ESTRO ACROP Guideline

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

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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
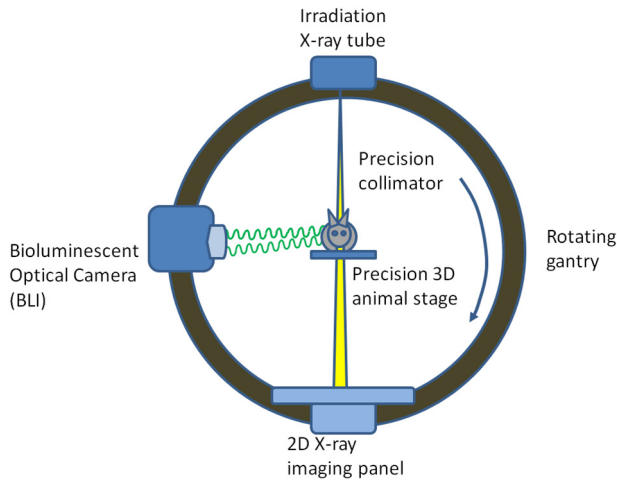
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Fig. 1. Generic sketch of an image-guided precision irradiator. In this implementation radiation can be administered in an arc, and cone beam CT imaging is performed by a rotating gantry mounted X-ray panel. In other implementations the animal may 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]

Table 2
Requirements for specification and reporting of small animal irradiation with particle beams.

Common requirements for studies with photons and particles (See also Table S1)	
Irradiation modality	Photon energy, filtration, kVp, half value layer, particle type and particle energy
Absorbed dose	Dose prescription point or volume, 1–2–3D dose distribution
Field size	
Margins	
Treatment fields	Number, size and orientation of beams
Optimization	Algorithm and parameters

Specific requirements for particle beam studies	
Depth dose profile	Pristine Bragg peak: energy and range of primary particles Spread Out Bragg Peak: range and depth of the proximal and distal edge of high-dose region
Position of the target tissue within the beam	
Linear Energy Transfer	Track-averaged or dose-averaged LET or another beam quality specifier including range of LET for extended targets
Setup	Detailed information on of setup and range adjustment (collimators, range shifters)
SOBP	Specification whether the SOBP was optimized in terms of absorbed or RBE-weighted dose. If the latter, which RBE-model and model parameters were used, and the type of photon reference radiation

Table 3
Comparison of dose calculation models currently implemented in treatment planning systems of small animal precision irradiators.

	Superposition–Convolution dose calculation	Monte Carlo simulation
Principle	Local photon energy fluence derived from the primary energy fluence emanating from the photon source multiplied by energy absorption coefficient gives total energy released to matter (terma). Ray-tracing with inclusion of 1st order Compton scatter	Modeling of particle transport, interactions with other particles and electromagnetic fields, and production of secondary particles based on cross sections and transport theories. Consideration of Compton scatter and photo-electric effect
Input	Photon spectrum or phase space file obtained from separate Monte Carlo simulation. Geometry and materials are defined from CT images.	Photon spectrum or phase space file obtained from separate Monte Carlo simulation. Geometry and materials are defined from CT images.
Dose reporting	Dose-to-water-in-medium, convertible into Dose-to-medium-in-medium	Dose-to-medium-in-medium and dose-to-water-in-medium
Limitation	Inaccuracies in non-water media with dose discontinuities (lung, bone)	Computing time (getting less important with new and faster computers)
Example treatment planning system	3D Slicer-based MuriPlan [40]	MatLab-based SmART-Plan [41][*]

[*] From July 2017 onward this is replaced by SmART-ATP (SmART Scientific Solutions BV, Maastricht, the Netherlands).

question how many tissue types are needed for proper dose calculation accuracy [34–36]. Dose reporting is another concern. Dose-to-water-in-medium and dose-to-medium-in-medium are two completely different quantities which are currently used in parallel, and it is so far entirely unclear which one correlates better with the biological effects of ionizing irradiation. Both should be available but conversion from one to the other introduces uncertainties [27]. As small animal planning will become more complicated, beam optimization will be needed [37,38]. Finally, intra-irradiation motion is a largely understudied aspect in preclinical radiotherapy which may be addressed by time-resolved imaging, gated beam delivery, and/or target tracking [39,91].

Image guidance systems

In the following sections we will discuss the commissioning and operation of various small animal imaging methods for precision irradiation. A recent report covered animal imaging quality control [42]. Table S4 gives an overview of guidelines and future development for the various imaging modalities.

Computed tomography (CT)

CT is a pre-requisite for heterogeneity corrections in dose calculation [27,43] for treatment planning. CT images in DICOM format can be visualized using common research software platforms (e.g. MatLab, Osirix, 3D Slicer). There are different technological solutions for preclinical CT [4,44]. Dedicated micro-CTs have a rotating X-ray tube and imaging panel configuration. Modern animal research platforms use either a fixed animal and rotating X-ray tube/imager or vice versa, resulting in a cone beam CT (CBCT) scan. Typical X-ray energies are between 35 and 90 keV. Amorphous silicon imaging panels are standard, and image reconstruction is based on the Feldkamp algorithm [45].

The technical realization and the underlying projection geometry vary and have a direct impact on the imaging parameters. There are geometric aspects and accuracy requirements for irradiation units with integrated CT imaging options, i.e. flex-correction maps during imaging and irradiation need to be determined and verified during regular quality assurance as well as Hounsfield Unit (HU) calibration [7,42]. The mechanical hardware accuracy is reported to be below 100 μm [15]. The typical image resolution (pixel dimension) for CBCT is in the range of 100–200 μm, and even lower for micro-CTs. The modulation transfer function (MTF) of CBCT and micro-CT at the 10% level are around 1 mm^{-1} and 2 mm^{-1}, respectively. To determine spatial resolution, contrast, etc. dedicated phantoms are required [46].

Imaging and treatments in the keV energy range imply the availability of dedicated dosimetry equipment [18]. Typical imaging doses to small animals are around 0.3 Gy or even higher for micro-CT [47]; and need to be considered in longitudinal studies especially for non-tumor tissue. Technical solutions for respiratory motion management have been reported [48], and next generation systems are expected to offer dual energy options [49].
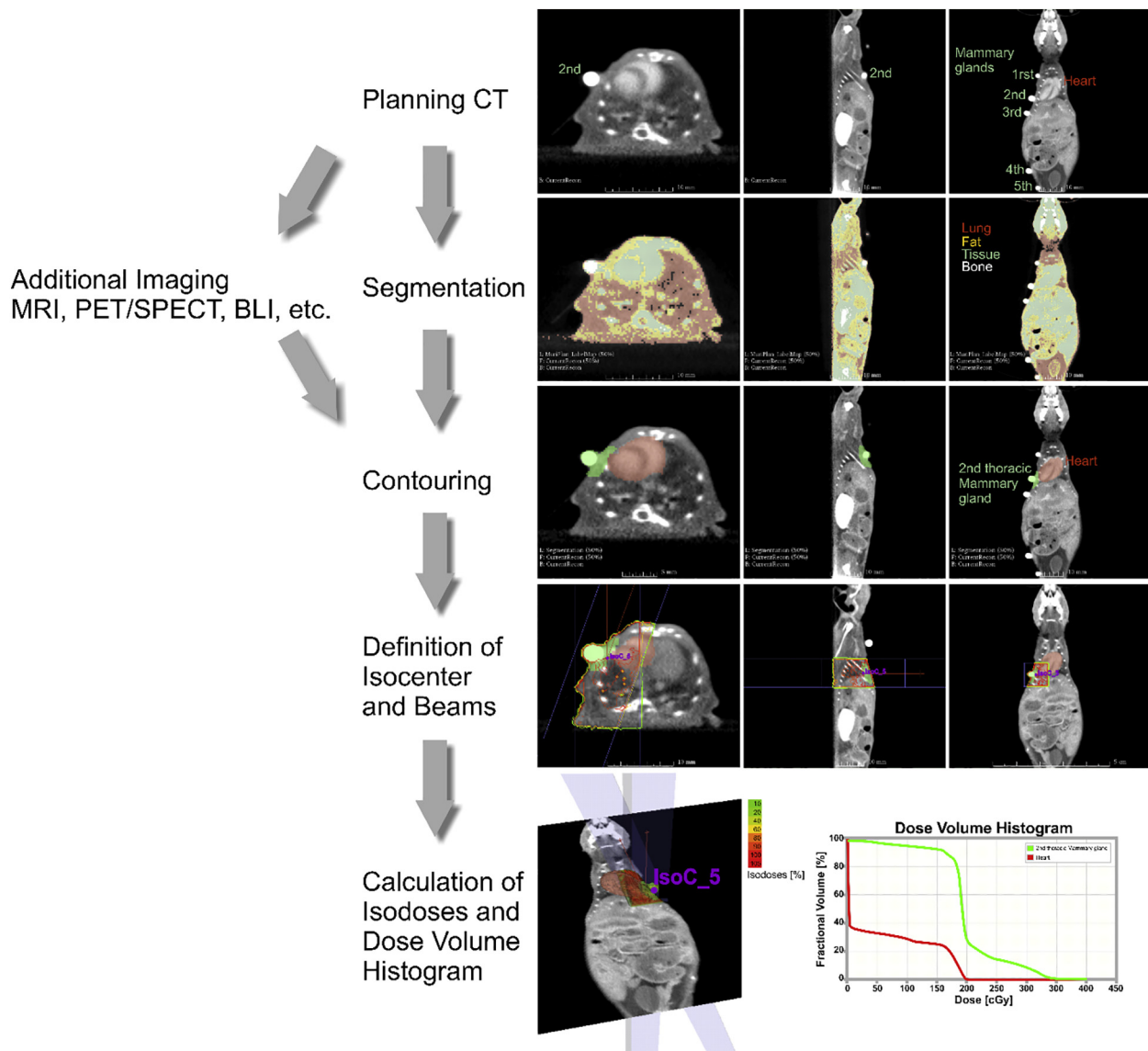
Fig. 2. Typical workflow of small animal treatment planning. As an example, a target volume around the second thoracic mammary gland is defined (green contours, 3rd row), and the heart is chosen as organ at risk (red contours, 3rd row). Firstly, information on electron and/or mass density and tissue type is acquired from an onboard CBCT image (1st row) [4]. Upon image reconstruction, every voxel is assigned a density based on its Hounsfield Units (HU) and a suitable calibration phantom which also provides tissue type information (2nd row) [27]. Secondly, the target volume (green) and potential organs at risk (red) need to be delineated by manual contouring (3rd row). Like for segmentation (2nd row), no automated algorithms are so far available, thus adding a certain degree of arbitrariness to these procedures [27]. Thirdly, an isocenter and a set of beams (static beams or arcs) are defined (4th row), and the TPS calculates the dose distribution. Finally, the results are reported as isodoses and dose–volume histograms (5th row), and the delivery settings are transferred to the irradiator.

Positron emission tomography (PET) and single photon emission tomography (SPECT)

Treatment planning for preclinical precision irradiators is predominantly based on CT imaging. Additional information from nuclear medicine based imaging techniques, i.e. PET and SPECT, can be used for (sub-)target volume definition in dose painting strategies, for response assessment in longitudinal studies, or in the context of imaging and therapeutic biomarker research [50–53].

Image quality in SPECT/PET is mainly determined by spatial resolution and sensitivity. Recent SPECT cameras obtain sub-millimeter spatial resolution using a multi-pinhole multi-detector design and can obtain sensitivities in the order of 0.1%. Preclinical PET cameras are downscaled models of human systems, usually with an axial field-of-view that enables whole-body mouse imaging. Spatial resolution in PET is around 1 mm and sensitivity

can be very high (14% is reported). Although SPECT offers several advantages in study flexibility, radiochemistry complexity, tracer half-lives and cost, PET is currently the most sensitive and quantitatively accurate nuclear imaging modality [54].

Because SPECT/PET are considered quantitative imaging techniques, image degrading effects, such as photon attenuation and scatter should be corrected during the reconstruction process. The reconstructed voxel size should be at least three times the spatial resolution of the imaging system to minimize partial volume effects [55]. Finally, SPECT/PET requires the injection of radioactive tracers and cross-calibrations between SPECT/PET camera and a dose calibration is required for accurate quantification [42,53]. This requires imaging dedicated phantoms with a known activity concentration. The same can be used to assess longitudinal quantitative accuracy of the scanner by comparing the known activity in the phantom with that in the reconstructed images [42]. Tracer

volumes in small animals are limited, often requiring high activity concentrations and, therefore, careful measurement of the injected activity is crucial for accurate quantification.

Magnetic resonance imaging (MRI)

The clinical use of MRI is rapidly growing, i.e. for MR based treatment planning including dose calculation, and multiparametric MRI for tissue characterization and response assessment. This trend is based on advantages such as a superior soft-tissue contrast compared to CT and imaging without dose burden, which also impacts pre-clinical research [56–59]. Main disadvantages of MRI are the relatively long acquisition times and its implication on animal anesthesia, the high cost of an MRI scanner and high operational costs.

In the standard irradiation setting, MRI scans are not directly used for dose calculations, but a registered CT/MRI dataset provides the necessary information for targeting (MRI) and for dose calculations (CT) [60]. Geometric aspects including distortion corrections, scanner calibration and image registration need to be considered, for which dedicated phantoms exist [42,61,62].

An MRI-only based workflow for radiotherapy planning becomes feasible with the introduction of dedicated MRI sequences, such as Ultra Short Echo time (UTE) and Zero Echo time (ZTE), where bony structures become visible [57]. For this, a common coordinate system between MRI images and micro-irradiator space is needed, e.g. via 3D/3D (MR/CT) registration or using 2D/3D image registration involving digitally reconstructed radiographs (DRRs).

Pre-clinical MR imaging is performed on dedicated micro-MR systems, which often have ultra-high field strength, or on clinical high field strength systems (i.e. 3T/7T) for which dedicated micro-coils can achieve the high-spatial resolution [52,63]. The high field strengths imply safety aspects. The resolutions of micro-MR units are below 100 μm and the ultrahigh fields facilitate spectroscopy research. However, sequences and acquisition protocols used for pre-clinical MRI need to be optimized toward 3D imaging to cover the whole tumor volume and to minimize distortion to guarantee geometric accuracy of the data.

Bioluminescence imaging (BLI)

For small animal radiotherapy BLI promises improved targeting of tumors not visible on other modalities [64–66], as well as longitudinal response-monitoring. While the BLI signal is weak, there is no background and so it is able to detect as few as 1000 cells injected in an animal. Also, it has a large dynamic range (several orders of magnitude) without delivering any radiation dose [67,68].

A BLI signal can be acquired using non-contact optical imaging or with optical fibers in contact with the tissue [69,70]. BLI collected at multiple wavelengths can aid in target reconstruction, since the signal is wavelength dependent (due to variations in tissue absorption and scattering) [71].

While acquiring BLI images is straightforward, 3D source reconstruction remains a challenge. With multiple techniques under investigation, solutions that allow radiation targeting and response monitoring can be expected in the near future.

Center-of-mass targeting using BLI is possible [72], but radiation targeting requires the 3D geometry of the tumor. However, the resolution and detection depth are limited by scattering of optical photons and the limited knowledge of tissue optical properties [73]. The main 3D reconstruction needs (and limitations to accurately achieving outcomes) are:

(a) a model of the surface and locations of detection points [74,75] (using CBCT [76] or optical scanning)
(b) the location/geometry and optical properties of major organs (requires segmentation on CBCT images; optical properties either measured in situ using diffuse optical tomography [77–80] or taken from library values [81])
(c) calculation of light propagation (using analytical [73,80] or Monte Carlo methods [77,78])
(d) accurate reconstruction algorithm [78,79,81,82] (ill-posed inverse problem)

Together, these steps take considerable time (10–20 min per mouse) that would severely reduce throughput on a system. The process speed for radiation targeting could be improved using accurate auto-segmentation or BLI could be performed at a separate session prior to treatment with the target transferred to treatment images using deformable registration.

Registration of different imaging modalities

To fully exploit the high precision of small animal image-guided radiotherapy the positioning error of the target has to be minimized. This may require registration of information from various images, possibly from different modalities, usually to a reference CBCT image. This can be done manually or ideally by software to provide spatial registration of the two images by optimization of a 'goodness-of-alignment' metric using appropriate features. Both rigid transformations (only translation and/or rotation) and non-rigid transformations may be needed to allow for changes in size and/or shape of sub-volumes. Although potentially providing better registration, care must be taken when employing the latter to ensure deformations are realistic. Relevant information that should be reported is detailed in Table S2 Additionally, non-rigid registration can be used in longitudinal studies between the initial CBCT image and subsequent scans. This can be used to follow accurately the deformation of organ contours [83].

Depending on which part of the body is being studied, movements may be a major limiting factor to using co-registered images for targeting. While the anatomy of the head remains relatively immobile, significant motion is possible within the abdomen and thorax with time and as a result of handling. In these cases it is essential that procedures are in place to minimize movement between initial imaging and subsequent beam delivery. Recommendations to help ensure accuracy of registration and minimize the effect of movement are summarized in Table S5.

Table 4
Data sets and standards for various preclinical and clinical fields.

Domain	Data set	Applicable standard
Molecular and clinical data	The Cancer Genome Atlas (TCGA) molecular and clinical data	N/A
Clinical imaging	The Cancer Imaging Archive (TCIA) in vivo imaging data	DICOM
Pre-clinical	Small animal models	Suppl 187: Preclinical Animal Imaging Acquisition Context of the DICOM standard exists but has not yet been adopted
Digital pathology	caMicroscope	DICOM is applicable but has not yet been adopted
All	Annotations and markup on images	µAIM is in development

Digital data processing

In the medical field data standards have been used for many years allowing for standardized storage and easy exchange between different systems and different clinics. In medical imaging, the DICOM standard (Digital Imaging and Communication in Medicine, [84]) was set up to address this and for clinical applications today the DICOM standard is well established among medical imaging equipment vendors and healthcare IT organizations. In the field of preclinical radiobiology and trials, however, far less effort has been put in data standardization, which has hampered data sharing and leveraging results across studies and institutes. Imaging-based cancer research is in the early phase of an integrative-biology revolution making the creation of more robust tools crucial for data interoperability across several domains like genomics (and other omics), diagnostic imaging, and digital pathology (Table 4). The newly available image-guided precision irradiation research platforms present a unique opportunity to develop data standards and powerful data analysis tools that will enable more efficient data extraction and data processing.

Indeed, some of the modern small animal platforms and treatment planning systems already support the DICOM standard for imaging and the DICOM-RT objects (RT Image, RT Structure Set, RT Plan, RT Dose,…). Recent efforts by the DICOM working group 30 have led to a DICOM standard Supplement 187 defining use-cases and templates for storage of information related to acquisition of small animal images during preclinical research ([85], Table S6). A common informatics infrastructure for small animal research must also provide researchers with a data warehouse combining various sources of data for easy storage and retrieval of large amounts of information such as pathology, genomics, histology, experimental designs, etc. In addition, a modern software environment for small animal studies should provide analysis tools that can be used to directly mine data from multiple high-volume information repositories, creating a foundation for research and translation of the results of animal studies into clinical trials.

Particle beam studies

As dedicated small animal irradiation devices are available only for photons, particle irradiations of animals are currently performed in clinical or experimental facilities [86–89]. Also, current TPS are usually not intended to be used for small irradiation fields and integrated imaging devices are mostly not available or not suitable for small animal irradiations with particles except in rare cases [90]. This compromises dosimetric and geometric irradiation accuracy. Together with limited experience with particle beams, this may affect the results and complicate inter-comparison of data between different facilities.

Many requirements for specification and reporting of precision small animal particle irradiations are similar to those of photons, however, particle irradiations require specification and reporting of several additional parameters (Table 2). When using a clinical TPS, one should be aware of the potentially limited accuracy of the predicted absolute dose and lateral field borders. In this respect, verification measurements by pinpoint ionization chambers and radiochromic films may be necessary [87]. When comparing results with photon experiments, the use of identical dose prescription points, dose verification methods and field sizes has to be assured.

In general, small animal irradiation studies should take care that there is a close link to clinical particle beam protocols to assure that results replicate patient exposures. As it is unlikely that there will be many dedicated small animal irradiation facilities in the near future, researchers are encouraged to develop and install dedicated TPS and imaging devices for small animal irradiations at

their clinical or experimental beam lines to improve dosimetric and geometric accuracy [90].

Conclusions

It is strongly recommended to develop protocols and guidelines to use the novel preclinical radiation research platforms to maximize their impact on translation of radiotherapy research into the clinic. This report provides an overview of the relevant technology issues to consider.

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Conflict of interest

The authors declare that they have no competing interests. None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2017.11.016.

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