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Original Article

Modifying a clinical linear accelerator for delivery of ultra-high dose rate irradiation

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ABSTRACT

Objectives: The purpose of this study was to modify a clinical linear accelerator, making it capable of electron beam ultra-high dose rate (FLASH) irradiation. Modifications had to be quick, reversible, and without interfering with clinical treatments.

Methods: Performed modifications: (1) reduced distance with three setup positions, (2) adjusted/optimized gun current, modulator charge rate and beam steering values for a high dose rate, (3) delivery was controlled with a microcontroller on an electron pulse level, and (4) moving the primary and/or secondary scattering foils from the beam path.

Results: The variation in dose for a five-pulse delivery was measured to be 1% (using a diode, 4% using film) during 10 minutes after a warm-up procedure, later increasing to 7% (11% using film). A FLASH irradiation dose rate was reached at the cross-hair foil, MLC, and wedge position, with $\geq$30, $\geq$80, and $\geq$300 Gy/s, respectively. Moving the scattering foils resulted in an increased output of $\geq$120, $\geq$250, and $\geq$1000 Gy/s, at the three positions. The beam flatness was 5% at the cross-hair position for a 20×20 and a 10×10 cm^2 area, with and without both scattering foils in the beam. The beam flatness was 10% at the wedge position for a 6 and 2.5 cm diametric area, with and without the scattering foils in the beam path.

Conclusions: A clinical accelerator was modified to produce ultra-high dose rates, high enough for FLASH irradiation. Future work aims to fine-tune the dose delivery, using the on-board transmission chamber signal and adjusting the dose-per-pulse.

FLASH radiotherapy (FLASH-RT) involves radiation treatment at ultra-high dose rates (30 to >10^6 Gy/s), at least a few hundred times higher than what is conventionally used in radiotherapy. Mainly in mice, it has been shown that there exists a larger differential effect between normal tissue and tumors when exposed to radiation of this intensity compared to radiation delivered with conventional dose rates [1–4]. Thus, there appears to be a pure radiobiological advantage of increasing the radiotherapy dose rate. In addition, treatments at such high dose rates could result in very short treatment times, often 0.1 s or shorter. These short treatment times would essentially remove the problem of intra-fraction patient motion (i.e. motion during treatment), potentially enabling a much more precise treatment delivery with less healthy tissue being irradiated [5]. Furthermore, short treatment times make it viable to treat more patients. Fully implemented, FLASH-RT could have a large impact on the field of radiotherapy.

In the reported research and pre-clinical studies on FLASH irradiation, mainly relatively simple prototype linear accelerators (linacs) have been used, with a fixed horizontal electron beam capable of ultra-high dose rate irradiation [1–4,6]. Synchrotron radiation at ultra-high dose rate has also been proven to produce the FLASH effect at the European Synchrotron Radiation Facility (ESRF) in Grenoble (France) [7], while no effect could be seen for pre-clinical studies performed at the Australian Synchrotron [8]. These irradiation devices are highly specialized and expensive research tools that are only available to few radiotherapy researchers. However, researchers at Stanford University School of Medicine (Stanford, California, USA) have shown, that with technical assistance from the linac manufacturer (Varian Medical Systems, Palo Alto, California, USA) it was possible to reach ultra-high dose rates with a conventional clinical radiotherapy linac [9]. Furthermore, researchers at Institut Curie (Orsay, France) have presented a setup enabling FLASH proton irradiation with their clinical proton

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beam-scanning radiotherapy device [10]. Although no published data yet exists supporting a FLASH effect for proton therapy, Varian Medical Systems recently presented the formation of a "FLASHForward™ Consortium" including 13 institutes and proton therapy centers in the US and in Europe, with a mission to continue research and build an evidence base for a clinical introduction of FLASH-RT with proton beams [11]. Proton therapy machines are highly complex, expensive, and scarcely accessible for research purposes. Thus, to enable a widespread scientific base in order to explore the benefits of FLASH-RT, more simplified research platforms are needed.

The aim of this work was to modify a conventional clinical linac, enabling the delivery of electron beams with dose rates high enough for FLASH-RT that can be controlled on electron pulse level, with a satisfying beam output stability, pulse constancy and beam flatness.

Materials and methods

To investigate if a pulsed ultra-high dose rate electron beam (FLASH) can be generated by using a clinical linac, an ELEKTA Precise (Elekta AB, Stockholm, Sweden) with Integrity software version 1.2 was temporarily modified. To be able to control the linac on a pulse-to-pulse basis, an in-house built electrical circuit was designed and connected to the linac. Measurements were performed at three different positions of the linac, with the Gantry at 180°: at the cross-hair foil (53 cm from target ref.), on top of the MLC (37 cm from target ref.) and at the wedge position (19 cm from target ref.), just downstream of the transmission chamber. For all our measurements, the MLC and collimators were positioned at their outer limits, i.e. representing a $40 \times 40\ cm^2$ field at isocenter.

Electrical control circuit

A diode (PIN-type, EDD 2-3G Diode, IBA Dosimetry GmbH, Schwarzenbruck, Germany) was used as a beam pulse radiation detector. The diode signal was fed into an in-house built electrical circuit consisting of a two-stage amplifier and conditioning circuit, in which a transimpedance amplifier converted the photocurrent into a small voltage signal with subsequent amplification. The gain was chosen in order to provide a suitable input signal to a Schmitt Trigger. This circuit produced pulses of approximately 5 V, which were used as input signals to the interrupt pin of a microcontroller unit (MCU, Atmega328, Atmel Corporation, San Jose, California, USA). The MCU was used to count the beam pulses, by measuring the rising flanks of the signal. Once the desired amount of beam pulses was delivered, a logical signal was sent to an optocoupler circuit, preventing any trigger pulse to reach the linac's thyratron. Thus, electrons could no longer be injected by the electron gun, and the magnetron's production of radiofrequency (RF) waves to accelerate the electrons was prevented (Fig. 1). The optocoupler circuit provided a fast way to interrupt the beam and was able to isolate the linac ground from the electrical circuit. To count the beam pulses connected to the MCU, an 8-bit Timer was used, with a timer resolution of 62.5 ns. Beam pulses were measured inside an Interrupt Service Routine (ISR), triggered by the rising flanks. When the desired (programmed) amount of pulses had been delivered, the beam was consequently stopped, without additional pulses being delivered.

Linac preparation and parameter tuning

To test and evaluate changes made to the linac's parameters, FLASH settings were stored as a non-clinical "beam energy" in the Integrity software. This allowed for changes in the linac's parameters, without affecting clinically used "beam energies". To be able to operate the linac in electron mode without using an electron applicator and to irradiate with high dose rate, specific interlock software items had to be overridden. To measure the number of pulses generated by the linac, the PIN diode was placed on the cross-hair foil with the Gantry at 180°. Normally, the transmission (ionization) chamber of the linac monitors the beam current and uses the measured signals to servo-control the gun filament current. However, to maximize the output, the values of the servo control items for the electron gun filament current (i.e. gun standby, gun aim and gun current) were manually adjusted to achieve maximum output. In addition, as a change in gun filament current leads to a change in beam intensity, the current through the linac's bending magnet had to be adjusted for maximum output (a combination of 10 MV X-ray and 10 MeV electron beam energy settings for the bending magnet was used). Also, the charge rate, controlling the total amount of charge produced by the modulator's pulse forming network (PFN), was slightly increased. To find the optimal settings for the electron gun, the output at different filament current values was measured using an EDP 20-3G Diode (IBA Dosimetry GmbH) positioned in the beam, on the cross-hair foil. A minimum of three repeated measurements of a five-pulse delivery were performed for each gun filament current settings. The same settings were used for gun standby, aim, and current (gun aim is the starting filament current for the gun servo and needs to be adjusted to set an appropriate starting point). The setting resulting in the maximum output was subsequently used for the gun standby, aim, and current.

Consistency measurements

To evaluate the consistency and reproducibility of FLASH beam delivery, using the high dose rate settings, repeated output measurements were performed. The motorized wedge was replaced by an empty slotted carriage, which allowed for accurate film placement at that position. GafChromic EBT^3 film (Ashland Specialty Ingredients G.P., Bridgewater, NJ, USA) was placed at the wedge position and an EDP 20-3G Diode was positioned on the cross-hair foil. A total of 20 repeated dose/charge measurements of a five-pulse delivery were performed, one measurement each minute following a warm-up procedure of the linac (3000–5000 MU delivery of a 6 MV photon beam).

Percentage depth dose curves and beam profiles

To measure the output (dose rate and dose-per-pulse) of the linac in FLASH mode, film (GafChromic EBT^3) was placed in a polystyrene phantom and irradiated at the cross-hair foil, on top of the MLC, and at the wedge position. Furthermore, percentage depth dose (PDD) curves were also measured with film in a polystyrene phantom, at the different irradiation positions. The possible measurement depths for the PDD curves were limited by the available room (volume) at the wedge and MLC positions. Beam profile measurements were performed, using film positioned at D_{max} in a polystyrene phantom, at the three positions. To avoid saturation of the film, 2 pulses were applied at wedge position, 5 pulses at the MLC position and a total of 20 pulses at the cross-hair level. The beam profile measurements were performed with different combinations of the primary and secondary scattering foils in or out of the beam. Normally, both of them are inserted into the electron beam. By rotating the filter carousels (primary and secondary scatter filter assemblies) to empty slots, the scattering foils could be removed independently from the beam path. This allowed for an evaluation of the foils' impact on beam shape and output.

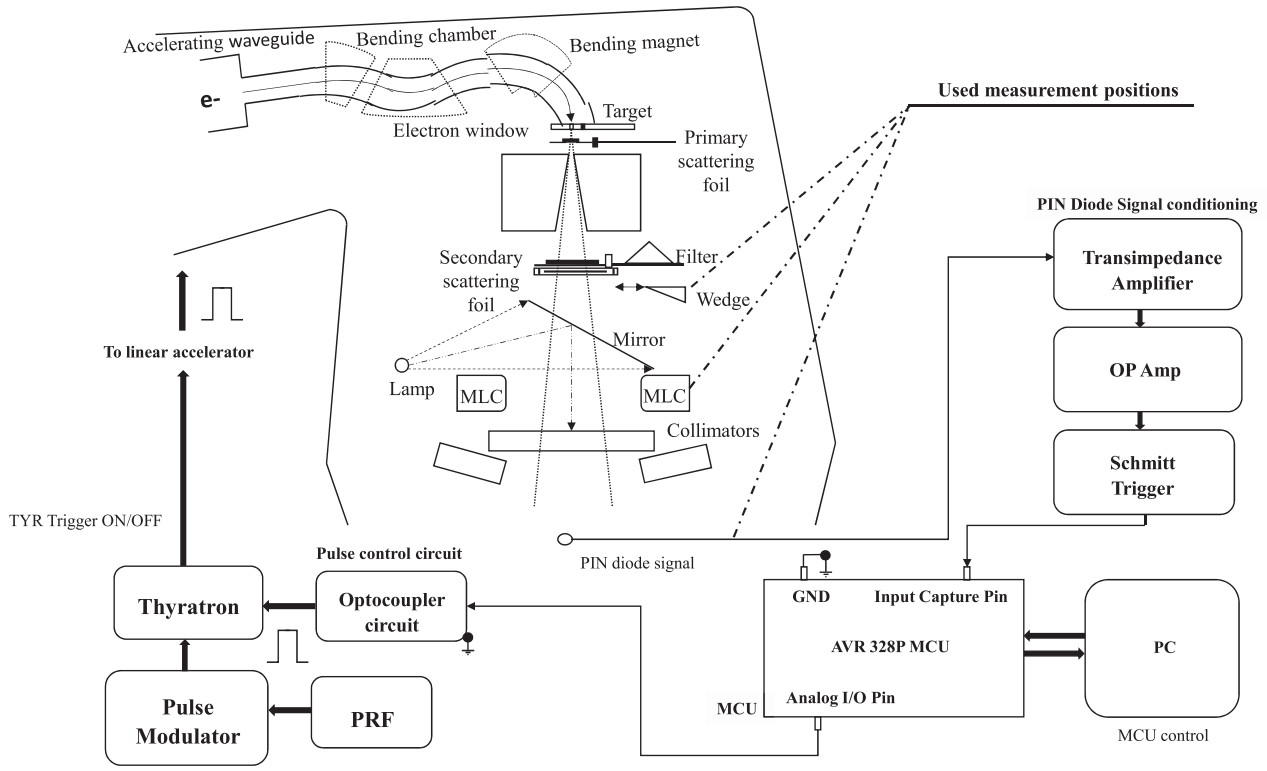

Fig. 1. Block diagram of the electrical circuit connected to the medical linear accelerator. Pulses are measured by a PIN diode placed inside the radiation beam. The diode signal is amplified and the resulting pulses are counted by a microcontroller unit (MCU). The number of pulses delivered is controlled by an optocoupler circuit connected to the linac's thyratron.

Diode and transmission chamber response

To verify the accuracy of the diode response when measuring in high dose-per-pulse beams, the diode response was compared to dose measured with GafChromic EBT^3 film in beams with different dose-per-pulse, ranging from dose-per-pulse values for conventional electron beam delivery to that of FLASH delivery. GafChromic EBT^3 film has previously been shown to be dose rate independent up to FLASH dose rates [12]. Similarly, an electrometer was connected to the current signal from the Elekta linac transmission (monitor) chamber, to test the accuracy of its response in beams with increasing dose-per-pulse. The response from ionization chambers is known to be dose-per-pulse dependent, with a decrease in ion collection efficiency with increased dose-per-pulse [13,14]. To further test the usability of the diode and the transmission chamber for measurements of FLASH beams, measurements were performed in FLASH beams using different number of pulses.

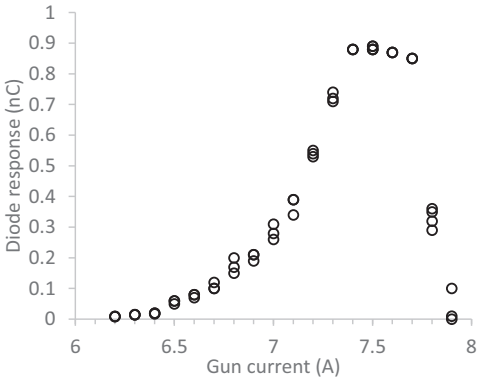

Fig. 2. Diode measurements at the cross-hair position of a five-pulse delivery with varying values for gun aim, gun control and gun filament current settings.

Results

The values of the servo control items for the electron gun filament current had a large impact on the linac output (Fig. 2). A setting of around 7.5 A (7.4–7.6 A) resulted in the highest output and was therefore used for our subsequent measurements.

The repeated dose/charge measurements showed that during the first 10 minutes after the warm-up procedure, the output was high and relatively stable. After that, the output began to drop and became more unstable (Fig. 3). For the first nine measurements (within 10 min of the warm-up procedure), the standard deviation (SD) was 1% and 4% for the diode and film measurements, respectively. For all 20 measurements, the SD was 7% and 11% for the diode and film measurements, respectively.

The PDD curves at the MLC and cross-hair positions were found to be very similar to an 8 MeV clinical beam with a dose maximum at around 15 mm depth (flat between 10 and 20 mm depth), but with a higher entrance dose (Fig. 4). However, at the wedge position the dose maximum was found to be at the phantom surface (at 0 mm depth), with dose fall-off at larger depth.

The beam profile measurements showed that the beam output and shape were both highly dependent on the irradiation position (its distance from the "target ref.") and on the electron scattering foils positioned in the beam (Fig. 5). With both primary and secondary scattering foils in the beam, the achievable dose-per-pulse in the center of the beam was 0.18, 0.44, and 1.9 Gy at the cross-hair, MLC, and wedge position, respectively. At a maximum pulse repetition frequency of 200 Hz, these dose-per-pulse values correspond to achievable dose rates of ≥30, ≥80, and ≥300 Gy/s,

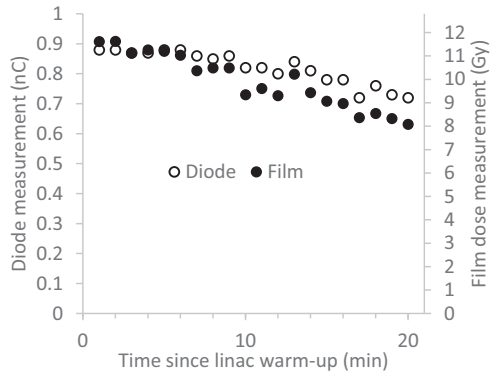

Fig. 3. Repeated measurements of a five-pulse delivery at different time points since a linac warm-up procedure, using film at the wedge position and a diode at the cross-hair foil position.

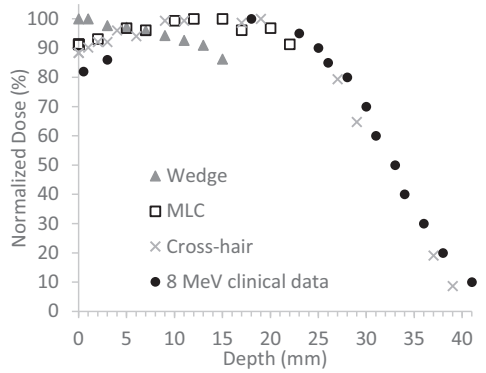

Fig. 4. Percentage depth dose curves measured with GafChromic EBT^3 film at different depths in a polystyrene phantom, at the different irradiation positions. Also shown is the clinical data for an 8 MeV beam.

respectively. With both foils moved out from the beam path, the achievable output in the center of the beam increased to 0.64, 1.3, and 5.1 Gy at the cross-hair, MLC, and wedge position, respectively. These dose-per-pulse values correspond to achievable dose rates of ≥120, ≥250, and ≥1000 Gy/s, respectively. However, the beam became less flat with smaller distance to the source and with less scattering material in the beam (Fig. 5). At the cross-hair position, the beam flatness was <5% for a 20×20 cm^2 area with the scattering foils in the beam but a similar flatness was only found for a 10×10 cm^2 area with the scattering foils moved from the beam path. Similarly, at the MLC position, a beam flatness of 5% was found for a beam area of 14×14 cm^2 with and 7×7 cm^2 without the foils in the beam path. At the wedge position, the beam was circular, of Gaussian shape with a ring pattern (from the secondary scattering foil), with a beam flatness of 5% only found in the diametric (circular) area around the beam center of 2 cm (10% in Ø 6 cm) with and 1.5 cm (10% in Ø 2.5 cm) without the scattering foils in the beam path (Fig. 5).

Measurements performed with the linac transmission (monitor) chamber and the EDP 20-3G Diode, positioned together with GafChromic film at the cross-hair position, showed that the diode response is linear with dose regardless of the dose-per-pulse at this position (Fig. 6). However, the response from the transmission chamber showed a clear non-linear response, with a decrease in ion collection efficiency with increasing dose-per-pulse. Measurements with the diode and the transmission chamber in FLASH beams with varying number of electron pulses showed a linear increase in response with an increase in number of pulses delivered (Fig. 6).

Discussion

In this study, a clinical linac was modified in order to be able to reach ultra-high dose rates, high enough for FLASH irradiation. Through simple modifications, a strong increase in dose rate was achievable from a few Gy/min to hundreds of Gy/s (dose-per-pulse values from a few 10^{-4} Gy to a few Gy), without compromising clinical treatments. Specifically, the gun filament current and modulator charge rate, as well as the current values applied to the linac's steering coils and the bending magnet were modified. The current through the steering and bending magnet coils had to be changed, in order to keep the electrons centered in the waveguide and to bend the beam correctly. These changes in combination with the change in gun current, showed to have the largest impact on the linac output. We expect and interpret that similar changes were made by the group at Stanford to their linac [9].

The beam pulses generated by the linac could be controlled accurately on a pulse level, by using an Atmega MCU and an optocoupler circuit connected to the linac's thyratron, preventing pulses to the PFN of the linac. The advantage of this approach is, that it is very cost efficient and easy to implement. Furthermore, no large modifications to the linac itself had to be made. Our approach allows for a more precise beam output control (regarding the number of pulses delivered) because of a shorter latency period than in the approach of the group at Stanford, who used the linac gating interface to control the beam delivery [9]. Nevertheless, controlling the beam on a pulse level comprises some limitations regarding an accurate dose delivery, which might be needed for other experiments and studies. To be able to achieve better control over the delivered dose and to assess pulse-to-pulse variations, the FLASH beam should be monitored on a dose level instead of pulse level. One possible solution would be to lower the gun current slightly and thereby the pulse amplitude, so that the delivery of a fixed number of pulses would result in the delivery of the desired dose. A more sophisticated solution could be to use the signal from the linac transmission chamber as a dose monitoring system, continuously measuring the dose delivered by each pulse in an external control system. This would enable real-time control over the length of the high voltage pulses, generated by the PFN. However, this method would include major modifications of the linac.

Some output stability issues occurred during FLASH irradiation. To ensure a high and stable output, a warm-up procedure (3000–5000 MU delivery of a 6 MV photon beam) was performed prior to FLASH irradiation. The stability decreased after approximately 10 minutes, requiring a new linac warm-up to restore stability. The linac cools down as beam-on time during FLASH irradiation is very short compared to a conventional beam. The linac's ability to accelerate electrons strongly depends on temperature and the functionality of some of the linac's components, e.g. the magnetron, the gun, the accelerating waveguide, and beam steering is affected as well. This seems to lead to a lower and more unstable output. However, we have some preliminary results suggesting that this issue can be resolved by fine-tuning the resonance frequency of the accelerator. By doing so, the output was stable over time (SD of 2.5% for film measurements) without any need for a warm-up procedure. Additionally, an increase in output by a factor 4 (compared to the output values presented in the results section) was observed when fine-tuning the resonance frequency.

By moving the primary and secondary scattering foils from the beam path, the output at the center of the beam was increased. Although the effect of an increased dose rate usable for FLASH irradiation is desirable, the Gaussian-shaped beam generated without the scattering foils in the beam path might be of disadvantage for other pre-clinical/clinical studies, due to the smaller flat area of the

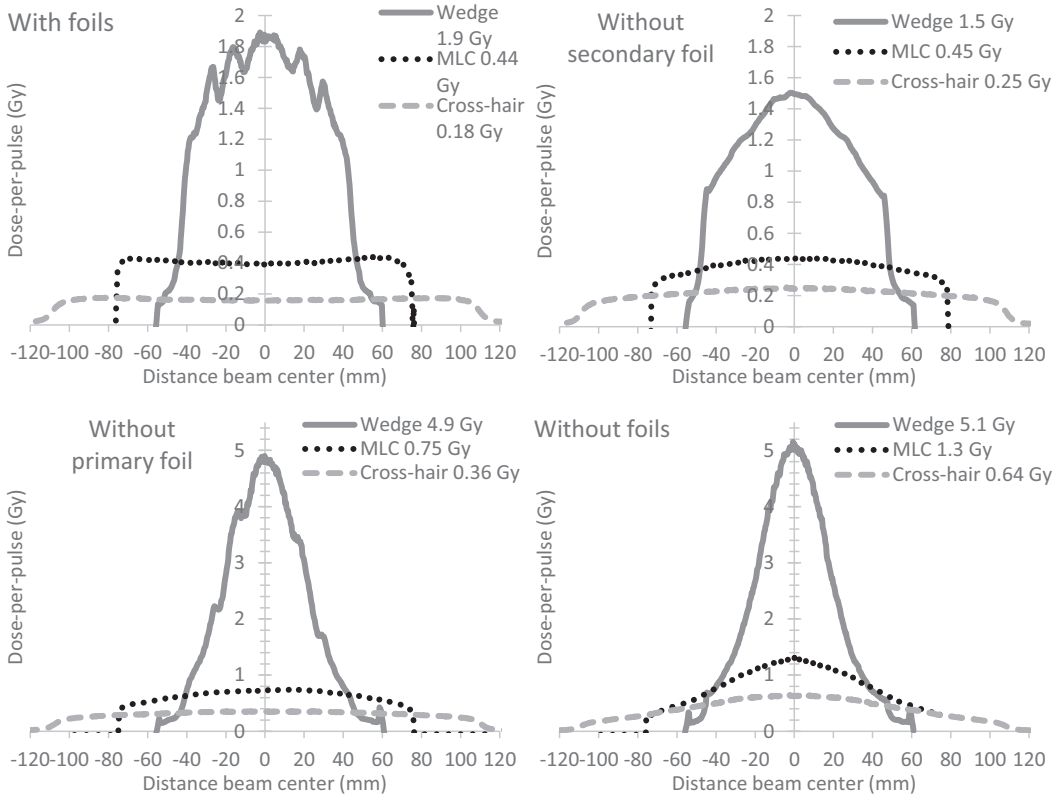

Fig. 5. Profiles measured for different foil combinations with GafChromic EBT^3 film, at depth of dose maximum (0 mm depth at the wedge position and 15 mm depth at the MLC and Cross-hair foil position), in a polystyrene phantom, at the different irradiation positions, with the maximum measured dose-per-pulse value specified. The MLC and collimators were positioned at their outer limits, i.e. representing a 40 × 40 cm^2 field at isocenter.

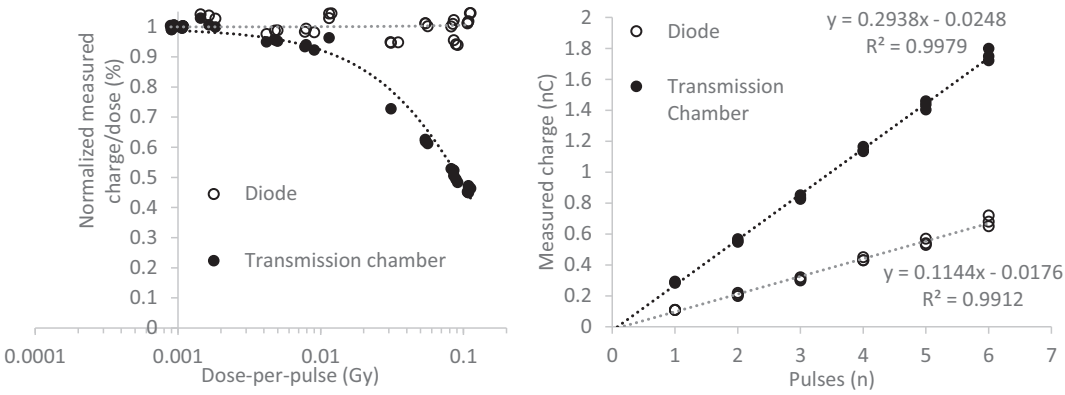

Fig. 6. Measured response (charge) for both the linac transmission chamber and an EDP 20-3G Diode at the cross-hair foil position. *Left:* In relation to simultaneously measured film response (absorbed dose), also situated at the cross-hair foil position for irradiation, with varying dose-per-pulse. *Right:* Measured charge for irradiation with varying number of electron pulses.

beam and likely (assumed but not measured) softer beam energy spectrum.

The EDP 20-3G Diode measurements showed a linear response while the transmission (monitor) chamber showed an expected decrease in response for measurements in beams with increasing dose-per-pulse [13,14]. However, both detectors showed a linear increase in response with an increase in number of pulses delivered (Fig. 6). Consequently, both are capable of monitoring/measuring dose in FLASH beams, following a proper dose calibration. For the transmission chamber, one calibration per output setting (i.e. dose-per-pulse) would be necessary if the decrease in ion collection efficiency with increased dose-per-pulse is not modeled and taken into account.

Future experiments using the modified linac will entail radiobiological experiments (pre-clinical studies) and clinical studies, further investigating the advantageous radiobiological FLASH effect.

In conclusion, in this study it has been shown that a clinical linac can be modified in order to achieve dose rates high enough for FLASH irradiation, with a beam flatness and an output stability useful for pre-clinical studies. The used method implies that other radiotherapy researchers, with access to a conventional medical linac, should be able to reach the dose rates needed to perform studies on FLASH radiobiology, without any costly modifications or new irradiation devices. However, it should be mentioned that any changes to a medical linac should be followed by an appropriate quality assurance routine, prior to any clinical usage.

Conflicts of interest

None.

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