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A review of treatment planning for precision image-guided photon beam pre-clinical animal radiation studies

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Abstract

Recently, precision irradiators integrated with a high-resolution CT imaging device became available for pre-clinical studies. These research platforms offer significant advantages over older generations of animal irradiators in terms of precision and accuracy of image-guided radiation targeting. These platforms are expected to play a significant role in defining experiments that will allow translation of research findings to the human clinical setting. In the field of radiotherapy, but also others such as neurology, the platforms create unique opportunities to explore e.g. the synergy between radiation and drugs or other agents.

To fully exploit the advantages of this new technology, accurate methods are needed to plan the irradiation and to calculate the three-dimensional radiation dose distribution in the specimen. To this end, dedicated treatment planning systems are needed. In this review we will discuss specific issues for precision irradiation of small animals, we will describe the workflow of animal treatment planning, and we will examine several dose calculation algorithms (factorization, superposition-convolution, Monte Carlo simulation) used for animal irradiation with kilovolt photon beams. Issues such as dose reporting methods, photon scatter, tissue segmentation and motion will also bediscussed briefly.

Eine Übersicht der Photonen-Bestrahlungsplanung für präzise, bildgesteuerte, präklinische Tierstudien

Zusammenfassung

Seit kurzem stehen Präzisions-Bestrahlungsgeräte mit einer integrierten, hoch auflösenden Röntgen-CT-Bildgebung für präklinische Studien zur Verfügung. Diese Forschungsplattformen bieten erhebliche Vorteile gegenüber Tier-Bestrahlungsgeräten der älteren Generationen hinsichtlich der Genauigkeit der bildgeführten, gezielten Strahlentherapie. Diese Plattformen werden wahrscheinlich eine entscheidende Rolle bei der Entwicklung von Experimenten spielen, welche die Übertragung von Forschungsergebnissen in klinische Situationen zum Ziel haben. Innerhalb des Fachgebietes Strahlentherapie, aber auch in anderen Bereichen wie zum Beispiel der Neurologie, bieten diese Geräte einzigartige Möglichkeiten, unter anderen Substanzen die Synergie zwischen Bestrahlung und Medikamenten oder anderen Agentien zu erforschen.

Um die Vorteile dieser neuen Technologie voll ausschöpfen zu können, sind genaue Methoden notwendig, um die Bestrahlung planen und die dreidimensionale Dosisverteilung im Organismus berechnen zu können.

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Keywords: Small animal, precision irradiation, image-guidance, treatment planning system, dose calculation, photon scatter

Spezielle, hierfür entworfene Bestrahlungsplanungssysteme sind hierbei essentiell. In dieser Übersichtsarbeit erörtern wir die spezielle Situation der Präzisionsbestrahlung von Kleintieren, wir beschreiben die Arbeitsweise der Bestrahlungsplanung bei Tieren, und wir untersuchen verschiedene Algorithmen zur Dosisberechnung (Ray Tracing, Superposition-Konvolution, Monte-Carlo-Simulation), die für die Tierbestrahlung mittels Kilovolt-Photonen verwendet werden. Des Weiteren werden Punke, wie zum Beispiel Methoden der Dosismeldung, Photonenstreuung, Gewebesegmentation und Bewegung kurz angerissen.

Schlüsselwörter: Kleintier, Präzisionsbestrahlung, Bildführung, Bestrahlungsplanungssystem, Dosisberechnung, Photonenstreuung

1 Introduction

The technical capabilities in human radiotherapy have reached a high level of sophistication with e.g. intensity modulated radiotherapy and volumetric modulated arc therapy whereby the photon fluence is modulated while a medical accelerator irradiates the tumor with a crossfire of beams from several directions [1,2]. Radiation dose distributions can now be sculpted intricately with techniques such as dose painting e.g. to preferentially target hypoxic tumor regions [3]. This degree of sophisticated beam delivery requires an equally complex level of planning and dose calculation which is nowadays available in clinical treatment planning systems (TPS). Arguably the next progress in radiation delivery comes in the form of hadron beams such as protons and carbon ions [4] where also sophisticated treatment planning methods are being developed [5].

Most progress in radiotherapy, real or perceived, has come from technological developments, and not from knowledge derived e.g. from animal irradiation experiments [6]. The latter were mostly performed with irradiation technology which bears little resemblance to modern radiotherapy equipment. The recent development of many animal tumor models has enabled the detailed study of the tumor micro environment and the interaction of radiation with tumors. Improved models of normal tissue response are also needed to assess optimal radiotherapy strategies.

The recent literature [6–8] has described some novel technology which, for the first time, allows precision image guided radiotherapy for pre-clinical studies in radiotherapy. It combines narrow radiation beams of photons which may be aimed precisely at tumorous or healthy tissues with the aid of x-ray imaging equipment. It is expected that this new technology may lead to meaningful translation of novel forms of cancer therapy, e.g. by exploiting the synergy between radiation and drugs or other agents.

In a recent review paper on the novel animal technology [6] it was explained why small animal precision irradiation with photons is preferably done with kilovolt (kV) instead of megavolt (MV) photons. The main rationale is to avoid extensive dose buildup regions near medium interfaces, and to avoid wide beam penumbras, sometimes encompassing the whole animal. Many animal studies done in the past didn't employ a TPS and usually no imaging was available. Using a human TPS for animal studies is not really advisable, at least not without precautions. Human TPS employ calculation models unsuitable for small beams (<3 cm field size). One of the few animal studies accurately modelling small beams of high energy photon beams with a dedicated TPS is [9] where rats were irradiated with small beams of ^{60}Co photons from a GammaKnife device. A human TPS may not be suited to handle the animal voxel phantoms from e.g. a CT or MRI scan with commonly a large number of very small voxels. There is also no human TPS that can reliably calculate dose distributions in heterogeneous phantoms irradiated by kV photon energies.

Recently, dedicated photon dose calculation methods for small animals have been proposed from relatively simple pencil beam type calculations to Monte Carlo simulations. The latter has the potential of being the most accurate dose calculation technique available for a wide range of conditions [10], provided accurate models are used. This review discusses several of these methods with an emphasis on the technical capabilities and not on treatment planning studies themselves. Sometimes precision proton [11] or hadron beams [12] are used for pre-clinical studies; treatment planning for these is not included in this review. Treatment planning for radiotherapy for pet animals is also excluded from the review.

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2 Issues for small animal radiation dose calculation

In the currently commercially available precision small animal irradiators a photon spectrum of about 225 kV is used with collimators shaping small beams with dimensions of 0.5 mm up to a few centimeters. Some in-house developed systems use other photon energies. In the commercial devices the x-ray tube is mounted to allow irradiation of the specimen from multiple sides, and also to enable arced beams. The same x-ray tube, with a lower tube voltage (typically 50-80 kV) and a wider field of view typically encompassing a whole animal, is used to acquire a cone beam CT (CBCT) image of the specimen. The CBCT imaging panel typically has a high spatial resolution of about 100-200 μm (compare to 1-3 mm in human CT scanners). The resulting 3D CBCT images may have a very large number of small voxels, easily in the tens of millions. Storing a large number of these images in studies involving many animals with each possibly undergoing several imaging sessions, may require special consideration for data archiving.

In contrast to the MV energy range of photons where Compton scatter is the only relevant photon interaction process, for kV photons the photo-electric effect becomes increasingly important at lower energies. Whereas the probability of the Compton effect for different tissues depends only on the electron density, the probability of photo-electric effect depends very strongly on the effective atomic number $Z^{3\sim4}$ of the tissues. Since Z ranges from about 6-14 for human tissues, the probability for photo-electric effect differs greatly between the tissues. Figure 1 shows that the mass energy absorption coefficients [13] for various human tissues [14] differ significantly from water. This quantity is closely related to absorbed radiation dose. Cortical bone and skeletal muscle, which often occur in each other's proximity anatomically, differ by more than a factor six in their energy absorption around 30 keV. Accurate dose calculation may require defining several bone types in this case. Even media such as soft tissue and adipose differ significantly in energy absorption. In MV photon energies dose calculations are much less sensitive to the tissue compositions. A potentially large source of uncertainty is that actual animal tissues appear to be unknown in their composition. However, it is clear that assigning water to all voxels will lead to significant over/underestimation of the absorbed dose in animals. The current practice in animal dose calculation is therefore to assign human tissue types to the voxels, but with the density derived from the CBCT (or CT) image. Almost certainly, anything resembling human cortical bone is not present in large regions in small animals, and certainly not with the densities as they occur in humans. From this discussion it is also clear that to avoid large uncertainties with heterogeneous dose distributions due to tissue absorption, photon energies above 100 keV should be used preferentially for small animal radiotherapy research. On the other hand, one may wish to irradiate with lower photon energies to e.g. assess effects of

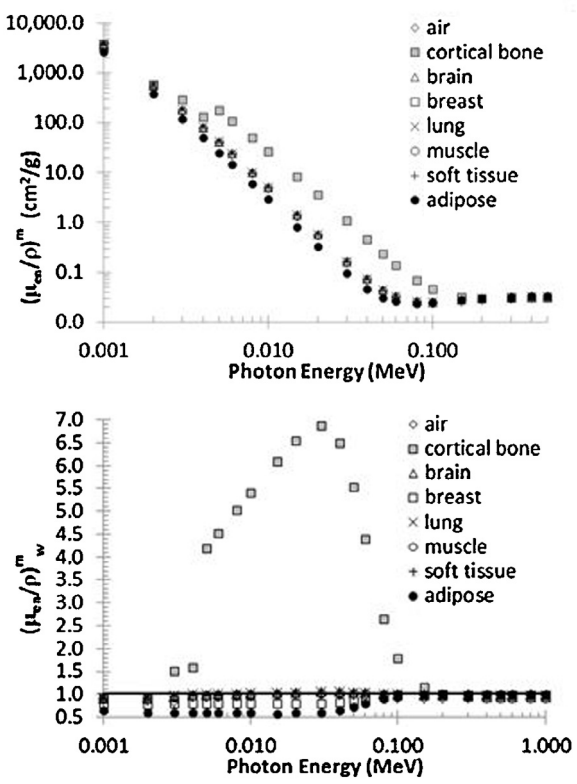

Figure 1. Photon mass energy absorption coefficients (top) and relative (to water) mass energy absorption coefficients (bottom) for various (human) media of interest.

relative biological effectiveness (RBE) in animals, which is known to be enhanced at lower photon energies [15]. In this case one should be aware of the dose uncertainties at lower energies. A state of the art TPS for preclinical studies should therefore be able to provide information on the photon spectrum in various animal tissues, thereby allowing estimates of RBE.

3 Imaging information for treatment planning

3.1 CT imaging

Chief among imaging modalities for human radiotherapy planning is CT imaging, with other modalities such as PET and MRI used complementary. This is mainly because information on electron density is needed for the dose calculation. The same holds for small animal dose calculations but in addition tissue types need to be identified for reasons explained in the previous section. The required spatial resolution is typically of the order of 100-200 μm to ensure a sufficient volumetric accuracy to image anatomical structures, tumors or sub-parts thereof. Modern commercial small animal irradiators have an onboard CBCT x-ray imaging device, but equally well could

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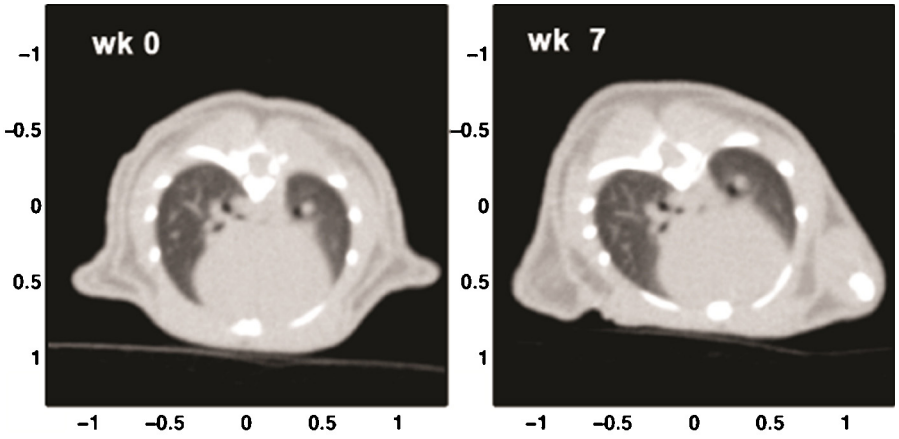

Figure 2. CBCT image of the onboard scanner from a X-RAD 225Cx irradiator (PXi, North Branford, USA). Axial sections of the same mouse are shown at different time points after irradiation (week 0 and week 7).

the planning process be based on an externally acquired CT image. Figure 2 shows CBCT images of the same mouse at different time points in a longitudinal study [16]. Obviously the position of the animal can be different during different imaging sessions, depending on the rigorousness of the animal fixation procedure. If also reirradiation of the same target in the specimen with precise beams is involved, care has to be taken to adjust the treatment plan accordingly. This may also involve using image registration techniques.

In human radiotherapy CBCT images usually have a significantly lower imaging quality than CT images, and are therefore known to potentially hamper the quality of dose calculations [17]. For small animal CBCT images this is less of an issue due to the very limited amount of scattered photons contributing to the image formation which degrades the image quality in human applications. On the other hand, the small voxels in animals necessitate a high radiation dose (up to about 0.2-0.4 Gy per exposure [18]) to reach acceptable noise levels. The images in Figure 2 exhibit high contrast, allow identification of many structures and are relatively free from CT artifacts. Further research into improving small animal CBCT imaging may improve e.g. autosegmentation of structures and the accuracy of the dose calculation since this depends strongly on correct tissue type identification.

The typical workflow for treatment planning for small animals starts with the acquisition of a 3D CBCT (or CT) image, consisting of many small voxels. The specimen then remains on the stage with as little motion as possible, while the CT image reconstruction occurs (this requires about 1 minute). To perform a dose calculation the Hounsfield units (HU) of every voxel need to be assigned a density. This is performed by acquiring an image of a calibration phantom with tissue-equivalent inserts of known densities (e.g. the Model 467; Gammex RMI, Middleton, WI) to derive a HU versus density calibration curve. The density could be either mass density or electron density, depending on the requirements of the used dose calculation algorithm (between both quantities there exists a simple relationship for human tissues and their numerical differences are small, except for lung [19]).

Figure 3 depicts a typical HU-mass density curve obtained from a calibration procedure with only 3 calibration materials in a phantom. A piecewise bi-linear curve was fitted through these points. Mass densities can then be assigned to every voxel. The calibration curve depends on the kV-filter combination (i.e. the radiation quality) so when animals are imaged with different imaging protocols multiple calibrations have to be performed. Many types of dose calculation algorithms, e.g. Monte Carlo radiation transport simulations, need additional information in addition to voxel densities, such as tissue type. A possible way to assign tissues to voxels is to subdivide the whole HU range into intervals that belong to the same tissue (figure 3). This procedure adds a degree of arbitrariness to the voxel conversion.

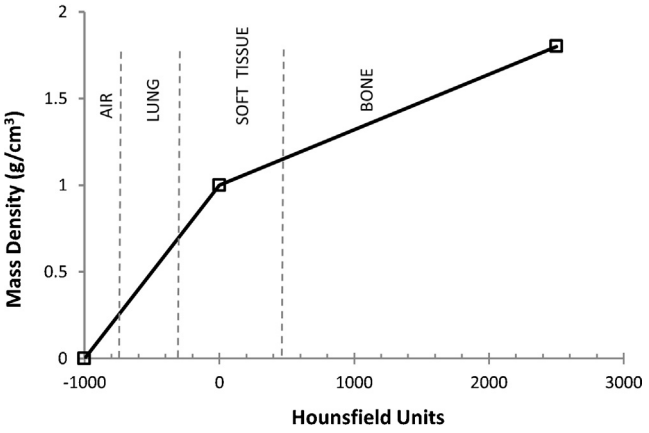

Figure 3. Typical HU vs mass density calibration curve, based on a calibration phantom. Only 3 calibration media were used (air at -1000 HU, water at 0 HU and bone equivalent material at 2500 HU). Four different media will be assigned to the voxels in this scheme (air, lung, soft tissue and bone).

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Table 1
Overview of various treatment planning systems developed for small animal radiotherapy. The last two entries are commercially available systems.

TPS	Company / Research Institute	Based on
microRTP	Washington University	Factorizaton of dose distributions in water and non-water geometries
DOSCTP	Princess Margaret Hospital (Toronto, USA)	Monte Carlo simulation
Nameless	Johns Hopkins University (Baltimore), McGill University (Montreal, Canada)	Pinnacle (Philips, Eindhoven, the Netherlands) + Monte Carlo simulation
RT_Image	Stanford University, USA	Monte Carlo simulation
Nameless	Dresden University	Monte Carlo simulation
Muriplan	XStrahl Ltd* / Johns Hopkins University (Baltimore, USA)	Superposition convolution
SmART-Plan	PXi** / Maastro Clinic (Maastricht, the Netherlands)	Monte Carlo simulation

* Camberley, UK.
** North Branford, USA.

Table 1.

Other methods to assign tissue types rely on dual energy CT imaging [20]. This form of imaging allows extraction of more information from the specimen compared to single energy CT imaging, e.g. the atomic number. This may support the correct identification of tissue types. In addition to correct tissue/density assignment one should also be aware of the imaging dose to the animals [21] which can significantly contribute towards the total radiation dose, especially in longitudinal studies involving repeated imaging.

In human radiotherapy a common coordinate system between imaging and treatment rooms is ensured by the use of laser alignment systems on the imaging devices and accelerators, and of robust fiducial systems (markers or frames attached to the patient) or direct imaging of patient structures. In animal radiation studies a similar issue is encountered, but the required accuracy is even higher. If an onboard CBCT imager is used then the image and the irradiation space are already in the same coordinate system. In case a separate CT imager is used or another imaging device is employed, a procedure to ensure a common system of coordinates is needed. This may be done e.g. through fiducial markers attached to the animal or to its carrier in combination with some form of imaging. This is a non-trivial issue which will determine the irradiation accuracy to a large extent. Robust animal fixation systems are required to avoid compromising the quality of precision irradiation studies. In radiotherapy images are also highly standardized via the DICOM (Digital Imaging and Communications in Medicine) imaging standard, which is largely absent in the small animal research community.

3.2 Additional imaging methods

As in human radiotherapy, additional imaging methods may be required to extract information for treatment planning for animals. From Single Photon Emission Computed Tomography (SPECT) or PET (Positron Emission Tomography) images information may be extracted to distinguish metabolically highly active regions by using the ^{18}F-deoxyglucose (FDG) tracer. The same imaging modality may be used to detect hypoxic (low in oxygen) regions in tumors with tracers such as 18F-fluoromisonidazole (FMISO) or ^{18}F-fluoroazomycin-arabinoside (FAZA). Such information may serve to assess sub-regions of tumors that e.g. could be the subject of radiation boost studies.

Also Magnetic Resonance (MR) imaging could be used in small animal treatment planning. Recently, a group from the University of Ghent, Belgium introduced a MRI-based workflow for irradiation of animal brain tumors [22]. This involves special MR sequences to generate pseudo CT images with a limited number of tissue classes.

Ultrasound imaging can in principle also be used for visualization of soft tissue structures for small animal treatment planning, especially if the scanning procedure can be automated without the need for a human operator to manipulate the transducer. So far, to our knowledge this technique has not yet been reported in combination with precision irradiators. A few recent reports mentioned the use of specialized ultrasound techniques for the characterization of tissue damage after irradiation [23,24]. For small animal studies there exist certain imaging techniques which are not useable in humans, such as optical [25] or photo-acoustic imaging [26], which may be useful to visualize certain processes in the tumor or healthy tissues. Phase contrast imaging [27] may be another imaging technique which could be integrated with small animal radiation research platforms. Multimodality imaging is expected to play a significant role in guiding treatment planning for preclinical studies or in assessing treatment outcome.

4 Dose calculation models for small animals

For accurate kV photon dose calculations the most suitable technique is Monte Carlo simulation [10]. Less accurate techniques can be based e.g. on dose factorization, ray-tracing,

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superposition convolution or other models. In what follows we will first discuss some of the simpler methods then followed by Monte Carlo simulation. An overview of TPS developed by various groups is given in Table 1.

4.1 Analytical method for ^{192}Ir irradiator

One of the pioneering efforts in building a small animal precision irradiator originated from Washington University where a system was built based on irradiation with narrow beams with the ^{192}Ir isotope. The system had a software interface for stage control, and a dedicated treatment planning system (microRTP) that was based on CERR, a Matlab based research TPS [28]. The TPS was based on water geometries only. ^{192}Ir emits photons with energies from a few keV to 885 keV, therefore, the differences in absorbed dose in the different mouse tissues are not as large as for kV x-rays (Fig. 1), but their dose calculation accuracy could improve by taking non-water heterogeneities into account. The authors developed a fast analytical dose calculation scheme which consisted of a multiplication of various factors, some of which were derived from Monte Carlo simulations. This approach resembles the fast dose calculation methods that were available in older TPS once commonly employed in radiotherapy. A more accurate approach taking into account heterogeneities was considered [29], but it is not straightforward to adapt their parametrized model to include tissue heterogeneities. The fast algorithm was reported to result in dose errors limited to 10% in water, near beam edges and close to the entrance region for small fields (<10 mm). These researchers [30] reported a buildup region of less than 1.5 mm and their papers indicate that the beam penumbra extends up to 3 mm. The latter is quite large compared to small structures in the animal that could be targeted in precision irradiation studies.

For animal kV irradiators a similar simple fast dose calculation model has been published [31]. Tissue heterogeneities were approximately taken into account by using estimates of radiological pathlenghts of photons through tissues. These simplified approaches are inaccurate in non-water geometries, in particular in the kV energy range. These methods cannot provide estimates of photon spectra in tissues, which are needed to assess RBE. These methods can also not easily report the dose in the form of dose to medium-in-medium or dose to water-in-medium (see section 5.4) since they only provide dose to water-in-water. It was also not clear how these simple methods can provide absolute dose distributions; in their work only relative dose distributions were shown. It has been shown that the absolute output of small radiation beams is much harder to model accurately [32,33].

4.2 Superposition-Convolution dose calculations

A team from the Johns Hopkins University (Baltimore, USA) has developed a superposition-convolution algorithm for dose calculation in small animals, inspired by their previous work for radiotherapy MV photon beams [34,35]. This method is based on the calculation of terma (total energy released to matter), which is obtained by multiplying the local photon energy fluence by the energy absorption coefficient. The local energy fluence is derived from the primary energy fluence emanating from the photon source, corrected for inverse square falloff with distance and photon attenuation. The method is essentially a ray-tracing approach, with inclusion of first order Compton scatter. An assumption in the model is that the dose deposition kernels are generated for different densities of water-like materials. Electron transport is included in the dose deposition kernel. For e.g. 225 keV electrons (the maximum electron energy for the commercial x-ray irradiators) the electron range in most materials is limited to about 0.3 mm, but in lung the range can be a few mm, which can exceed several times the voxel dimensions. This method can use as input a photon spectrum or a phase space file (list of coordinates, energy, momentum etc for a collection of particles collected at a certain position in space) obtained from a separate Monte Carlo simulation. Dose reporting is in terms of dose to water-in-medium, but can be converted to dose to medium-in-medium by multiplying the former by ratios of photon energy absorption coefficients of medium and water [36,37], although this requires calculation of the local photon spectrum. It has been reported before that the superposition-convolution approach for kV photons may lead to problems in non-water media where dose discontinuities arise (e.g. bone, lung) [38].

The Johns Hopkins team recently described [39] the use of 3D Slicer [40,41] to create a user interface for their TPS and their irradiator (SARRP, XStrahl Ltd, Camberley, UK). 3D Slicer is popular freeware for medical image visualization and analysis. Such an interface allows a broad range of users (not necessarily experts in treatment planning) to efficiently produce treatment plans for small animal studies. The Johns Hopkins team implemented the dose calculation on graphical processing units (GPU) in the cuda language for fast processing (sub-minute dose calculations). This dose calculation method is now commercially available as Muriplan (XStrahl Ltd).

4.3 Monte Carlo simulation

Monte Carlo simulation is the method of choice for accurate calculation of radiation dose and particle spectra in a voxelized animal, irradiated with kV x-rays. This is because of the dominance of the photo-electric effect, the presence of photon scatter and the ability to easily obtain photon spectra which can be used in radiation quality studies. The Monte Carlo technique models particle transport, interactions with other particles and electromagnetic fields, and production of secondary particles based on cross sections and transport theories. For applications in small animal treatment planning Monte Carlo simulations can attain an accuracy of 1-2%. An

important issue in Monte Carlo transport is the cutoff at which to terminate the particle transport. For photons this is commonly set at 10 keV, whereas for the secondary electrons the cutoff has to be selected taking the voxel sizes into account, such that electrons do not erroneously contribute towards the dose in incorrect voxels. Particle transport cutoffs have been investigated in detail [42].

Recently, the Monte Carlo method has been used to model small animal radiation research platforms [6,32,43]. The in the past frequently heard complaint that Monte Carlo simulations are slow due to the large numbers of interactions to model, is nowadays less relevant with the availability of fast computers and parallel processing techniques. GPU computers are now also available to run simulations very efficiently [44] which will probably allow Monte Carlo simulations to play an important role in small animal treatment planning. A restriction could be in inverse planning [45] where a great number of dose calculations for individual 'beamlets' need to be performed. It is imaginable that the beamlet dose calculations could be performed by a faster, less accurate method (e.g. a track length scoring Monte Carlo approach, or a faster analytical dose scoring technique) and that the final dose calculations after optimization of the beamlets would be performed by a slower full Monte Carlo simulation.

A group in Toronto (Princess Margaret Hospital) developed DOSCTP [46], which is a graphical user interface enabling basic treatment planning of kV beams of 0.5-5 cm diameter for small animals. The TPS initiates and calls the Monte Carlo code DOSXYZnrc [47] from within DOSCTP to execute dose calculations in a voxelized geometry. This basic TPS can be used to create 3D conformal plans. Figure 4 shows an example of an arc beam delivery in a mouse specimen.

Another pioneering effort from the team at Johns Hopkins University, in collaboration with McGill University (Montreal, Canada) led to the development of a 3D kV Monte Carlo based TPS for their SARRP irradiator. They coupled the aforementioned Monte Carlo code DOSXYZnrc [47] as a dose engine to a commercial human radiotherapy TPS (Pinnacle; Philips, Eindhoven, the Netherlands). The latter is used to create the beam geometry, the beam weights and the animal phantom. This information is then sent to the dose engine. Once the dose engine completed the calculations, the results are returned to the TPS for dose display and analysis. The Pinnacle scripting environment is used to communicate with the Monte Carlo engine.

The combined TPS/dose engine uses a set of pre-computed phase space files for the SARRP nozzle collimators generated with BEAMnrc [43] Monte Carlo simulations. An early demonstration of their system was described in 2008 [7]. The Johns Hopkins group abandoned their efforts in Monte Carlo treatment planning in favour of the convolution-superposition method described in the previous section. Therefore, the abovementioned Monte Carlo based TPS is not commercially available.

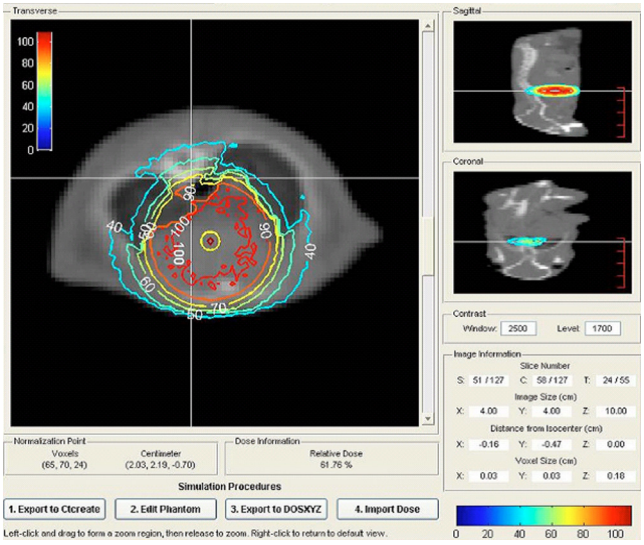

Figure 4. Monte Carlo calculated isodose distribution from an arc irradiation with 225 kVp x-rays of a small target in a mouse chest, overlaid with a CBCT image. Reproduced from [46] with kind permission.

More pioneering efforts came from a group at Stanford University where a micro-irradiator was developed by modifying a 120 kV micro-CT scanner [48] (efforts now abandoned). They also developed an in-house TPS, RT_Image, based on Monte Carlo simulations with the BEAMnrc/DOSXYZnrc codes. They were the first to extensively study the optimization of dose calculation times for small animals (via so called variance reduction techniques) [42]. This group investigated the achievable dose conformality to small spherical and ellipsoidal targets in a phantom irradiated by discrete beams spread out in an arc [49]. They modelled centered and off-centered targets in a simple phantom. They showed that animal dose distributions are close approximations to human lung tumor cases. These kinds of exercises are useful since in the new field of small animal treatment planning much experience still needs to be gained. These authors were also among the first to use dose volume histograms as a dose comparison tool for animal studies, which is a valuable tool for optimizing and comparing dose plans.

Recently a group in Maastricht (the Netherlands) developed a standalone TPS SmART-Plan (Small Animal RadioTherapy planning system) [50]. The TPS is developed as a MatLab program with a workflow that is similar as for a clinical TPS, but simplified. Since a recent publication describes SmART-Plan in detail [50], we will only present a brief synopsis here. The workflow of SmART-Plan is very simple and robust; the tasks to be performed sequentially are (1) uploading the DICOM-compliant images of an animal of an imaging modality (e.g. CT), resampled on a different grid resolution and size if necessary; (2) image processing to assign densities and materials to each voxel in the CT to density and material (CT2MD) step,

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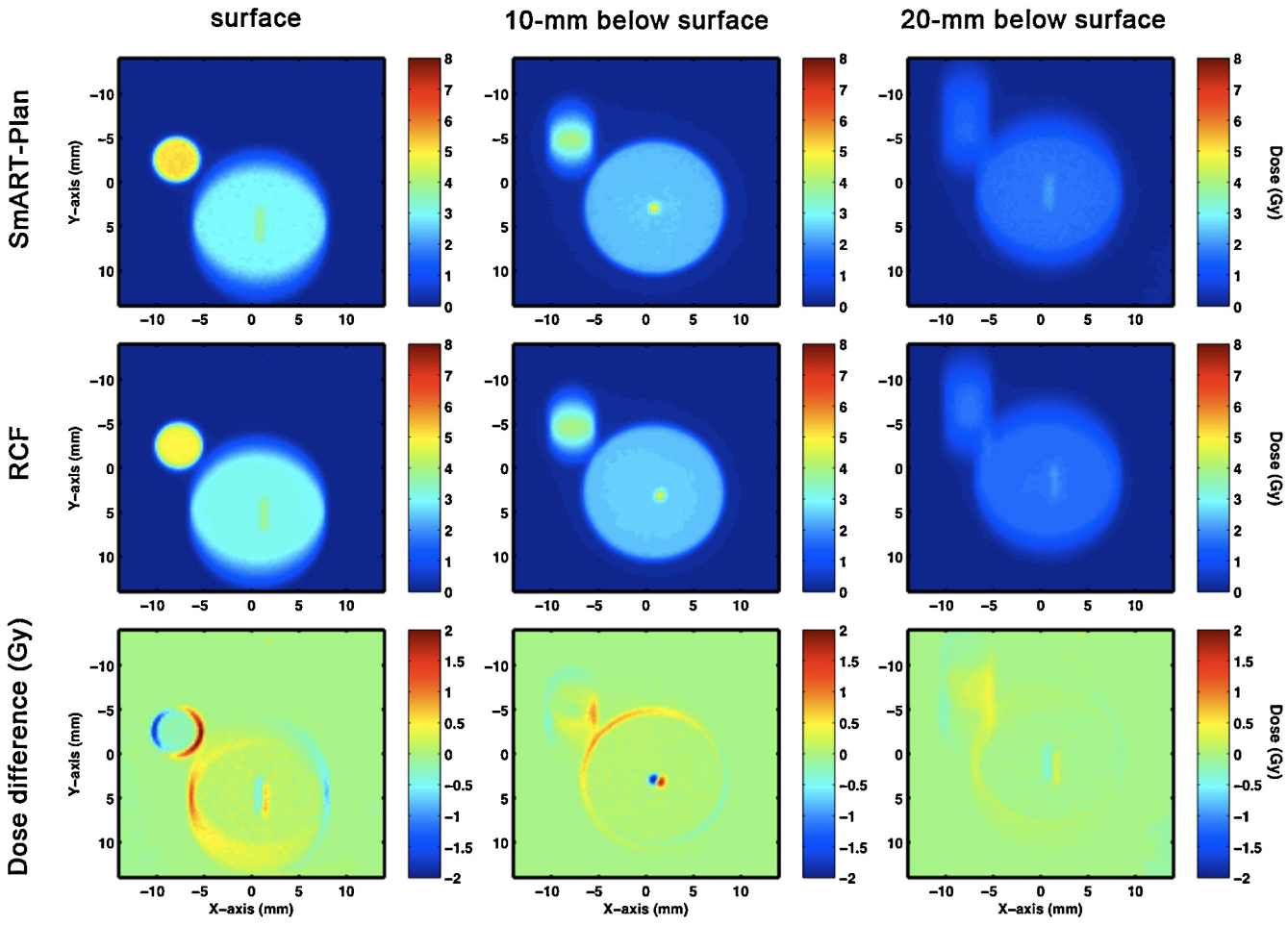

Figure 5. Comparison of SmART-Plan Monte Carlo calculated (top row) and radiochromic film measured (middle row) dose distributions at different depths in a solid water/solid bone/solid water slab phantom. Also shown are the dose differences (calculated – measured) in the bottom row. Dose differences are mostly limited to small regions in the beam penumbrae.

leading to a numerical phantom for Monte Carlo simulation; (3) structure definition (contouring) for tumor and healthy tissue delineation (structure contours are stored e.g. for later dose analysis); (4) definition of the static or arced radiation beams, resulting in a treatment plan and the input file for the simulations; (5) dose calculation with the DOSXYZnrc Monte Carlo dose engine, where parallel processing techniques are used to speed up the calculations; (6) dose analysis e.g. with dose volume histograms; (7) delivering a control file to the irradiator, which directs motion of the animal stage, positioning of the beams and irradiation of the specimen. SmART-Plan is commercially available from PXi (North Branford, USA).

The Maastricht group used the BEAMnrc Monte Carlo code to build one of the most detailed Monte Carlo models reported for the X-RAD 225Cx irradiator, including a sophisticated model for the electron focal spot on the x-ray target [33]. Monte Carlo dose calculations in animals can be performed in reasonable times nowadays, but simulation of an x-ray device still requires long calculations times, up to several tens of hours. This group also developed a faster analytical photon source model which allows speeding up the generation of an output phase space file, up to more than a thousand times faster.

SmART-Plan was validated by measurements with radiochromic film in various homogeneous and heterogeneous phantoms [50]. These were irradiated by three collimators under different irradiation angles and with two target isocenter locations each targeted with a dose of 5 Gy. For a heterogeneous solid water/solid bone/solid water slab phantom in the regions were the dose was between 80-100% of the maximum slice dose, about 1% of the voxels exhibited a dose difference of more than 10% of the maximum dose in that slice. Maximum absolute dose deviations of about 2 Gy were found but these were localized in small regions near the penumbra of the beams (figure 5). They noted that

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the 1 mm collimator was difficult to align precisely, which led to some dose discrepancies at 20 mm depth. They point out that the alignment of the smallest 1 mm collimator is critical for irradiation studies of small targets with these small beams.

Finally, we mention the effort to build a Monte Carlo simulation platform based on the Geant4 Monte Carlo code [51] for animal dose calculation from a consortium in Dresden [52]. They interface the Geant4 code with an in-house developed irradiator to perform contouring and setting up beams. As far as we know, no current animal TPS is capable of handling various types of irradiators, but this will undoubtedly change in the future.

4.4 Absolute dosimetry

To deliver an accurate radiation dose to small animals the irradiator needs to be calibrated in terms of absolute dose, for which a calibration protocol such as AAPM TaskGroup 61 [53] needs to be followed. This is explained in more detail in e.g. [32,54]. The dose calculation algorithm employed also needs to produce absolute dose distributions; this was covered in more detail in [32,50].

5 Issues related to treatment planning for small animals

5.1 Commissioning TPS

An essential part in setting up a radiation research facility for small animals is the commissioning of the small animal irradiator and the associated TPS. This specialized subject may require particular equipment and measurement procedures for which we refer to the literature [43,54,55] and the manufacturer's instructions.

5.2 Specimen photon scatter

Photon scatter for narrow beams of kV photon energies irradiating small animal geometries is a poorly studied subject. Photon scatter is important because it may degrade the CBCT imaging quality, and therefore compromise the conversion of the geometry into a voxel phantom. Scatter is also not or, at best, approximately modelled in most dose calculation algorithms for small animals, with the exception of Monte Carlo codes. Therefore, photon scatter may also degrade the dose calculation accuracy. In a recent study [56] it was shown that for a large field animal irradiator (160kVp; Faxitron CP-160, Tucson AZ) the surface dose to a small 2.8 cm diameter phantom could be overestimated by 15% when the conventional x-ray dosimetry protocol AAPM TG-61 protocol [53] is used, compared to GATE [57] Monte Carlo simulations of the same setup. At the exit side of the phantom the dose overestimation amounted to more than 30%. This study focused mostly on the lack of scatter for larger beams irradiating a very small phantom. For the narrow field precision irradiators no studies on photon scatter have been published yet, to our knowledge.

5.3 Tissue segmentation for small animals

In section 3.1 we outlined the procedure to assign soft tissue and bone media to voxel geometries, based on mass densities. For MV photons in most studies only four media are assigned for Monte Carlo simulations (air, lung, soft tissue, cortical bone), which appears to be sufficient. For kV irradiation of animals the question arises how many tissue types are needed to attain a certain dose calculation accuracy. Recent work from Stanford University [58] demonstrated that the relative weight fraction of Ca and P correlates well with bone density in bone tissues; this allows easy segmentation of the bone type from the measured density. Another Stanford study [59] quantified the influence of tissue assignment on Monte Carlo dose calculations for different radiation sources (kV x-ray units: 120 kV + 2.5 mm Al, 225 kV + 4 mm Al, 225 kV + 0.5 mm Cu, 320 kV + 1.5 mm Pb + 5 mm Sn + 1 mm Cu + 4 mm Al, and a brachytherapy ^{192}Ir source). The authors concluded there is no simple relationship between absorbed dose in tissue and mass density for photon energies ≤ 225 kV, indicating that mass density alone doesn't suffice to obtain accurate dose calculations. Dual energy CT images may aid in tissue segmentation, as discussed earlier [60–62].

They also compared a simple 4-tissue assignment scheme to an 8-tissue scheme and a 39-tissue scheme. Large dose errors were reported when the simpler tissue assignment schemes are used. The largest dose errors were obtained when adipose was inadvertently identified as muscle or cartilage. For a treatment plan of a mouse lung irradiation they also noticed that the target dose volume histogram (in the lung) was rather insensitive to tissue miss-assignment in the surrounding regions, whereas larger errors may occur in the organs at risk. This clearly shows the importance of correct tissue recognition, and of course all studies up to now assigned human tissues to animals, due to lack of information on animal tissue compositions.

5.4 Dose reporting

From previous sections it is clear that tissues need to be properly identified to ensure correct dose calculation in kV photon beams. An additional issue is dose reporting. The natural way for Monte Carlo simulations to score dose is in terms of dose to medium-in-medium ($D_{m,m}$). Hereby photons are transported in all media, and when dose is scored in a voxel due to an interaction, the material interaction coefficients of the medium are used. However, dose may also be scored as dose to water-in-medium ($D_{w,m}$). This is a quantity that is easier to measure, on which clinical practice is built,

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and most non-Monte Carlo algorithms report this quantity. To score $D_{w,m}$ photon transport is performed in the medium but the photon interaction coefficients of water are used when scoring the dose. $D_{m,m}$ and $D_{w,m}$ are two entirely different quantities, although they are both absorbed doses. For MV photons this issue also exists but it is of less significance with the difference limited to about 12% in cortical bone and much smaller in most other tissues. For kV photons the difference between the two dose quantities can be much larger (fig. 1). Conversion of one of the dose quantities into the other involves knowledge of the ratios of energy absorption coefficients for low energy photons [37]. More complex conversions are also possible depending on the so called cavity theory employed [63]. The conversion adds uncertainty to the dose reporting procedure. These two dose quantities exist, somewhat confusingly, next to each other [19,64,65]. Which one correlates better with biological radiation effects is currently an open question and may eventually settle which dose quantity will be most frequently reported. In studies it should be clearly mentioned which dose reporting quantity is employed.

5.5 Motion

When a dose calculation in an animal is based on a relatively slowly acquired CBCT scan, motion of e.g. the lungs will smear out the organ volumes. When the aim is to precisely target certain structures, motion during the imaging and irradiation stages is an issue that needs to be addressed but which hasn't received much attention yet in the literature. This may require implementation of techniques such as time-resolved imaging and gated beam delivery, which are state of the art technologies known from human radiotherapy.

6 Future developments

Treatment planning for precision irradiation of small animals is not yet a mature field. Much effort is still needed to develop precise and accurate radiation planning software to achieve the full potential of the novel research platforms. These may then empower animal studies which may be translated successfully to human radiotherapy. TPS are only now becoming available that can handle the complexities of the combination of small beams, low energy photons and small geometric structures in animals. Future TPS will also be able to handle a rich variety of imaging modalities e.g. CT, PET, MRI, ultrasound, phase contrast x-ray, bioluminescence, fluorescence, photo-acoustic imaging etc. Other beam modalities than low energy photons are emerging for precision-irradiation animal studies, such as low energy protons [66,67]. Due to the complexities and uncertainties in low energy photon dose calculations there is also a need for beam delivery verification techniques e.g. based on onboard imagers [32].

As the research platforms become more versatile, TPS will have to cope with techniques such as simultaneous motion of beam and stage, energy modulated beams, current modulated beams, gated beam delivery, motion-corrected beam delivery etc. To advance treatment planning for small animals many techniques can be borrowed from the mature field of treatment planning for human radiotherapy. An example is inverse treatment optimization [45], whereby certain dose objectives and constraints are defined and then the most optimal plan is designed. Planning and radiation dose delivery to small animal models of unprecedented accuracy will be available in the near future, at a comparable level to human radiotherapy, enabling a wealth of studies.

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