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Original Article

Dosimetric and preparation procedures for irradiating biological models with pulsed electron beam at ultra-high dose-rate

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ABSTRACT

Purpose: Preclinical studies using a new treatment modality called FLASH Radiotherapy (FLASH-RT) need a two-phase procedure to ensure minimal uncertainties in the delivered dose. The first phase requires a new investigation of the reference dosimetry lying outside the conventional metrology framework from national metrology institutes but necessary to obtain traceability, repeatability, and stability of irradiations. The second consists of performing special quality assurance procedure prior to irradiation.
Materials and Methods: The Oriatron eRT6 (PMB-Alcen, France) is an experimental high dose-per-pulse linear accelerator, delivering a 6 MeV pulsed electron beam with mean dose-rates, ranging from a few Gy/min up to thousands of Gy/s. Absolute dosimetry is investigated with alanine, thermo-luminescent dosimeters (TLD) and radiochromic films as well as an ionization chamber for relative stability. The beam characteristic and dosimetry are prepared for three different setups.
Results: A cross-check between alanine, films and TLD revealed a dose agreement within 3% for dose-rates between 0.078 Gy/s and 1050 Gy/s, showing that these dosimeters are suitable for absolute dosimetry for FLASH-RT. In absence of appropriate setup dependent corrections, active dosimetry can reveal dose deviations up to 15% of the prescribed dose. These differences reduce to less than 3% when our dosimetric procedure is applied.
Conclusion: We developed procedures to accurately irradiate biological models. Our method is based on validated absolute dosimeters and extends their use to routine FLASH irradiations. We reached an agreement of 3% between the delivered and prescribed dose and developed the requirements needed for workflows of preclinical and clinical studies.
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The progress of radiotherapy (RT) over the last few decades was mostly obtained in improving the spatial and dosimetric accuracy of the delivered dose to the patient [1,2]. Lately, a RT technique called FLASH-RT has emerged and questioned some established RT concepts regarding the effects of radiation on healthy tissue. Indeed, preclinical studies in FLASH-RT have shown that irradiations with an ultra-high dose-rate increase the differential response between normal tissues and tumors [3–6]. In order to reveal differential biological effects, radiobiological studies required a traceable, accurate and repeatable dose delivery.

The Oriatron 6e (eRT6) (PMB-Alcen, France) is a high dose-per-pulse prototype linear accelerator (linac) delivering a 6 MeV pulsed electron beam capable of reaching a higher beam current than standard clinical machines [7]. This machine offers the possibility of varying the dose-per-pulse and dose-rate over a large range. It differs from a clinical linac by the absence of a standard monitoring system.

Absolute dosimetry on the eRT6 linac for FLASH-RT modality was first developed using passive dosimeters. Previous studies validated the use of Radiochromic films for reference dosimetry in high dose-per-pulse electron beam [8,9]. In addition, thermo-luminescent dosimeters (TLD) were also validated [9–11] and lately alanine was successfully commissioned [12–14].

Ionization chambers, which are commonly used in radiotherapy, suffer strong saturation effects, which cannot be corrected without adding large uncertainty contributions [15]. Recently, specific models have been developed to characterize this saturation and compute the absolute dose [15]. However, this saturation effect may vary depending on the beam characteristics and

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irradiation setup, which makes the establishment of the correction factors time-consuming. Indeed, for biological irradiations, the beam quality can be modified with respect to the reference setup used for the commissioning by the presence of a secondary collimator or by a change in Source-to-Surface Distance (SSD) in order to fulfill dose-rate and/or dose homogeneity requirements. Measurements at the extrema SSD usually chosen for biological experiments show that the relative surface dose varies by about 10%. Additionally, a variation in the beam quality indexes R_{50} and R_{85} as defined in international recommendations [16] of about 5% is measured between the smallest and largest SSD. Therefore, additional specific dosimetric preparation measures are required.

In this article, we compared the dose response from the three previously discussed passive dosimeters irradiated under dose-rates ranging from conventional (few Gy/min) up to ultra-high (>1000 Gy/s). The general procedure to accurately irradiate biological models in FLASH-RT as well as three typical dosimetric preparations for biological irradiations in the context of preclinical studies with their related setup are presented.

Materials and methods

Nomenclature

The nomenclature of the beam parameters used here follows the one in Jaccard et al. [7]. The eRT6 linac is able to perform electron beam irradiations at conventional dose-rates (few Gy/min) up to ultra-high dose-rates (>1000 Gy/s).

Unless stated otherwise, all given uncertainties in the text are standard uncertainty at level $k = 1$, following the conventions from the ISO guide on the expression of uncertainty [17].

Dosimetric systems

We used two Advanced Markus ionization chambers from PTW (PTW-Freiburg GmbH, Freiburg, Germany) associated with a PTW UNIDOS electrometer to measure the beam output. Both chambers were corrected for ion recombination [15]. The casing of the chambers was degraded by irradiation and a replacement of the chamber was needed at least every 2 years. Thanks to the PTW quality assurance system, the chambers have comparable response [15]. The standard uncertainty in measurements in high dose-per-pulse beams was 2.8% (chamber-specific ion recombination model applied [15]).

Alanine pellets of 4.9 mm diameter and 3.0 mm thickness (Bruker Corporation, Billerica, Massachusetts, USA) were used. The dose reading on a Bruker e-scan EPR spectrometer (Bruker Corporation) was optimized for a dose range between 10 Gy and 100 Gy in order to achieve a 2.2% uncertainty using three repeated readouts. The readout was performed between 1 and 48 hours after irradiation. Alanine pellets were calibrated in terms of absorbed dose to water using Co-60 and an additional calibration factor for electrons was applied in accordance with Zeng et al. [16].

We used Gafchromic EBT3 and EBT-XD film sheets (Ashland Specialty Ingredients G.P., Bridgewater, NJ, USA) defined by their batch number and followed the calibration procedure as detailed by Jaccard et al. [8]. For the chosen dose levels, the uncertainty in measurements was 2%.

LiF-100 TLDs (Thermo Fisher, USA) of $3.2 \times 3.2 \times 0.9$ mm^3 individually calibrated in terms of absorbed dose to water with our Co-60 unit were used. The absorbed dose to water is traceable to international standards through the water calorimeter of the Swiss institute of metrology (METAS). The correction factor for electrons and reading procedure are presented in Jaccard et al. [8]. In this case of electrons, typical uncertainty is around 4%.

The eRT6 is not equipped with semi-transparent monitor chamber to control the beam as usually found in clinical linacs. However, beam signals are recorded from a current transformer measuring the beam current at the exit window of the accelerating section and from the primary collimator signal [7]. A PXIe-1071 National Instruments high-speed oscilloscope implemented with a LabVIEW™ 2014 program (National Instruments, USA) processes the signals in real time and computes the total charge of the electrons exiting the machine. In addition, all pulses are recorded. These data were used to diagnose any issues with the dose delivery during daily checks and biological irradiations. This system is used for FLASH irradiations as a relative diagnostic tool because of its limited precision.

Comparison of dosimetric systems

A comparison between the previously introduced dosimetric systems was performed in order to increase the confidence in FLASH-RT dosimetric measurements. The input beam parameters and setup used for the irradiations can be found in the supplementary data.

Biological experimental setup

The Oriatron eRT6 is currently in full operation and preclinical irradiation studies are being performed [3,4,18]. Such studies require specific setups and dosimetry compliant with typical radiotherapy standards and routine clinical procedures.

Every biological experiment was preceded by the characterization of the beam in the experimental conditions. Only irradiations at ultra-high dose-rate (FLASH-RT) will be discussed in what follows.

Beam characterization

Beam profiles were measured with EBT3 Gafchromic films at prescription depth (in general 10 mm depth). Field sizes were determined by measuring full width at half-maximum (FWHM) and penumbras (defined as the distance between the 80% and the 20% isodoses).

Percentage depth dose (PDD) curves were acquired with EBT3 films for each setup. Films were positioned at the surface and at various depths down to 35 mm. The beam quality index R_{50} was obtained from the PDD.

Measurements were done in a 30×30 cm^2 solid water phantom made of RW3 slabs or in the water tank T41023 from PTW depending on the biological setup.

Dosimetric preparation

The calibration of an ionization chamber mainly depends on the beam spectrum, which varies with depth in matter, SSD and the presence of objects in the beam, typically collimator, tubular applicator, or shielding. Thus, the computation of an additional correction factor was necessary, because the biological setups were not corresponding to the reference conditions of the ionization chamber calibration.

A dedicated dosimetric preparation was performed with each setup and beam parameters planned for the biological experiment to account for electron scattering and change in dose-per-pulse. The dosimetric preparations were done at the prescription depth in solid water unless stated otherwise. If the biological setup did not allow such measurement, the PDD was used to extrapolate the measured dose to the dose at the prescription depth.

The Advanced Markus chamber was used as a relative dosimetry system because the uncertainties associated with the saturation corrections and the influence of the setup on the beam spectrum were too high. In order to ensure the accuracy of the dosimetry, the responses of the ionization chamber and passive

dosimeters (TLD, alanine or films) were compared. The ratio R (specific to each setup) was defined as the average dose of the measurements with the ionization chamber D_{IC} divided by the mean dose of the passive dosimeters D_{PD}:

$$R = D_{IC}/D_{PD}. \quad (1)$$

This procedure was repeated by adapting the irradiation parameters (pulse length, beam current, SSD, etc...) until the prescription dose lied within the uncertainty interval of the mean dose from the passive dosimeters D_{PD}.

Biological irradiations

Output stability checks on the machine showed a mean variation in output from day-to-day of ±3% with respect to the average value [7]. However, a satisfactory short-term stability of the output could be obtained over repeated measurements (SD < 0.7%).

On the day of the biological experiment, the Markus chamber was irradiated in the same configuration as during the dosimetric preparation. Its response corrected by R (Eq. (1)) was used to make a fine adjustment of the irradiation parameters (pulse width, beam current, SSD, etc...) to take into account the output variation with respect to the day of the dosimetric preparation and ensure the delivery of the prescribed dose.

Passive dosimeters such as alanine, TLD or films could usually be used during the biological irradiation as *in-vivo* dosimeters to validate the experiment dosimetry. Measurements under the same conditions were always repeated with the ionization chamber immediately after the experiment for verification purposes. In the absence of *in-vivo* dosimetry, the dose delivery during the biological experiment was taken as the average of the output measurements before and after the biological experiment.

Routine irradiation setups

For Total Body Irradiation (TBI) of mice, a cylindrical PMMA box (6 cm diameter and 1.5 cm width) was created to hold mice in the center of the beam during irradiation. The box was fixed on the irradiation bench at a distance resulting in the optimal compromise between field homogeneity and a sufficiently high dose-rate. As an *in vivo* measurement during a mouse irradiation, a wrapped TLD was placed between the mouse and the exit side to measure the exit dose and compare it to the prescription dose (Fig. 1a). The dosimetric preparation was performed with a 15 mm thick solid water phantom to suppress the contribution from backscattered electrons coming from depths greater than 15 mm that are not present during the biological experiment.

For the irradiation of biological samples placed in a 2 ml Eppendorf tube (e.g. zebrafish embryos [18]), the T41023 water tank was used. The tube was flipped and inserted into the holder in place of the Advanced Markus ionization chamber. The center of the tubes was placed at the prescription depth. The biological sample location was centered with respect to the center of the beam and a wrapped TLD was placed inside the tube to support the experiment dosimetry (Fig. 1b). The dosimetric preparation was performed in the water tank with the same tubes by putting the TLDs at the same position as the eggs.

For localized irradiations, custom-made graphite applicators were used to define the field size, e.g. a $13 \times 13 \times 2.5$ cm^3 applicator with a 1.7 cm circular aperture for whole brain irradiation (WBI) of mice [3,18]. The collimator was positioned directly in contact with the animal's skin to optimize the penumbra sharpness of the dose profiles. For large animals like a mini-pig [4], an applicator with a 2.6 cm circular aperture was used with an additional 3–5 cm thick PMMA shielding screen around the applicator to limit the body dose resulting from scattered radiation. For dosimetry verification during the mini-pig irradiation, EBT-XD Gafchromic films (lot #12101501) were positioned between the skin and the carbon collimator. For the validation of the absorbed dose in the mouse brain, TLD chips were used as *in vivo* dosimeters [3].

The irradiation parameters, dosimeters and adjustable parameter (SSD or pulse width) of each of the three dosimetric preparations are presented in Table 1.

Results

Comparison of dosimetric systems

In conventional dose-rate (0.078 Gy/s), the measured dose with the ionization chamber, the TLD, the alanine and the Gafchromic films agreed within less than 2% (Fig. 2). For higher mean dose-rates (210 Gy/s and 1050 Gy/s), the alanine, the Gafchromic films

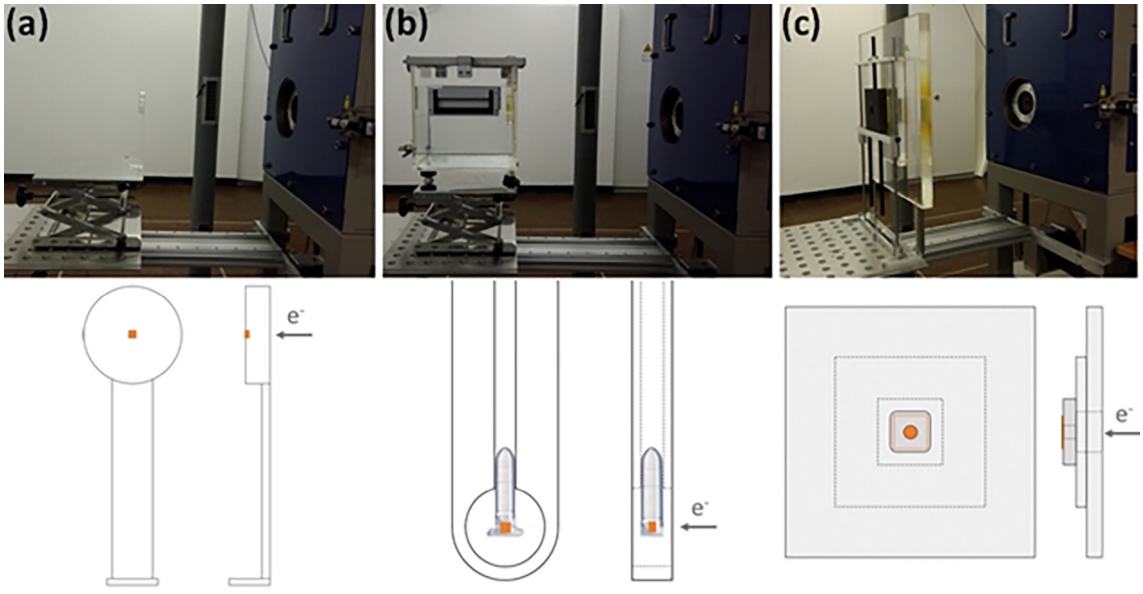

Fig. 1. Oriatron eRT6 and setup for (a) mice Total Body Irradiation (TBI), (b) zebrafish embryos and (c) mini-pig irradiation. Under each picture is a scale diagram of the target seen from the front and side (left and right respectively). The position of the in vivo dosimeters is indicated with the orange symbol.

Table 1
Initial irradiation parameters of the dosimetric preparation for Total Body Irradiation of mice (TBI), the zebrafish and the mini-pig irradiation. The passive dosimeter used and the adjustable variable for the dosimetric preparation are indicated.

	D_{presc} [Gy]	Number of pulses	w [μs]	f [Hz]	Depth [mm]	SSD [m]	Passive dosimeter	Adjustable parameter
Mice TBI	4	3	1.8	100	15	0.800	TLD	SSD
Zebrafish	8	1	2.0	100	12	0.358	TLD	w
Mini-pig	28	10	1.8	100	0	0.600	Alanine	SSD

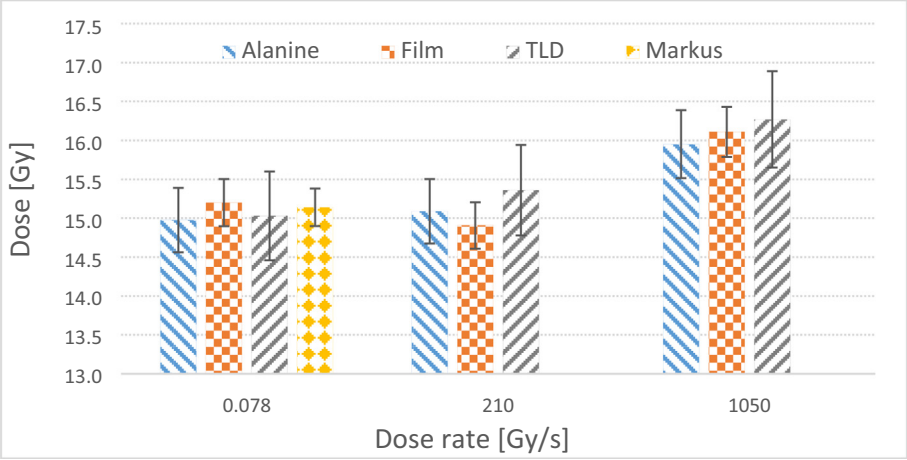

Fig. 2. Measured absorbed dose for different mean dose-rates of 0.078, 210 and 1050 Gy/s for different dosimeters (alanine, Gafchromic film, TLD and Advanced Markus ionization chamber).

and the TLD were in agreements within 3%, thereby showing the absence of dose-rate dependence for these dosimeters within the investigated range.

Biological experiments

During the dosimetric preparation for the mini-pig irradiation, the PDD was measured with the same setup planned for the irradiation (Section 'Routine irradiation setups') and compared to the open field case (Fig. 3). The penetration of the beam remained unchanged, but an increase of surface dose was observed. The presence of the carbon collimator and PMMA screen did not affect the beam quality index R_{50} and therefore the mean energy of the electron beam at the surface of the phantom derived from R_{50} according to the IAEA code of practice (Table 2). Beam profiles with the carbon collimator were compared to the ones in open field at the same SSD (Fig. 3). The field size with the carbon collimator agreed with its physical size and the penumbra was smaller than 1 mm (Table 2).

The day of irradiation (Section 'Biological irradiations'), the output stability checks as well as the preliminary measurements with the ionization chamber using the new irradiation parameters (left

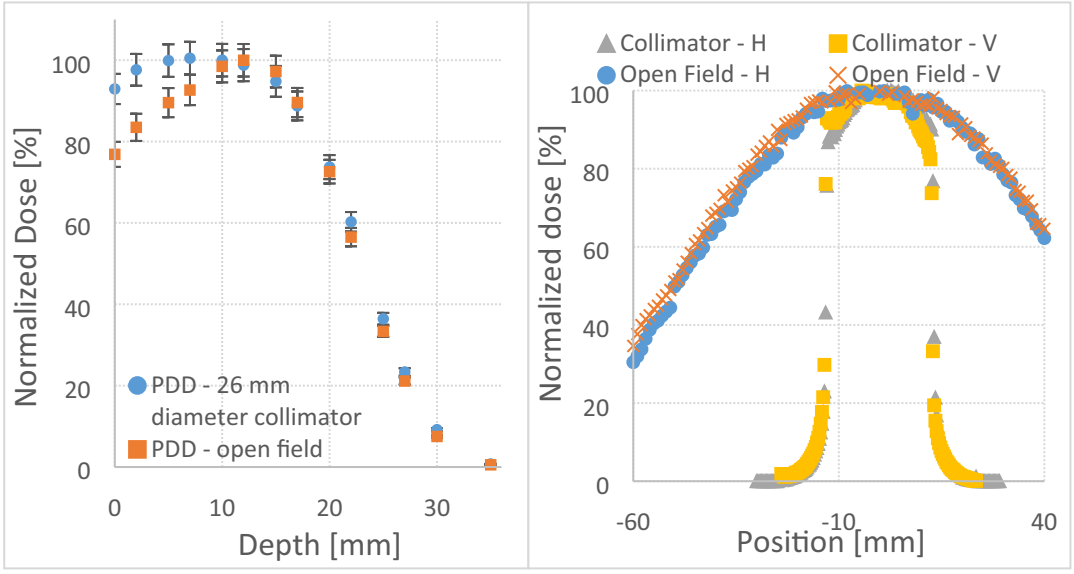

Fig. 3. PDD (left) and relative Horizontal (H) and Vertical (V) beam profiles at the surface of a solid water phantom (right) in open field and with a 26 mm diameter carbon collimator. For the PDD, data are normalized to the maximum absorbed dose and the error bars correspond to the expanded uncertainty ($k = 2$).

Table 2
Beam quality indices R_{50}, corresponding energies, field sizes (defined at FWHM) and beam penumbras for open field case and with the carbon collimator.

	R_{50} [g/cm^2]	E [MeV]	FWHM [mm]	Penumbra [mm]
Open field	21.2	4.9	98.3	37.5
Carbon collimator	21.4	4.9	26.2	0.8

Table 3
New irradiation parameters from dosimetric preparation (left). Final parameters used for the biological irradiation and in vivo dose measurement of passive dosimeter $D_{PD,in\ vivo}$ (right).

	From dosimetric preparation				For biological irradiation		
	D_{presc} [Gy]	SSD [m]	w [μs]	R	SSD [m]	W [μs]	$D_{PD,in\ vivo}$ [Gy]
Mice TBI	4	0.780	1.80	0.960	0.767	1.80	3.9
Zebrafish	8	0.358	1.93	1.039	0.358	1.96	8.2
Mini-pig	28	0.570	1.80	1.079	0.560	1.80	27.7

column in Table 3) from the dosimetric preparation (Section 'Dosimetric preparation') showed a slight dose variation with respect to the day of the dosimetric preparation. The adjustable parameter (SSD or w) was modified accordingly. The final SSD or pulse width w of the experiment and the dose from the *in vivo* passive dosimeter $D_{PD,in\ vivo}$ are presented in Table 3 (right column).

Discussion

Comparison of dosimetric systems

At conventional dose-rate, international reference guidelines were followed for dosimeters calibration and an agreement between all the passive dosimeters and the ionization chamber was observed as expected.

The TLD, alanine and film dosimetry are based upon three different physical principles. Thus, we can expect these three dosimeters to have a different dose-rate dependency. The agreement between all the passive dosimeters at ultra-high dose-rates (Fig. 2) implies the absence of dose-rate dependency in the studied range. Additional dose-rates conditions between 0.078 and 210 Gy/s were studied but not included in this paper as the conclusions were redundant. Therefore, thanks to the efficient cross-check of the beam with different dosimeters, we can base the absolute dosimetry on TLD, alanine and films.

The lack of primary traceability is still a strong issue and national metrology institutes need to develop adequate beams in order to provide standards for the FLASH community and traceable active dosimeters. In complement, a comparison scheme with other centers performing FLASH-RT is under evaluation to bring a global consensus on ultra-high dose-rate dosimetry.

Biological experiments

The deviations between the prescription dose and the *in vivo* dosimetry remained lower than 3% and within the uncertainty of the dosimeter (Table 3). The accuracy of the dosimetric procedure for the biological experiments is therefore adequate for the three presented setups. Given this agreement and the dosimeters comparison (Fig. 2), the uncertainty in the delivered dose is estimated to be about 3%.

Without this dosimetric procedure, dose measurements would be done only with the Advanced Markus ionization chamber (corrected for ion recombination). In this case, the uncertainty in the delivered dose would depend on the setup. The deviation of the dose measured with the ionization chamber with respect to the prescribed dose is given by the ratio R (Table 3). In the case of the mini-pig, this deviation was the largest of the three experiments (about 8%) due to the presence of multiple objects is the beam.

In the case of WBI, deviations of the order of 15% were observed. The irradiation was performed with a single 10 Gy pulse and a prescription at the surface. Such a deviation is due to the presence of a graphite applicator, a prescription depth different from the reference depth and a dose-per-pulse corresponding to the upper limit of the saturation correction of the chamber.

These results show that preliminary dosimetric procedures are mandatory given the actual limitations of the eRT6. In the future for a clinical transfer, clinical devices should be monitored with measurement means and ideally corrected in the case of fluence variation.

Conclusions

Dosimetry at conventional dose-rate at the eRT6 was confirmed to be consistent by the agreement of the Advanced Markus ionization chamber, Gafchromic films, alanine and TLD. At higher dose-rates, films, alanine and TLD doses agreed within 3%. The cross-check of the beam with different passive dosimeters allows us to perform absolute dosimetry with confidence for biological experiments.

We have described the establishment of routine dosimetric procedures of the Oriatron eRT6 for biological experiments. We successfully implemented routine metrological procedures, which are compatible with preclinical and clinical studies. We are able to determine the delivered dose for biologic experiments with an uncertainty of 3%.

The Oriatron eRT6 machine combines different beam parameters to modulate the beam output over several orders of magnitude which is useful to study radiobiological effects at different dose-rates. Because day-to-day variations of the beam output are non-negligible, the quality assurance procedure, daily corrections and setup specific dosimetry were critical to support radiobiology experiments.

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Disclosure of conflicts of interest

The co-author Philippe Liger works for the company that built the Oriatron eRT6 prototype linac (PMB-Alcen). The other authors have no relevant conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.004.

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