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Original article

ESTRO ACROP: Technology for precision small animal radiotherapy research: Optimal use and challenges

Frank Verhaegen^{a,*}, Ludwig Dubois^a, Stefano Gianolini^b, Mark A. Hill^c, Christian P. Karger^{d,e}, Kirsten Lauber^f, Kevin M. Prise^g, David Sarrut^h, Daniela Thorwarthⁱ, Christian Vanhove^j, Boris Vojnovic^c, Robert Weersink^k, Jan J. Wilkens^l, Dietmar Georg^m

^a Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; ^b Medical Software Solutions GmbH, Hagendorn, Switzerland; ^c CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Gray Laboratories, UK; ^d Department of Medical Physics in Radiation Oncology, German Cancer Research Center; ^e National Center for Radiation Research in Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg; ^f Department of Radiation Oncology, University Hospital, Ludwig-Maximilians-University of Munich, Germany; ^g Centre for Cancer Research & Cell Biology, Queen's University Belfast, UK; ^h Université de Lyon, CREATIS, CNRS UMR5220, Inserm U1044, INSA-Lyon, Université Lyon 1, Centre Léon Bérard, France; ⁱ Section for Biomedical Physics, Department of Radiation Oncology, University Hospital Tübingen, Germany; ^j Institute Biomedical Technology (IBiTech), Medical Imaging and Signal Processing (MEDISIP), Ghent University, Belgium; ^k Department of Radiation Oncology, University of Toronto, Department of Radiation Medicine, Princess Margaret Hospital, Canada; ^l Department of Radiation Oncology, Technical University of Munich, Klinikum rechts der Isar, Germany; ^m Division of Medical Radiation Physics, Department of Radiation Oncology and Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria

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ABSTRACT

Many radiotherapy research centers have recently installed novel research platforms enabling the investigation of the radiation response of tumors and normal tissues in small animal models, possibly in combination with other treatment modalities. Many more research institutes are expected to follow in the coming years. These novel platforms are capable of mimicking human radiotherapy more closely than older technology. To facilitate the optimal use of these novel integrated precision irradiators and various small animal imaging devices, and to maximize the impact of the associated research, the ESTRO committee on coordinating guidelines ACROP (Advisory Committee in Radiation Oncology Practice) has commissioned a report to review the state of the art of the technology used in this new field of research, and to issue recommendations. This report discusses the combination of precision irradiation systems, small animal imaging (CT, MRI, PET, SPECT, bioluminescence) systems, image registration, treatment planning, and data processing. It also provides guidelines for reporting on studies.

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Translational and radiobiological research is currently undergoing a revolution due to two key developments: (1) the availability of advanced tumor models with more clinically relevant tumor environments, and (2) the availability of technology that allows precise radiation targeting, using onboard integrated image-guidance which can mimic clinically advanced radiotherapy treatments in an experimental setting (Fig. 1). Such precision irradiators facilitate studies that explore temporal and spatial dose modulation, and novel combinations of radiation with other therapeutic or protective agents, both for radiation response of tumors and normal tissues. The aim of these studies is then to generate results that can be translated more rapidly into clinical trials, benefitting patients [1,2].

These new technologies, for small animal research, bring an extensive range of challenges that need careful assessment to

allow their future optimal use for translational research. Specific challenges include: (1) What are the key technologies required to downscale clinical treatments into small animal models? (2) How to deal with target motion? (3) Which imaging modalities should be integrated into the radiation platforms? (4) What are the optimal irradiation margins? (5) What is the accuracy and precision of small field dosimetry? (6) Which methods should be developed to verify the dose distribution? (7) Which imaging modalities should be used for treatment planning, given the evolving clinical scenarios? (8) What is the difference between high and low-energy photon irradiation?

In the framework of ACROP (ESTRO's Advisory Committee in Radiation Oncology Practice), the ESTRO committee coordinating guidelines, this newly established writing committee's mandate is to review and discuss the state of the art in this new field of research, covering the technology [3,4] currently available for image-guided small animal radiation research such as precision

* Corresponding author.

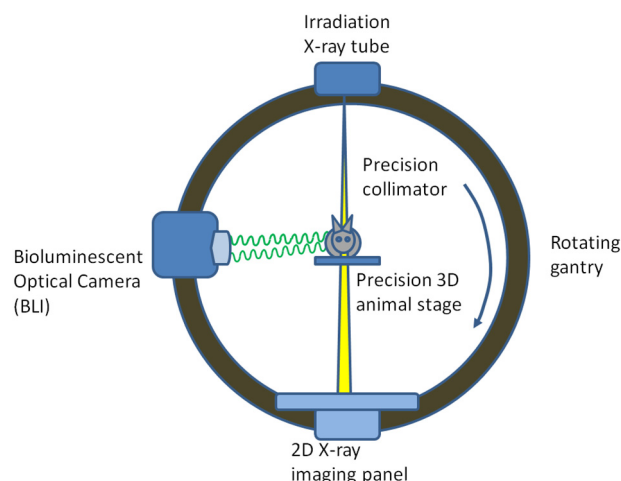


Fig. 1. Generic sketch of an image-guided precision irradiator. In this implementation radiation can be administered in an arc, and cone beam CT imaging is performed by a rotating gantry mounted X-ray panel. In other implementations the animal may rotate to acquire a CT image. In this example there is also a bioluminescent camera mounted on the gantry, which allows capturing optical photons emitted by labeled structures in the animal. Once the target volume has been identified, a collimated X-ray beam is used to deliver the therapeutic dose, either in the form on multiple stationary beams or a continuous arc.

irradiation systems, imaging (CT, MRI, PET, SPECT, bioluminescence) systems, image registration, treatment planning, and data processing. Finally, animal radiation research with light ion beams is also briefly addressed, although the latter is usually not performed with dedicated small animal beams, but rather with specialized setups at ion beams for radiotherapy.

Basically, three categories of users of radiation in animal studies can be identified: ones that need a known arbitrary but reproducible radiation dose (e.g. to study synergistic effects), ones that need a precise dose or range of doses (e.g. to establish a dose-response curve) and ones that need a modulated dose distribution (in time and/or space). This review is intended to be a first step toward aiding users to define optimal studies and toward guiding developers with respect to future improvements, with a strong focus on the latter two categories.

Commissioning and operating precision irradiators

Preclinical research platforms which have been developed, commercially or otherwise, are summarized in Table 1. The precision and accuracy of the novel irradiators are critically dependent on how well they have been commissioned and the subsequent quality control [5–7].

Table S1 lists the main issues that need to be considered during commissioning. Ideally commissioning should be performed by a medical/radiation physicist, who has expertise in radiation source commissioning using suitable phantoms. For inexperienced users, commissioning may be done by the manufacturer, but in this case it is recommended that a report is provided with the raw data and any processed data. A key part of this is absolute dosimetry using

standardized protocols (e.g. [18–20]) and calibrated equipment traceable to a primary standard. To ensure continuous accuracy it is essential that regular quality assurance measurements are made, this may vary from daily for critical but simple output checks, to monthly for more detailed checks. If real-time dosimetry is desired, small radiation detectors such as mosfets or optical fibers may be considered, or the onboard X-ray imager may be used to verify the treatment [21].

In practice the dose distribution is dependent on many factors, including the photon spectrum, irradiation geometry, the composition and geometry/anatomy of the animal being irradiated and surrounding scattering/attenuating materials. Each of these needs to be adequately described along with the details of the dose measurement/calculation. In addition to the physical dose, the ultimate biological response can also depend on factors such as dose rate and radiation quality [22,23]. Unfortunately, the experimental setup, dosimetry and exposure details are often inadequately reported in the scientific literature, emphasizing the necessity to develop standard operating procedures [24,25] with the key issues summarized in Table S2. This information is required to assess the quality and limitations of preclinical data, to ensure that any effects observed are not artifactual, and thus to evaluate the translational potential of the data and hypotheses generated for the development of clinical trials [26].

Recommendations for reporting studies can be found in Table 2.

Treatment planning systems

Treatment planning systems (TPS) for small animal irradiators face several challenges [27]. Commonly, the target volume is small, rarely exceeding a cubic cm. Thus, irradiation is preferentially performed with about 225 kV instead of MV photon beams to avoid large dose-build-up effects at medium interfaces and wide penumbrae [4]. Together with the small field sizes, this renders calculation models implemented in clinical MV treatment planning systems (TPS) unsuitable, since apart from Compton scatter the tissue-dependent photo-electric effect needs to be considered, and the resulting inaccuracies for small beams would be unacceptable [27]. Different calculation models have been implemented in small animal irradiators with Monte Carlo simulation and Superposition-Convolution being the most prominent ones [4,6,21,28–31] (Table 3).

The workflow of preclinical treatment planning generally mimics clinical radiotherapy (Fig. 2). The main difference is that treatment planning and dose administration are performed in one session while the animal is under anesthesia. Multi-modal functional or molecular imaging is also available for preclinical treatment planning [32], see also subsection on imaging devices.

Despite all technical advances in preclinical treatment planning, several critical issues still remain. As such, commissioning of the TPS represents major challenges (Table S3), particularly for very small beams [6,7,33]. Moreover, photon scatter is poorly studied for narrow beams of kV energies in small animals. It may interfere with CBCT imaging quality as well as with accuracy of dose calculation [7]. The procedure of tissue segmentation also involves several open issues, including the aspect of arbitrariness and the

Table 1
Examples of commercial and non-commercial image-guided small animal irradiators.

Commercial	Non-commercial research machines
SARRP system (Xstrahl Ltd, UK) [8–10]; X-RAD 225Cx (Precision X-ray Inc., USA) [11]	Brachytherapy-based system using an Ir-192 source [12] System based on the GE micro-CT scanner [5,13,14] X-ray image guidance system [15] Carbon nanotube [16] SAIGRT system [17]

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