Modality comparison for small animal radiotherapy: A simulation study

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(Received 11 April 2013; revised 30 October 2013; accepted for publication 7 November 2013; published 23 December 2013)

Purpose: Small animal radiation therapy has advanced significantly in recent years. Whereas in the past dose was delivered using a single beam and a lead shield for sparing of healthy tissue, conformal doses can be now delivered using more complex dedicated small animal radiotherapy systems with image guidance. The goal of this paper is to investigate dose distributions for three small animal radiation treatment modalities.

Methods: This paper presents a comparison of dose distributions generated by the three approaches—a single-field irradiator with a 200 kV beam and no image guidance, a small animal image-guided conformal system based on a modified microCT scanner with a 120 kV beam developed at Stanford University, and a dedicated conformal system, SARRP, using a 220 kV beam developed at Johns Hopkins University. The authors present a comparison of treatment plans for the three modalities using two cases: a mouse with a subcutaneous tumor and a mouse with a spontaneous lung tumor. A 5 Gy target dose was calculated using the EGSnrc Monte Carlo codes.

Results: All treatment modalities generated similar dose distributions for the subcutaneous tumor case, with the highest mean dose to the ipsilateral lung and bones in the single-field plan (0.4 and 0.4 Gy) compared to the microCT (0.1 and 0.2 Gy) and SARRP (0.1 and 0.3 Gy) plans. The lung case demonstrated that due to the nine-beam arrangements in the conformal plans, the mean doses to the ipsilateral lung, spinal cord, and bones were significantly lower in the microCT plan (2.0, 0.4, and 1.9 Gy) and the SARRP plan (1.5, 0.5, and 1.8 Gy) than in single-field irradiator plan (4.5, 3.8, and 3.3 Gy). Similarly, the mean doses to the contralateral lung and the heart were lowest in the microCT plan (1.5 and 2.0 Gy), followed by the SARRP plan (1.7 and 2.2 Gy), and they were highest in the single-field plan (2.5 and 2.4 Gy). For both cases, dose uniformity was greatest in the single-field irradiator plan followed by the SARRP plan due to the sensitivity of the lower energy microCT beam to target heterogeneities and image noise.

Conclusions: The two treatment planning examples demonstrate that modern small animal radiotherapy techniques employing image guidance, variable collimation, and multiple beam angles deliver superior dose distributions to small animal tumors as compared to conventional treatments using a single-field irradiator. For deep-seated mouse tumors, however, higher-energy conformal radiotherapy could result in higher doses to critical organs compared to lower-energy conformal radiotherapy. Treatment planning optimization for small animal radiotherapy should therefore be developed to take full advantage of the novel conformal systems. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4842415>]

Key words: small animal radiotherapy, microCT, SARRP, single-field irradiator, Monte Carlo

1. INTRODUCTION

Modern clinical radiation therapy machines deliver high doses of radiation conforming to the target under image guidance.^{1–3} Studies to evaluate tumor control probability and late normal tissue toxicity following a certain treatment schedule require months to years to complete in the clinical setting. These studies can potentially be carried out more rapidly in a preclinical setting. However, in order to efficiently study tumor response to radiation in the laboratory, preclinical radiotherapy machines must simulate treatment conditions comparable to those of clinical systems. The degree of complexity of small animal radiation therapy systems has lagged behind those used clinically until recently, as several dedicated small animal conformal radiotherapy systems have now been developed. The goal of this paper is to assess the differ-

ence between previous and current small animal radiotherapy methods, in order to evaluate the merit of emerging conformal radiation treatment devices for the laboratory and to recommend applications for each approach. We compared Monte Carlo dose distributions for two preclinical cases delivered with both conventional nonconformal irradiation methods and with two novel conformal image-guided systems.

The first *in vivo* radiation therapy experiments date back to late 1950s (Ref. 4) when total body irradiation of mice was performed with a ⁶⁰Co unit. Other total body rat irradiations followed, using either radioactive nuclides^{5–7} or x-ray tubes^{8,9} as sources of radiation. The response of tumor tissues to radiation was also studied with single-field targeted irradiations. The experiments were commonly carried out using an orthovoltage (200–300 kV) x-ray tube and a lead shield with an opening positioned over the tumor,^{5–7} or using a linear

accelerator and thick lead blocks.¹⁰ Subsequently, these simple nonconformal single-field approaches were used for studies of glioblastoma multiforme,¹¹ retinoblastoma,^{12,13} and repair kinetics of kidney¹⁴ in mice, and for lung cancer fractionation studies in rats.¹⁵

Dose in clinical radiotherapy is, however, typically delivered with multiple beams in multiple fractions. The beams intersect at the isocenter of the treatment machine, which is generally set at the center of the tumor volume. Until recently, similar machines for small animal radiation therapy did not exist. However, several preclinical conformal radiotherapy platforms have recently been developed. For example, the group at Washington University has used a collimated ¹⁹²Ir source to treat small animals.^{16,17} Our group has developed a small animal radiation therapy system based on a modified microcomputed tomography (microCT) scanner, and this system is used as one of the two models of preclinical conformal radiotherapy in this paper.^{18,19} A two-stage adjustable collimator producing 120 kV beams in the shape of a twelve-sided polygon and a two-dimensional translation stage added to the microCT scanner have made it possible to use the imaging device for delivery of conformal doses of radiation to small animals. Other groups have developed conformal small animal radiotherapy systems using treatment beams collimated by a removable collimator generated by an x-ray tube mounted on a rotating gantry.^{18,20,21} The Johns Hopkins University system,²² also known as the Small Animal Radiation Research Platform (SARRP, XStrahl, formerly Gulmay, Surrey, UK), with a 220 kV x-ray tube is used as the second model of small animal conformal radiotherapy in this paper. Dose distributions generated by another commercially available small animal radiotherapy system, the X-RAD225Cx (Precision X-ray Inc., North Branford, CT), are expected to be similar to dose distributions generated by the SARRP due to their comparable treatment beam properties.²³

2. MATERIALS AND METHODS

This study presents a comparison of treatment plans calculated for a nonconformal single-field irradiator with a lead shield [Fig. 1(a)] and two conformal irradiators [Fig. 1(b)]. Mouse dose distributions for a subcutaneous tumor and for a spontaneous lung tumor for the three treatment modalities were calculated using Monte Carlo simulations. Treatment plans were generated for the nonconformal single-field irra-

FIG. 1. Previous preclinical single-field nonconformal radiotherapy approach using a single x-ray beam angle with a shield placed in direct contact with the animal (a) and conformal radiotherapy with a number of collimated isocentric beams (b).

diation using a 200 kV x-ray beam, for the conformal Stanford University microCT system using a 120 kV x-ray beam and the conformal Johns Hopkins University system using a 220 kV beam. Target dose uniformity and dose to critical organs were evaluated for all plans.

While the dose for megavoltage beams can be calculated with high accuracy using analytical methods,²⁴ the dose for kilovoltage beams can be accurately calculated with the Monte Carlo (MC) method,^{25,26} and this strategy was employed here.

2.A. Monte Carlo simulations: Beam modeling

MC models of an orthovoltage RT 250 radiation therapy unit (Royal Philips Electronics, Eindhoven, the Netherlands), an eXplore Locus RS120 microCT scanner (GE Healthcare, London, Ontario, Canada), and the Johns Hopkins University system (commercialized as SARRP by XStrahl, formerly Gulmay, Surrey, UK) were created in the 2011 versions of the EGSnrc,²⁷ BEAMnrc,²⁸ and DOSXYZnrc codes.²⁹ A detailed description of the MC physics settings can be found in our previous publication.³⁰ Radiation treatment parameters for all three systems are summarized in Table I.

2.A.1. Single-field irradiator

The single field irradiator modeled for this work consists of a treatment table and an RT 250 x-ray tube operating at 75–250 kV in 25 kV intervals with currents of 15–20 mA,

TABLE I. Dose delivery parameters, including source-to-isocenter distance (SID) for animal irradiation and source-to-surface distance (SSD) for phantom validation.

	Beam			Measured HVL (mm)	SID (cm) Animal irradiation	SSD (cm) Phantom validation
	Voltage (kV)	Current (mA)	Filtration (mm)			
Single-field	200	17	2.0 Al + 0.15 Cu	1.08 Cu	58.5	58.5
MicroCT	120	50	2.5 Al	4.36 Al	34.5	34.5
SARRP	220	13	0.8 Be + 0.15 Cu	0.66 ^a Cu	34.0	35.0

^aHVL value obtained from the manufacturer.

mounted on a stand. Beams generated by the x-ray tube have half value layers (HVLs) from 1.7 mm Al to 4 mm Cu. For radiation therapy, the x-ray tube is operated at 200 kV and 17 mA. Animals are irradiated in animal jigs placed on a table 64.5 cm away from the focal spot, which results in typical target location of 58.5 cm away from the focal spot.

The tungsten anode of the single-field irradiator x-ray tube has an angle of 26° . The focal spot size of the 200 keV electron beam was not known and was chosen to be 3 mm, which is a typical spot size for a small animal irradiator. Since the beam is collimated at ~ 58 cm from the source, just above the irradiation target, the focal spot size has a negligible effect on beam penumbra. A 3.2 mm thick lead shield with 8–14 mm circular openings in 1 mm steps was modeled for beam collimation. An open beam with no shield was simulated for validation purposes.

2.A.2. Stanford University system based on a modified microCT scanner

The Stanford system consists of a GE eXplore Locus microCT scanner, a 2D translational stage, and a two-stage iris collimator.^{18,19} For radiation therapy, the microCT scanner x-ray tube operates at 120 kV and 50 mA. A 0.3 mm diameter electron beam strikes a tungsten target at an angle of 10° . The treatment beam can be further collimated to 1–100 mm using the variable aperture collimator. Phase-space files for different beam sizes were created just below the collimator. Dose deposition in solid water for 5, 10, 20, 30, and 40 mm beams were simulated for validation purposes.^{30,31}

2.A.3. Johns Hopkins University system (SARRP)

SARRP radiotherapy is delivered with a 220 kV beam generated with an x-ray tube mounted on a rotating gantry using a set of circular collimators of 0.5–40 mm in diameter and rectangular collimators of 5×5 to 100×100 mm.

A model of the SARRP system was built based on publications³² and manufacturer's specifications. The tungsten anode x-ray tube was modeled with a 20° angle. For small animal conformal radiotherapy circular beams of 8–12 mm in 1 mm steps were simulated. We should point out that circular collimators in 1 mm steps are not included in the standard version of the SARRP system. Note that circular collimators of 1–40 mm in 1 mm steps can be custom-made by the manufacturer. Collimators were modeled as three-stage 6-cm long brass cones 5 cm upstream of the isocenter. In addition, dose deposition for a 5×5 mm square field and a 15-mm diameter circular beam (nozzle without collimator at 17 cm upstream of the isocenter) based on experimental data obtained from Dana Farber Cancer Institute³³ was simulated for validation purposes.

2.B. Validation of MC models

2.B.1. Depth dose curves and beam profiles

MC simulations of treatment beams were validated with measurements by means of depth dose curves and beam pro-

files. Doses were measured with EBT Gafchromic films (ISP, Wayne, NJ) calibrated in a kilovoltage beam sandwiched between slabs in a solid water phantom. We measured single-field irradiator dose for an open beam and a 10 mm diameter beam, microCT dose for 5, 10, 20, 30, and 40 mm beams, and SARRP dose for 5×5 mm square and a 15 mm circular beams.³³ Additionally, the open-field depth dose curve for the single-field irradiator was measured with a 0.6 cc ionization chamber (PTW, model TN31014). The estimated composite uncertainty on film measurements was 3.5%.³⁴

2.B.2. Half-value layer evaluation

Treatment beam HVL was measured for the single-field irradiator and the microCT scanner in open field. First HVL, the thickness of a material at which the initial air kerma K_{init} decreases to half of its initial value K_{init} was extracted from measured air kerma attenuation. Air kerma was measured with a Farmer type ionization chamber model TN30013 (PTW, Freiburg, Germany) and Cu and Al filters for the single-field irradiator and microCT scanner, respectively. First HVL in thickness of Cu or Al, respectively, was calculated from the simulated spectra using the following:

$$\frac{K_{\text{att}}}{K_{\text{init}}} = 0.5 = \frac{\sum_i N_i E_i \left(\frac{\mu_{\text{en}}}{\rho} \right)_i e^{-\mu_i \text{HVL}}}{\sum_i N_i E_i \left(\frac{\mu_{\text{en}}}{\rho} \right)_i},$$

where N_i is the number of photons in energy bin E_i , and $(\mu_{\text{en}}/\rho)_i$ is the mass energy absorption coefficients of air at energy E_i , and μ_i is the linear attenuation coefficient of Cu or Al at energy E_i , respectively.³⁵

2.C. Small animals

Treatment plans for two mouse cases were created for the conventional single-field irradiator and the two novel conformal radiotherapy systems. The first mouse had two 0.10 cc subcutaneous tumors growing in the flanks [Fig. 2(a)], and the second mouse had a large 0.24 cc spontaneous lung tumor growing *in situ* [Fig. 3(c)]. The 5 Gy dose was prescribed to 50% of PTV volume (D_{50}). MicroCT images with 100 μm voxels acquired on the microCT scanner with a 70 kV beam and a 4-min scan time were used for treatment planning. Planning target volumes (PTVs) for the tumors as well as organs at risk were delineated using the multimodality image analysis and treatment planning software RT_Image.³⁶

2.D. Treatment planning

Treatment planning was performed in RT_Image that takes advantage of the features and degrees of freedom of the novel small animal conformal radiotherapy systems. First, treatment beam angles were manually selected depending on the treatment modality. Second, RT_Image was used to optimize beam widths using simple geometrical optimization by matching the shape of the target to a collimator size and to calculate the isocenter for each beam. Note that plans with multiple

FIG. 2. Anatomy of the mouse with subcutaneous tumors (a) and with spontaneous lung tumor (b). Tumor (PTV), right and left lung, spinal cord and heart and control tumor [orange, tumor implanted but receiving no direct radiation, only in (a)] are shown. The PTV in the mouse with lung tumor can be clearly seen in Figs. 3(c) and 3(d).

isocenters can be selected for conformal irradiators. Such plans can be easily delivered by repositioning the motorized animal bed between beams. The animal bed shifts for each beam were also calculated in RT_Image.

Due to positioning difficulties of the single-field irradiator, posterior-anterior (PA) beams were chosen for treatment. Due to the lack of small animal imaging and subsequent subject positioning uncertainties for single-field irradiations, two scenarios were assumed for both cases. First, accurate single-field irradiator animal positioning was assumed and a small 0.5 mm margin was added to the target. Second, the inaccuracy in tumor positioning was taken into account by adding a more realistic 2.0 mm target margin. We should point out that the 0.5 and 2.0 mm target margin was more realistic for the subcutaneous and orthotopic lung case, respectively.

For the conformal microCT and SARRP plans, beam angles minimally intercepting organs at risk were manually selected during the treatment planning stage. For the microCT and SARRP plans, no additional margins were included. We assumed that thanks to the image-guided nature of the novel small animal radiotherapy systems, tumor motion dur-

ing treatment was only due to physiological motion and it was captured during the 4-minute microCT scan. We assumed that physiological motion was captured in CT images used for treatment planning.

The subcutaneous tumor case was planned in the single-field irradiator with an 11 mm PA beam for the tighter 0.5 mm target margin [Fig. 3(a)] and a 14 mm PA beam for the wider 2-mm margin. Conformal radiotherapy plans for the subcutaneous tumor case delivered on the microCT and the SARRP system consisted of two 10 mm equally weighted 80° and 270° beams intersecting in the center of the tumor volume [Fig. 3(b)]. The slightly oblique 80° beam was selected due to the slightly anterior location of the target with respect to midline. Note that left lateral and PA beams correspond to 0° and 270° beam angles, respectively.

The lung case was planned with a 10 mm PA beam for the 0.5 mm target margin [Fig. 3(c)] and a 13 mm PA beam for the 2.0 mm target margin on the single-field irradiator. The planning for the lung case for conformal radiotherapy systems was more complicated. Out of a number of treatment plans, a nine-beam plan was chosen [Fig. 3(d)] and used for both the microCT plan and the SARRP plan. The beam angles were chosen manually, so that the dose to the spinal cord is minimized. Beams of 9–10 mm in size were uniformly spread between 150° and 230° in 10° intervals. All nine beams were uniformly weighted in terms of irradiation time due to similar distance from the skin to the target. The varying beam collimator sizes and isocenters were automatically calculated in RT_Image based on each beam's eye view. Even though delivery of non-coplanar beams with the SARRP system is possible, coplanar beams were chosen in this study.

2.E. Monte Carlo simulations: Mouse dose calculation

DOSXYZnrc input files were generated directly in RT_Image. The beam angles, sizes, and isocenters were saved in each input file. MicroCT images were converted into mass density information based on a microCT calibration phantom. For accurate dose calculations with kilovoltage beams, tissues were segmented in 37 types based on assumed atomic numbers calculated from the microCT images.²⁶ The generated anatomy file was used for dose calculations on all systems. Before the microCT data were converted into a MC geometry file, they were down-sampled by a factor of 2, resulting in $200\ \mu\text{m}$ voxels, which is a suitable size for small animal MC dose calculations.

Dose volume histograms (DVHs) were normalized to 5 Gy prescribed to D_{50} . Target uniformity, defined as the percentage standard deviation in PTV dose, was calculated. Beam-on times were calculated based on output-normalized MC dose distributions for each treatment modality.

3. RESULTS

3.A. Monte Carlo beam modeling

MC models of the small animal radiotherapy beams were validated with depth dose measurements. The results for the

FIG. 3. Beam setup for the subcutaneous tumor-bearing mouse using a single-field irradiator (a) and conformal irradiators (b) and for the lung mouse using a single-field irradiator (c) and conformal irradiators (d).

FIG. 4. Depth dose curves for 1-min irradiation for the single-field irradiator 200 kV beam (a), for the microCT 120 kV beam (b), and for the SARRP 220 kV beam (c) for various beam sizes. Percentage depth dose curves for a 10 mm circular beam delivered on all systems are shown in (d). MC simulations are represented by squares, film measurements by triangles, and ionization chamber measurements by circles. For clarity, statistical uncertainties of MC simulations are not shown in (a)–(c) and are below 1%.

validation of the single-field irradiator 200 kV beam MC model are presented in Fig. 4(a). A good agreement between the measured and calculated depth dose curves was observed with the mean difference on all data points being 1.4%. A good agreement between simulated and measured data for the 5, 10, 20, 30, and 40 mm beams of the microCT 120 kV beam is demonstrated in Fig. 4(b). The mean difference between the measured points and simulations was 2.0%. The simulated SARRP depth dose curves for both the 5×5 mm square field and the 15-mm circular field presented in Fig. 4(c) agreed with measured values to within 2%. For comparison of relative beam attenuation, percentage depth dose curves for 10 mm circular beams generated by the three systems are presented in Fig. 4(d). Figure 5 presents beam profiles for the 10 mm single-field and microCT beams and the 5×5 mm SARRP beam at three depths. The measured and simulated data agreed to within 2.5%.

Due to the extensive filtration of the single-field irradiator 200 kV x-ray beam, the SARRP 220 kV beam attenuated in

tissue faster than the single-field irradiator beam [Fig. 4(d)]. HVLs for all beams were calculated based on the simulated spectra presented in Fig. 6. The simulated HVL values were 1.04 mm Cu, 4.49 mm Al, and 0.66 mm Cu for the single-field irradiator, the microCT, and the SARRP system, respectively. The simulated values agreed with the measured values (Table I) to within 5%.

3.B. Monte Carlo dose distributions

3.B.1. Subcutaneous case

The dose distributions for the subcutaneous case are shown in Fig. 7, DVHs are plotted in Fig. 9(a), and the mean organ doses for all three plans are summarized in Table II. As a result of similar beam geometries, the idealized single-field treatment plan with the 0.5 mm target margin [Fig. 7(a)], the microCT plan [Fig. 7(c)], and the SARRP plan [Fig. 7(d)] generated similar dose distributions sparing most critical structures. The single-field irradiator [Fig. 7(b)] plan

FIG. 5. Beam profiles for single-field irradiator 200 kV beam (a), for the microCT 120 kV beam (b), and for the SARRP 220 kV beam (c) at various depths d . MC simulations are represented by squares and film measurements by solid lines.

FIG. 6. Energy spectra of the single-field (200 kV), microCT (120 kV), and SARRP (220 kV) treatment beams.

with the 2 mm target margin generated the poorest dose distribution. The mean dose to the right lung and bones was highest in the single-field irradiator plans (0.4 and 0.4 Gy for the 0.5 mm target margin and 1.1 and 0.7 Gy for the 2.0 mm target margin) compared to the microCT (0.1 and 0.2 Gy) and SARRP (0.1 and 0.3 Gy) plans. Due to the heterogeneity of the subcutaneous tumor or possibly due to image noise, the dose to the PTV in the microCT plan was heterogeneous. The tumor heterogeneity affected the SARRP system dose to a much lower degree and almost did not affect the single-field irradiator dose because of the higher treatment beam energies. Target uniformity was 4.8%, 9.1%, and 5.5% for the single-field irradiator plans, microCT, and SARRP plan, respectively.

3.B.2. Lung case

Dose distributions for the lung case are shown in Fig. 8, the DVHs are presented in Fig. 9(b), and the mean organ

FIG. 7. Monte Carlo dose distributions for subcutaneous tumor plans delivered on a single-field irradiator with 0.5 mm (a) and 2.0 mm target margin (b), the microCT system (c), and the SARRP system (d). Target is delineated.

doses are summarized in Table II. Better tumor conformality and critical organ sparing in the microCT and SARRP plans delivered with nine beams is demonstrated in Fig. 8. Due to the multibeam plan of the conformal treatments compared to the single-field treatments, the maximum spinal cord doses were 6.5, 2.7, and 2.5 Gy for the single-field irradiator plans, the microCT, and SARRP plan, respectively. Due to the close proximity of the target to the spinal cord it was impossible to create a plan with treatment beams completely avoiding the spinal cord if the target was to be fully covered with either treatment modality.

The mean doses to the right lung, the spinal cord, and bones were the highest in the single-field plans (3.9, 3.7, and 3.3 Gy for the 0.5 mm target margin and 4.5, 4.8, and 3.6 Gy for the 2.0 mm target margin), compared to the microCT (2.0, 0.4, and 1.9 Gy) and SARRP (1.5, 0.5, and 1.8 Gy) plans. The mean doses to the left lung and the heart were the highest in the single-field plan with the 2.0 mm margin (2.5 and 2.4 Gy), compared to the SARRP plan (1.7 and 2.2 Gy), the microCT plan (1.5 and 2.0 Gy) and the single-field plan with

FIG. 8. Monte Carlo dose distributions for lung tumor plans delivered on a single-field irradiator with 0.5 mm (a) and 2.0 mm target margin (b), the microCT system (c), and the SARRP system (d). Target is delineated.

the 0.5 mm target margin (1.2 and 1.2 Gy). Overall, the conformal plans resulted in better tissue sparing than the single-field treatment plans. Similar to the subcutaneous tumor case, target uniformity was poorer in the microCT plan. Target uniformity was 6.7%, 10.9%, and 8.1% for the single-field irradiator plans, the microCT and SARRP plan, respectively.

3.C. Treatment times

Beam-on times to deliver the 5 Gy prescription dose to D_{50} are summarized in Table III. Beam-on times were the longest for the single-field irradiator due to the large treatment SSD. The microCT beam-on times were longer compared to the SARRP beam-on times due to the slightly lower beam output and the higher beam attenuation (Fig. 4). For conformal radiotherapy, gantry rotation time must be added to the beam-on time to calculate the total treatment time. Assuming maximum gantry rotation of 2.5 rpm, the total treatment time per animal increased by 12 and 6 s for the subcutaneous and lung case, respectively.

TABLE II. Mean doses (in Gy) for the target and critical organs for the subcutaneous tumor case and lung case planned with single-field irradiator (200 kV) with 0.5 and 2.0 mm target margins, conformal microCT (120 kV), and conformal SARRP (220 kV) systems. Highest doses for each organ at risk are marked in bold. Total dose calculation uncertainties are within 10%.

	Subcutaneous tumor				Orthotopic lung tumor			
	Single-field		MicroCT	SARRP	Single-field		MicroCT	SARRP
	0.5 mm margin	2.0 mm margin			0.5 mm margin	2.0 mm margin		
PTV	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Right lung	0.4	1.1	0.1	0.1	3.9	4.5	2.0	1.5
Left lung	0.0	0.0	0.0	0.0	1.2	2.5	1.5	1.7
Heart	0.0	0.0	0.0	0.0	1.2	2.4	2.0	2.2
Spinal cord	0.0	0.1	0.0	0.0	3.7	4.8	0.4	0.5
Bones	0.4	0.7	0.2	0.3	3.3	3.6	1.9	1.8
Control	0.0	0.0	0.0	0.0

FIG. 9. Dose volume histograms for the subcutaneous (a) and lung (b) case irradiated on a single-field irradiator (dashed lines) with the 0.5 mm (diamonds) and 2.0 mm (squares) target margin and on conformal systems (solid line) with the microCT (triangles) and SARRP (circles) systems. Right lung in (b) is the right lung minus PTV. PTV dose is planned to $D_{50} = 5$ Gy.

4. DISCUSSION

This paper demonstrates that owing mainly to the use of multifield arrangement, dose distributions delivered using conformal planning techniques tend to be superior to those delivered using single fields. Two small animal conformal radiotherapy systems were studied and doses delivered with a microCT-based radiotherapy using a 120 kV treatment beam and radiotherapy delivered with a higher energy 220 kV x-ray tube were compared.

Figure 8 and Table II demonstrated high dose to bone for all treatment modalities. Assuming we scale these plans such that the lung case prescription dose is 60 Gy in one fraction, bones will receive mean doses of 43, 23, and 22 Gy in the single-field, microCT, and SARRP plan, respectively. It has been shown that rat maximum load at fracture does not decrease after 30 Gy of radiation, it decreases by 16% at 40 Gy.³⁷ As a result, bones could be weakened and possibly fractured in the single-field irradiator plan, which can limit dose regimes used in a study. Conformal treatment plans could be further optimized, should bone fractures affect the results of a study.

For the same 60 Gy single-fraction treatment dose, the lungs will receive mean doses of 42, 21, and 19 Gy in the single-field, microCT, and SARRP plan, respectively. Liao et al.³⁸ published lethal doses (LD_{50}) from radiation pneumonitis in mouse for whole lung (12.6 Gy) and half-lung

(18.7 Gy) irradiations. As a result, mice would more likely die of pneumonitis after radiotherapy in the single-field irradiator plan compared to the presented conformal radiotherapy plans. As in clinical radiotherapy, a compromise between target coverage and dose to critical structures must be found by means of a sophisticated treatment planning optimization tool.

The microCT plan presents the worst-case scenario with regards to dose to bone and target heterogeneity of small animal conformal radiotherapy, as microCT-based radiotherapy uses the lowest treatment beam energy. The lung SARRP plan results in greater target dose uniformity and in lower maximum dose to ipsilateral ribs compared to the microCT plan. Moreover, the SARRP treatment can be delivered more rapidly because of the higher dose rate of the system. However, most critical organs receive more dose in the SARRP plan because of the lower beam attenuation due to the higher treatment beam energy.

The single-field irradiator is convenient for studies where higher doses must be delivered to a large number of animals in short periods of time. In our institution, up to six animals can be irradiated during a single irradiation with an animal jig and a lead shield with six openings. Although the dose rate of the single-field irradiator is to some extent limited by x-ray tube heat dissipation, it can be as high as 120 Gy/h at 30 cm SSD. Due to overheating of the generator and the x-ray tube, the microCT irradiator can typically deliver dose rates of 20 Gy/h for a 10-mm diameter beam. Dose rates of high-energy conformal systems, such as the SARRP systems, have been quoted to be 120 Gy/h for a 10-mm diameter beam.²²

In some studies, a single-field irradiator using an x-ray tube or a radionuclide may be preferred over conformal radiation therapy systems. Legs of small animals, for example, can be conveniently irradiated with a single-field irradiator because dose conformality is not an important factor for such a study. A leg can be easily placed in the beam while a lead shield protects the rest of the animal.³⁹ A single-field irradiator is

TABLE III. Beam-on times to deliver 5 Gy to D_{50} for the subcutaneous and lung case for the studied modalities.

	Subcutaneous tumor			Orthotopic lung tumor		
	Single-field	MicroCT	SARRP	Single-field	MicroCT	SARRP
Treatment time (min)	11.9	4.2	2.9	12.1	3.8	2.7

also preferred for total body irradiations in which animal anesthesia is not required or not desirable.^{40,41} A conformal small animal radiation therapy system, on the other hand, is required for studies in which critical organs are nearby the irradiation target and where normal tissue must be spared. Most deep-seated targets therefore necessitate use of a conformal radiation therapy system.

Tissue segmentation scheme with 37 tissues was used for MC dose calculations. In our previous work, we showed that this segmentation scheme resulted in dose calculation differences from true dose values of less than 10% for the 120 kV microCT beam.²⁶ For higher energy beams, such as the single-field irradiator and SARRP beams, dose calculation errors were lower. Thanks to the accurate MC models of treatment beams (<2%) and low statistical dose calculation uncertainty (<2%), the overall dose calculation errors presented in this work were within 10%.

We suggest that treatment planning optimization for irradiation of small animals should be developed in order to take full advantage of the potential of small animal conformal radiotherapy platforms. The beam sizes in the SARRP 220 kV plan were chosen to match beam sizes in the microCT plan, so that the target was fully covered in each beam's eye view. Moreover, the higher energy of the SARRP system resulted in a much higher exit dose increasing some critical organ mean doses with respect to the microCT plan. These results suggest that a lower treatment beam energy than 220 kV may be beneficial for irradiations of mice. Optimal treatment beam energies for irradiations of rats will most likely be higher due to the larger size of the animal. In addition, the choice of technique should vary with the preclinical application, such as deep-seated tumors should be treated with higher energy and more filtration, and subcutaneous tumors should be treated with lower energy and less filtration. Optimization of treatment planning energy could also be incorporated into a pre-clinical treatment planning system.

As in the clinical setting, the delivered dose distribution is highly dependent on patient positioning during treatment and can be significantly different from the planned dose distribution if treatment setup techniques are not accurate. Mouse positioning for a single-field irradiator is not an easy task, especially if the tumors are not subcutaneous and cannot be seen by naked eye. Deep-seated irradiation targets may be missed if no image guidance is available. In this case, larger beam sizes should be used; however, such treatment plans will result in reduced sparing of healthy tissue and critical organs. From a positioning point of view, treatment with a current small animal conformal radiotherapy system with image guidance represents an optimal scenario, as 3D microCT images for treatment planning are acquired just prior to treatment. We suggest that target margins are not expanded for irradiations with small animal conformal radiotherapy systems. On the other hand, positioning in single-field irradiators is more challenging and target margins should be expanded by at least 0.5 mm for visible subcutaneous tumors and by 1.5–2.0 mm for deep-seated tumors.

High animal throughput is essential for small animal radiotherapy studies. As a result, treatment planning should not

be a time-consuming task. At our institution, after small animal microCT images are acquired and the target is delineated, beam angles minimally intercepting organs at risk are manually selected in RT_Image. RT_Image then calculates collimator sizes and animal bed shifts for each beam angle and estimates the dose to the isocenter based on tissue-maximum-ratio (TMR) data.¹⁸ This simple treatment planning process takes ~5 min. For accurate quantification of treatment dose, full MC dose calculation is performed after the animal is treated.

Ideally, treatment plans are optimized with a high level of accuracy. With enough CPU or GPU power, MC dose distribution for a selected plan could be calculated in a short period of time. The user could then manually modify the beam weights for higher target uniformity and lower dose to organs at risk. Alternatively, with an accurate dose calculation engine, treatment planning optimization could be as automated as in the clinical setting. It is important to note that irradiation times are limited by the maximum time small animals can be under anesthesia, which should not exceed 1 h.⁴²

5. CONCLUSIONS

Small animal radiation therapy can be realized in two ways, using either nonconformal single-field irradiations or conformal image-guided irradiations with multiple beams. Dose distributions for three systems, a nonconformal single-field irradiator, a conformal microCT-based irradiator, and the commercial SARRP irradiator were compared for treatments of a mouse with a subcutaneous tumor and of a mouse with a spontaneous lung tumor by means of Monte Carlo dose calculations.

The study demonstrates that particularly for orthotopic tumors, current small animal conformal radiotherapy systems generate treatment plans superior to conventional treatments with a single-field irradiator. Due to the higher exit dose of the higher energy beams used in commercial small animal conformal radiotherapy systems, such as the SARRP system, dose to critical structures might be higher compared to the microCT plans. As a result, careful treatment planning should be performed in order to take full advantage of the potential of small animal conformal radiotherapy systems.

ACKNOWLEDGMENTS

The authors would like to thank Ross Berbeco and his team from Dana-Faber Cancer Institute for providing the film measurements of their SARRP system and to Adrian Treverton from XStrahl for SARRP system specifications. The authors thank the laboratories of Dean Felsher and Joseph Wu at Stanford University for providing the mouse data for this study. The GE microCT scanners are a part of the Stanford Center for Innovation in *In Vivo* Imaging (SCI³). This work was supported by NIH Grant No. CA131199.

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