Development of dosimetric procedures for experimental ultra-high dose rate irradiation at a clinical linear accelerator

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Abstract. As radiotherapy using ultra-high dose rates has gained new interest, the dosimetric challenges arising at these conditions need to be addressed. Ionization chambers suffer from a large decrease in ion collection efficiency due to ion recombination, making on-line dosimetry difficult. In this work we present experimental setups and dosimetric procedures for FLASH irradiation of cells, zebrafish embryos and small animals using a 10 MeV electron beam at a modified clinical linear accelerator, and describe the dosimetric steps required to initiate clinical trials. The dosimetric equipment used for our pre-clinical experiments consisted of radiochromic film, thermoluminescent dosimeters, a Farmer-type ionization chamber and phantom material mimicking the experimental setup for irradiation. In preparation for small animal irradiation, dose profiles and depth dose curves were measured for all collimator sizes. The average dose rates were ≥620 Gy/s, ≥640 Gy/s and ≥400 Gy/s for cells, zebrafish embryos and small animals, respectively.

1. Introduction
Recent discoveries have drawn new attention to radiotherapy delivered with ultra-high dose rates (>40 Gy/s), i.e. FLASH radiotherapy. In several pre-clinical in vivo studies, irradiation with ultra-high dose rates has shown to reduce normal tissue toxicity compared to conventional radiotherapy [1-7]. Yet, further radiobiological research remains to elucidate the underlying mechanism of this effect. Our research group has previously modified a clinical linear accelerator to enable delivery of ultra-high dose rate electrons [8], and as a step towards clinical trials with this novel technique we have conducted several radiobiological experiments, such as presented by Adrian et al. [9]. However, dosimetry at these extreme conditions is complicated and there are some associated technical challenges that must be addressed. As dose rate increases from conventional (a few Gy/min) to ultra-high (>10’s of Gy/s), the ionization chambers commonly used for on-line dose measurements are affected by ion recombination, causing a drop in ion collection efficiency [10,11]. Thus, there is a need for novel dosimetric procedures that enables accurate delivery of the desired dose in FLASH irradiations.
In this work we present experimental setups and dosimetric procedures for FLASH irradiation of cells, zebrafish embryos and small animals, as well as a proposed dosimetric procedure for upcoming clinical trials on veterinary and subsequently human patients, using a modified clinical linear accelerator.

2. Materials and methods

2.1. Irradiation source

Our irradiation source is a clinical linear accelerator (Elekta AB, Stockholm, Sweden) modified for FLASH irradiation with a 10 MeV electron beam, previously described by Lempart et al. [8]. To achieve maximal radiation output, the accelerator was operated without the primary and secondary scattering foils. The radiation was delivered in short (3.5 μs) pulses with a pulse repetition frequency of 200 Hz.

2.2. Setup, dosimetric procedure and beam characterization

The dosimetric equipment consisted of dose rate independent [12,13] radiochromic film (GafChromic EBT³ and EBT-XD) and thermoluminescent dosimeters (TLD), as well as a Farmer-type ionization chamber. Film and TLD were calibrated against an ionization chamber traceable to a standard laboratory for a dose range of 1-30 Gy (1-40 Gy for EBT-XD film). The agreement between dose measured with EBT³ and TLD was determined by simultaneous measurements at 20 mm depth in a solid water phantom. The Farmer-type ionization chamber was used as a relative dosimeter at low dose rates (<0.1 Gy/s), where ion recombination is not an issue.

2.2.1. Irradiation of cells and zebrafish embryos

For cell irradiations, the gantry angle was at 180° and T12.5 cell flasks (Thermo-Fisher Scientific™, Waltham, MA) were placed one-by-one on top of the cross-hair foil in the centre of the beam. The collimators were set to their outer limits, i.e. creating a field size of 40x40 cm² at isocentre distance. The beam profile at the position of the cross-hair foil was measured using EBT³ film at dose maximum (15 mm depth) in a polystyrene phantom, and the full width at half maximum (FWHM) and penumbra width were determined. Before and after cell irradiations, EBT³ film measurements were carried out by placing the film at the bottom inside a cell flask, under a 2 mm sheet of polystyrene mimicking cell media (Figure 1). To ensure accurate dose delivery during the cell irradiations, the Farmer-type ionization chamber was positioned in the ceiling where the dose rate was low enough to ensure dose rate independence (although high enough to be measurable), making it useful as a relative dosimeter to correlate to the film measurements. A similar setup was established for irradiation of zebrafish embryos, but instead of using flasks, embryos were collected in 1.5 ml Eppendorf tubes that were fitted into a 3D printed plastic phantom (Figure 2). Dosimetric measurements were carried out before and after irradiation of the embryos by 1) fitting a 3D printed insert (in the shape of an Eppendorf tube), with TLD slots, into the phantom, and 2) using a similar 3D printed phantom constructed for film measurements (Figure 3).

2.2.2. Small animal irradiations

An experimental setup for small animal irradiations was established using an electron applicator with a source-to-applicator-end distance of 650 mm. Cerrobend blocks of various sizes were created for field collimation, and for each size; dose profiles, output factors (at 20 mm depth, i.e. at depth of dose maximum) and depth dose curves (0-42 mm depth) were measured in a solid water phantom using EBT-XD film. FWHMs and penumbra widths (80%-20%) were determined. In addition, gap factors were measured with 0, 5, 20 and 40 mm distance between the collimator and the surface of the phantom. For mice irradiation, the animals were immobilized in a plastic box and positioned in direct contact with the Cerrobend block. The Farmer-type ionization chamber was placed in a polystyrene phantom under the box to enable relative output measurements that could later be correlated to dose via film measurements. In addition, EBT-XD film was used for in vivo measurements.
3. Results and discussion

3.1. Irradiation of cells and zebrafish embryos

The dose profile on top of the cross-hair foil had a FWHM of 14.2 cm and a penumbra width of 6.8 cm. In the small area covered by the cell flask (12.5 cm²) or 3D printed phantom (16 cm²), the beam flatness was +/-2.2% or +/- 2.7%, respectively. The absolute mean deviation between dose measured with EBT³ film and TLD was 2.4% (range: 0.2-5.4%), which is considered acceptable given the uncertainties of these techniques. The response of the ionization chamber positioned in the ceiling was linear to the dose measured with film within the given dose range, making it useful as a relative dosimeter. The average dose delivered to the cells and zebrafish embryos were 3.1 Gy/pulse and 3.2 Gy/pulse, respectively, corresponding to average dose rates of ≥620 Gy/s and ≥640 Gy/s.

3.2. Small animal irradiations

Dose profiles and depth dose curves for each collimator are presented in Figure 4. The measured FWHMs, penumbra widths, R₅₀-values and output factors are showed in Table 1. Gap factors at distances 0, 5, 20 and 40 mm between the collimator and the phantom surface was 1.0, 0.98, 0.93 and 0.86, respectively. For a total of six in vivo measurements, the absolute deviation between dose measured with film and dose estimated by the Farmer-type ionization chamber reading was 2.0% (range: 0.1-4.2%). The average dose delivered to the animals was 2.0 Gy/pulse, corresponding to an average dose rate of ≥400 Gy/s.

3.3. Preparation for clinical trials

In upcoming clinical trials with veterinary patients and humans, the same electron applicator as for the small animal irradiations previously described will likely be used, with an extended selection of collimator sizes. However, before initiating clinical trials, some technical challenges must be overcome. As currently operated, interruption of the beam after the desired number of pulses is solely dependent on a diode placed in the radiation field functioning as a pulse counter. To increase the safety during ultra-high dose rate delivery, we are working on a solution where the two independent channels in a transmission monitor chamber can be used to interrupt the beam, similar to the method used for monitoring the output in conventional radiotherapy. Furthermore, it is desirable to use the transmission monitor chamber for on-line dosimetry, which is complicated due to the drop in ion collection efficiency at these high dose rates. We have previously investigated the ion collection efficiency in the built-in monitor chamber at FLASH dose rates and established an empirical model to correct for the ion recombination [14]. In future work, this model will be integrated with the accelerator to enable accurate on-line dose measurements in clinical trials.
Figure 4. Dose profiles at 20 mm depth (a) and depth dose curves in solid water (b) for collimator sizes used for small animal irradiations, i.e. 10x10 cm$^2$ (light blue), d=4 cm$^2$ (light grey), d=3 cm$^2$ (dark blue) and d=2 cm$^2$ (dark grey).

Table 1. Output factor, FWHM, $R_{50}$-value and penumbra width at 20 mm depth in solid water, for the collimator sizes used for small animal irradiation.

|             | 10x10 cm$^2$ | d = 4 cm$^2$ | d = 3 cm$^2$ | d = 2 cm$^2$ |
|-------------|-------------|-------------|-------------|-------------|
| Output factor | 1.0         | 0.96        | 0.89        | 0.76        |
| FWHM [cm]    | 10.3        | 4.1         | 3.0         | 2.0         |
| $R_{50}$ [cm] | 3.8         | 3.7         | 3.5         | 3.2         |
| Penumbra (80-20%) [cm] | 1.1         | 0.9         | 0.8         | 0.1         |

4. Conclusion
In this work we have established dosimetric procedures that enable accurate dose delivery to cell cultures, zebrafish embryos and small animals at ultra-high dose rates, delivered with a modified clinical linear accelerator. We also propose a possible solution that would allow for the built-in monitor chamber to function as a dose monitor. Such a system for controlling beam-hold will allow safe delivery of FLASH radiotherapy in future clinical trials. Radiobiological experiments are currently being performed using the setups and dosimetric procedures described here.

5. Acknowledgments
This research was supported by Mrs Berta Kamprad Foundation and the Swedish Cancer Society.

6. References
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