mm above the center of the target.

FIG. 8. The dose distribution for a $2 \times 8 \times 2$ mm³ target generated by ten beams, shown as a 3D reconstruction (left), cross-section (upper right), and vertical slice (lower right). The lines numbered 1 through 4 indicate the boundaries of the in-plane and out-of-plane nontarget regions. The in-plane nontarget region was defined as the region between #2 and #3. The out-of-plane nontarget region was defined as the regions between #1 and #2 and between #3 and #4.

were determined by the projection of the target from a given angle, the dose distribution deviated from the target not only in the cross-sectional plane as with the spherical targets, but also deviated in the direction perpendicular to gantry rotation (Fig. 8). The total amount of dose delivered to the out-of-plane nontarget region was not significantly decreased by

increased beam numbers, but the DVH increased in smoothness, just as for the in-plane nontarget region [Figs. 7(d)–7(f)].

III.D. Dose distributions in mouse microCT data

Dose distributions were found to have sufficient conformity to the mouse tumor. The tumor was located in the left lung above the heart, as shown in the volume rendering in Fig. 9(a). The dose distribution and DVH for the tumor, heart, left lung, right lung, and spinal column are shown in Figs. 9(b) and 9(c). As in the homogeneous phantom studies, a large percentage of the target received the maximum dose, while dose to the other important structures was minimized. As expected, doses to the heart and left lung were higher than dose to the right lung as a result of the tumor location.

IV. DISCUSSION

We have demonstrated a quantitative method for assessing treatment plans for small animal radiotherapy. For centered spherical targets, we found that increasing the number of beams used in the treatment plan increases the uniformity of the dose distribution, which is seen in DVH as an increase in curve smoothness. The size of the target impacts the number of beams required to achieve a particular smoothness. For smaller target sizes, more beams are required to achieve greater smoothness. To achieve a smoothness effect below 100 (arbitrary units), 80 beams are required for 1, 2, and 3

FIG. 9. 3D rendering of mouse CT data (a), with left lung, right lung, spinal column, tumor, and heart regions shown. The dose distribution for the spontaneous lung tumor treatment plan with 30 beams is shown in (b). The corresponding DVH for the tumor, spinal column, heart, left lung, and right lung are shown in (c).

mm targets; 70 beams are required for 5 mm targets; 60 beams are required for 7 mm targets; and 40 beams are required for 10 mm targets. This result is sensible based on geometric reasoning; for smaller targets, the beam width is smaller and therefore delivers dose to a smaller area in the phantom, and thus to achieve a smoother distribution across the entire phantom, more beams are required. For a larger target, on the other hand, the beam width is greater, and the beam therefore covers a larger region, and thus fewer beams are required to cover the entire phantom.

Although increasing the number of beams increases the uniformity of the dose distribution, the marginal increase in uniformity per added beam decreases as the total number of beams increases. The decreased marginal benefit of adding beams suggests that high beam numbers approach the dose distributions that would be achieved by having continuous gantry motion during treatment. Indeed, a recent Monte Carlo study of the doses delivered in tomotherapy modeled the delivery as 51 discrete static fields per rotation and found agreement with film measurements.²⁴

From a practical standpoint, these results suggest that there is some advantage to increasing the number of beams in a treatment plan, but only to a certain point. Beyond this point, the added effort of rotating the gantry to an additional angle and delivering an additional beam has no practical value in terms of dose distribution. The question, then, is where this cutoff should be determined in practice; above we have highlighted the different number of beams to achieve 100 a.u. of smoothness, but this cutoff is largely arbitrary. In practice, the required smoothness of the curve would depend on the radiosensitivity of each different type of tissue. Some tissues are more tolerant of small, high dose regions, as would occur with lower beam numbers, while other tissues are less so.²⁵ In addition, in some tissues, such as lung and liver, that have low whole-organ dose tolerances, a higher number of beams may not be beneficial, since the limiting factor is whole-organ dose as opposed to dose to particular regions.²⁶ It is also worth noting that in some cases, it may be preferable to have an inhomogeneous dose. A particular structure may be so radiosensitive that it is preferable to avoid entirely delivering a beam from a certain angle, or an experimental protocol may require minimal dose to particular structures, so that they may serve as a control. This could be achieved by using a lower number of beams to avoid having a beam in the sensitive area, or by having unevenly spaced beams.

When we shifted the target away from the center of the phantom, we found that dose distribution was qualitatively similar to the dose distribution for a centered target. This indicates that there is sufficient beam penetration through the phantom for targeting superficial targets. We did, however, observe that as the target was moved closer to the surface of the phantom, the dose delivered to the target region exhibited a slight increase, while the dose delivered to the nontarget region exhibited a slight decrease. These effects, which were independent of beam number, appear to be due to more

beams hitting a superficial target at shallow depths, thus depositing more dose and skewing the target DVH to the right and the nontarget DVH to the left (Fig. 6).

For the ellipsoidal targets, we observed that the both the in-plane and out-of-plane DVH increased in smoothness with increasing numbers of beams, as in the spherical target simulations. The significant out-of-plane dose delivered is a result of the planning method used in this study. The width of a beam at any given angle was set to be the maximum width of a projection of the target at that angle; given this method, there will always be an out-of-plane component if the dimension of the target perpendicular to the gantry rotation is smaller than the largest dimension in the plane of rotation. Conversely, an ellipsoidal target with its long axis perpendicular to the gantry rotation would result in more dose delivered to each in-plane cross-section in the plane of rotation. The case of an ellipsoidal target, in particular, highlights the need for more sophisticated planning algorithms in non-spherical geometries. Treatment plans that allow for raster scanning of the radiation beams using smaller apertures would allow for much more effective targeting of ellipsoid-like shapes. This could theoretically be achieved using our current system, since it allows for the isocenters to be changed between beam deliveries.

In the mouse CT data, we found that the dose exhibited reasonable conformality to the tumor. Some dose was received by the heart, lungs, and spinal cord, but this was unavoidable due to tumor location. As shown in Fig. 9, the right lung received the lowest dose of the analyzed areas, while there was greater dose to the heart and left lung. These results were expected, since the tumor was located in the left lung immediately adjacent to the heart. The shape of our DVH for this tumor is comparable to the DVH achieved in clinical treatment of human tumors in the left lung treated with three-dimensional conformal radiation therapy.²⁷ It is important to note, however, that there are significant limitations to our findings on dose distributions in mouse microCT data. The issues arising in Monte Carlo calculations for actual heterogeneous subjects are much more complex than we have addressed here; understanding of the material properties of murine subjects and the ability to accurately conduct tissue segmentation are still areas of ongoing research in small animal radiotherapy. However, our simplified approach allows for the demonstration of the applicability of the principles and methodology developed here in homogeneous phantoms to more realistic subjects.

In this study, we have demonstrated a method for quantitative analysis of dose distributions using our variable-aperture collimator. The results suggest that for spherical or near-spherical targets, an ideal number of beams can be chosen to balance both the tissue radiosensitivity and the labor-intensive process of delivering a treatment in a large number of beams. Our system can achieve sufficient dose conformality to spherical and near-spherical targets using current treatment planning algorithms; future work should examine using more complex algorithms that adjust the isocenter in all three dimensions between beams, using the capabilities for stage movement that are already incorporated into our system. A

combination of more complex treatment planning and automated isocenter adjustment will allow for more precise targeting of nonspherical targets.

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