Commissioning of an ultra-high dose rate pulsed electron beam medical LINAC for FLASH RT pre-clinical animal experiments and future clinical human protocols

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Purpose: To present the acceptance and the commissioning, to define the reference dose, and to prepare the reference data for a quality assessment (QA) program of an ultra-high dose rate (UHDR) electron device in order to validate it for pre-clinical animal FLASH radiotherapy (FLASH RT) experiments and for FLASH RT clinical human protocols.

Methods: The Mobetron® device was evaluated with electron beams of 9 MeV in conventional (CONV) mode and of 6 MeV and 9 MeV in UHDR mode (nominal energy). The acceptance was performed according to the acceptance protocol of the company. The commissioning consisted of determining the short- and long-term stability of the device, the measurement of percent depth dose curves (PDDs) and profiles at two different positions (with two different dose per pulse regimen) and for different collimator sizes, and the evaluation of the variability of these parameters when changing the pulse width and pulse repetition frequency. Measurements were performed using a redundant and validated dosimetric strategy with alanine and radiochromic films, as well as Advanced Markus ionization chamber for some measurements.

Results: The acceptance tests were all within the tolerances of the company's acceptance protocol. The linearity with pulse width was within 1.5% in all cases. The pulse repetition frequency (PRF) did not affect the delivered dose more than 2% in all cases but 90 Hz, for which the larger difference was 3.8%. The reference dosimetry showed a good agreement within the alanine and films with variations of 2.2% or less. The short-term (resp. long-term) stability less than 1.0% (resp. 1.8%) and were the same in both the CONV and UHDR modes. PDDs, profiles, and reference dosimetry were measured at two positions, providing data for two specific dose rates (about 9 Gy/pulse and 3 Gy/pulse). Maximal beam size was 4cm and 6cm at 90% isodose in the two positions tested. There was no difference between CONV and UHDR mode in the beam characteristics tested.

Conclusions: The device is commissioned for FLASH RT preclinical biological experiments as well as FLASH RT clinical human protocols.

Keywords: Ultra-high dose rate, FLASH, commissioning, clinical transfer

1. INTRODUCTION

Since its discovery by Favaudon et al in 2014[1], FLASH radiotherapy (FLASH RT) has recently gained attention in radiation therapy research[2]. When delivered at ultra-high dose rate (UHDR), the dose induces a specific biological effect (i.e. normal tissue sparing associated with sustained tumor control) that constitutes one of the major benefit of FLASH-RT [3]. Typically, the FLASH effect was obtained for irradiations of less than 100ms and a mean dose rate of at least 100Gy/s. It has been observed in pre-clinical studies for different species and with different beam types[4-8], and a first patient was treated in 2019[9]. Most of the experiments were performed with UHDR electron beams, but also with photons[6] and protons[10]. Owing to the success of the data gathered using animals, FLASH RT has become relevant for clinical transfer[11,12]. However, an important prerequisite for the safe and reliable use of FLASH RT is the physical characterization of UHDR electron beams for pre-clinical experiments as well as for human clinical protocols.

All previous biological experiments were performed on prototype or experimental devices where specific dosimetric procedures had to be developed and carefully validated in order to reach a reasonable accuracy[13]. Different radiation devices have been proposed to deliver UHDR electron beams compatible with proven FLASH effect beam characteristics[14-17]. Alongside the challenging work to provide adequate beams for pre-clinical experiments, further developments are necessary as most of the aforementioned devices produce a homogeneous beam (dose difference of typically less than 5%) of only a few cm which is not compatible with clinical requirements.

In conventional RT, it is considered good practice when validating a new linear accelerator (LINAC) for clinical use to perform an acceptance and commissioning procedure in order to define the reference absorbed dose to water, and to set references for the quality assessment (QA) program. The objective of this study is to present these preparatory phases for an UHDR electron medical LINAC, and its validation for pre-clinical animal FLASH RT experiments and future FLASH RT clinical trials in humans.

2. MATERIALS AND METHODS

2.A. Material used

2.A.1. Irradiation device

The Mobetron® (IntraOp, Sunnyvale, CA, USA) is a medical linear accelerator (LINAC) delivering electron beams of 6 to 12 MeV. The current conventional use of the device is for intraoperative radiation therapy and dermatologic treatments.

The version of the Mobetron® that we evaluated in this study was modified from the usual one to operate in two dose rates modes, which are designed as conventional (CONV) and UHDR for, respectively, the low and high dose rate regimes. The LINAC produces electron beams of 9 MeV in CONV mode and 6 MeV and 9 MeV in the UHDR mode (nominal energy). The CONV mode operates like any standard Mobetron® commercial device, whereas the UHDR mode was achieved by modifying CONV delivery beam parameters within acceptable operating regimes of the major system components and providing user control of the fine beam structure (number of pulses, pulse width and pulse repetition frequency) in UHDR mode while retaining the clinical functionality of the system. In CONV mode, the beam is still controlled using an internal ion chamber. This chamber fulfils all the regulatory / IEC requirements and provides flatness, symmetry information as well as two dosimetry channels for MU1 and MU2 control. For the UHDR beam delivery, the control system has been modified to proactively prescribe the number of pulses to be delivered setting the number of pulses for both the electron gun and solid-state modulator. The control system then monitor precisely the synchronization of each pulse to ensure repeatability across the range of pulse widths and records each pulse delivered. The pulse width and pulse frequency are programmable and the user can set those to the desired conditions prior to beam delivery. Table 1 summarizes the settings available in the modified UHDR special mode delivery.

2.A.2. Dosimetric means

Taking advantage of our previous studies, the reported dosimetric measurements in the UHDR mode were performed with radiochromic films[18] and alanine pellets[19].

The Advanced Markus chamber (PTW, Germany) was used to perform specific acceptance tests and the daily check in the UHDR mode. The chamber was not corrected for saturation, because these measurements were relative and compared within defined dose rate regime. Additionally, they were only used as indicators of a given physical value (for example a relative dose to check the long-term stability of the device). However, we used this ionization chamber (IC) for the reference dosimetry in the CONV mode. Our IC is metrologically traceable to the primary standards of the Swiss Institute of Metrology (METAS) for clinical beam qualities.

Relative measurements of the percent depth dose (PDD) and dose profiles were performed with radiochromic films placed at different depths in solid water slabs (Figure 1). A PDD was obtained in four separate irradiations where four or five films (for 6 or 9 MeV) were placed in the solid water slabs, each time at a different depth (1st irradiation: 0, 10, 20, 30, 40mm; 2nd irradiation 2, 12, 22, 32, 42mm; third irradiation: 5, 15, 25, 35, 45mm; 4th irradiation: 7, 17, 27, 37, 47mm). That procedure was performed to minimize the number of irradiations because of radiation protection issues (see 2.B.4) and also so that the effect of films does not significantly change the results compared to what would happen if all 20 films were put together in a single irradiation. For the PDD measurements, one film per depth was irradiated, and three films have been irradiated for each profile. The films were scanned with an Epson V800 flatbed scanner (Epson, USA) at 300 dpi resolution. The film calibration procedure is described elsewhere[18]. We used Mephysto software V3.2 (PTW, Germany) to obtain the measured absorbed dose to water and profiles in two orthogonal directions. The uncertainty on the absorbed dose to water was 4%[18]. When more than one film was used, the combined uncertainty was given.

The reference dose in UHDR mode was performed with both alanine pellets and films to take advantage of a redundant dosimetry to circumvent the lack of metrological traceability for UHDR beams[13]. The alanine measurements were read with a Brucker e-scan EPR spectrometer (Brucker Corporation, Germany)

according to our routine procedure described elsewhere and the uncertainty on dose measurement was 2%[19].

2.A.3. Set-up configuration and beam characteristics

Measurements were performed so that the solid water surface was the closest possible to the LINAC exit window, which corresponded to an effective source-to-surface distance (SSD) of 17.3 cm (called "Position A"), and 20 cm further, corresponding to source-to-skin distance (SSD) of 37.3 cm (called "Position B"). For the latter, a 20cm long and 6cm diameter Polyoxymethylene (POM) cylindrical applicator was set between the exit of the device and Position B (Figure 1).

Position A is the point where the maximal mean dose rate can be achieved, and so it can be used to evaluate the performance of the device for the highest possible dose rate. Position B corresponded to a mean dose rate similar to the one used in many pre-clinical experiments and for the first patient[9] (about 3 Gy per pulse). Position B is planned to be used for a FLASH RT clinical protocol.

The pulse width (PW) was varied between 1 and 4 μs and the pulse repetition frequency (PRF) between 30 and 90 Hz depending on the experiment (see next paragraphs).

2.B. Experiments

Following the conventional commissioning of a medical LINAC as closely as possible, we performed the following tests on the Mobetron: acceptance, reference dosimetry, commissioning, and establishment of a reference setup for QA. These were based mainly on recommendations of AAPM Radiation Therapy Committee Task Group No. 72 (AAPM TG-72) on intraoperative radiation therapy using mobile electron linear accelerators[20]. Some tests were also performed according to a previous description of commissioning a Mobetron for CONV beams[21] and of eRT6 for UHDR beams[14].

We simultaneously performed the tests in both CONV and UHDR modes, but we used the CONV results to ensure the quality of our tests and only the UHDR mode results are reported here, unless stated differently. The CONV mode commissioning results were equivalent to the ones previously published[21].

Additionally, we performed a radiation protection (RP) survey in accordance with AAPM TG-72 recommendations. As the results presented in Supplementary File show the measured radiation levels were compatible with our national regulations.

2.B.1. Acceptance

The acceptance tests were performed according to IntraOp acceptance testing protocols (ATP). Standard tests of ATP like e.g. tests of power supply, mechanical parts, interlocks, other safety features, etc…, as well as beam energy (with a tolerance defined by depth of 80% dose or 30% dose), X-ray contamination (with a tolerance ≤ 2%) were tested for both modes.

Additional measurements were performed in the UHDR mode. The repeatability was calculated as the maximum deviation from the average of five measurements (SSD=100cm) of 10 pulses each, PW=4μs and PRF=60Hz. The linearity was determined by measuring the dose per pulse of 2, 5, 10, and 15 pulses set at SSD=100cm, PW=4μs and PRF=60Hz and evaluating the maximum relative distance to the linear fit of the data. The linearity with pulse width was also evaluated by calculating the maximum deviation from average dose per microsecond for PW between 0.5 and 4 μs. Finally, the stability of the delivered dose with the PRF was evaluated for 5, 15, 30, 45, 60, 75 and 90 Hz when delivering 2 pulses of 2 or 4 μs.

2.B.2 Reference dosimetry

The reference dosimetry was performed in both position A and B. Each individual measurement was done with an alanine pellet placed at 1cm depth in solid water and with a film placed at the top of the alanine holder. It should be noted that the reference depth should be 0.9cm for 6 MeV according to IAEA code of practice[22], but it has be rounded to 1cm for practical reasons (same depth for both energies). The irradiations were performed at Position A (resp. B) with 2 (resp. 7) pulses set at PW=4μs and PRF=60Hz. We repeated each measurement 6 times for each irradiation condition.

2.B.3 Commissioning

We commissioned the Mobetron for 6 and 9 MeV nominal energy beams for the UHDR mode.

A daily check of the beam was performed by irradiating the Markus chamber placed at SSD = 100 cm in solid water at 1.2cm depth for 6 MeV in UHDR mode (2 pulses, PW=4µs, PRF=60 Hz) and at 1.6cm depth for 9 MeV in CONV (1000 Monitor units, PW=1.2µs, PRF=30Hz) and UHDR mode. These depths correspond to the depth of the maximum dose (R_{max}) for each beam energy. The measurements were repeated three times for each configuration to obtain a daily dose check. Additionally, a beam energy measurement was performed with the same set-up, setting the Markus chamber at 2cm additional depth (i.e. 3.2 and 3.6cm for 6 and 9MeV respectively, which roughly correspond to the depth of 50% of the dose, R50). We used the ratio of the two measurements as a beam energy check (called energy index).

Short-term stability was obtained by averaging ten consecutive daily measurements of the dose and energy checks. The long-term stability was evaluated in the same way as the short-term stability over a period of about three months.

Three-cm-thick graphite collimators were added at the output of the device (Position A) or at the exit of the POM applicator (Position B) to obtain circular field sizes of 2, 3, 4, and 5cm in diameter. We measured the PDDs and profiles for 6 and 9 MeV beams for each collimator and open field. The mean energy at the phantom surface was obtained from equation[23] : E_0=2.33 x R50. Values of distal depth of 90% (R90) of the maximum dose were also extracted from the PDDs. The profiles were determined at 0.5 and 3cm (resp. 0.5 and 4 cm) depth in virtual water for 6 MeV (resp. 9 MeV). These depths were used for both positions A and B. The output factors (OF) were calculated using absorbed dose to water measurements at R_{max} for the open beams measured in Position A and B, for each collimator, and using three films per irradiation.

The PDDs were measured for PW of 1 and 4 µs and PRF of 60 and 90 Hz in order to evaluate a possible change in beam characteristics due to the variation of these parameters.

2.B.4. QA program

The references for the QA program of the UHDR mode were obtained by following the recommendations of AAPM TG-72 for intraoperative devices[20]. Some of the tests were performed in CONV mode only to ensure the proper functionality of the device. These are summarized in Table 2. The tolerances were set identically for CONV and UHDR modes. These tests were performed with a low number of pulses, typically 10-20 pulses to

reduce the beam on duration. The methods used for the QA were dictated by radiation protection reasons. Due to the high dose rate, a typical CONV mode irradiation time like 30 seconds is not reasonable because it would lead to a very high dose (30 seconds at 100 Gy/s means 3 kGy) and to shielding that would be very thick compared to usual ones. Therefore, we chose to use a low number of pulses for the QA tests (10 to 20). That number is representative of the number of pulses that would typically be delivered to the target to trigger the FLASH effect and also does not lead to a significant increase of shielding compared to CONV mode irradiations for QA tests.

3. RESULTS

3.A. Acceptance tests

All tests performed in CONV and UHDR modes gave results within the tolerances of the company's acceptance tests protocol. The UHDR mode reproducibility was less than 1% for both energies. The linearity with pulse number was 1.3% for 6 MeV beam and less than 1% for 9 MeV beam. The maximum observed dose difference from average when varying the PRF was less than 2% in in all cases, but 90 Hz, where the larger difference was 3.8%. Figure 2 shows the linearity of dose with PW and for different PRF.

Figure 2. Linearity of the dose with pulse width (a) and at different frequencies (b). The error bars represent one standard deviation.

3.B. Reference dosimetry

Table 3 presents the results for the reference dosimetry at Positions A and B, using film and Alanine and for 6 and 9 MeV UHDR energy beams.

3.C. Commissioning

We found a short-term stability of 0.8% for both 6 and 9 MeV. The long-term stability of the output (respectively the energy index) variation had a standard deviation of 1.8% (resp. 1.5%) for 6 MeV and 1.7% (resp. 2.3%) for 9 MeV UHDR modes.

Figure 3 presents the PDDs of the UHDR modes in Position A for the open beam and in Position B for the 6cm collimator. The mean energy at the phantom surface was 7.5 (resp. 7.2) and 8.9 (resp. 8.6) MeV for nominal 6 and 9 MeV beams at Position A (resp. B). Table 4 presents R90 and R50 for both beam energies and for each collimator at Position A and B. Figure 4 presents the PDD of both CONV and UHDR modes at 9 MeV for comparison.

Figure 5 presents PDD of the 9 MeV UHDR mode for open field and graphite collimators at Position A and B (PDDs of 6 MeV are presented in Supplementary Figure S1).

Figure 6 presents the PDD of the 9 MeV open field for different PW and PRF and Figure 7 presents the output factors for 6 and 9 MeV at Position A and B.

Figure 8 presents typical profiles at R_{max} and R30 of the 6 and 9 MeV UHDR, and 9 MeV CONV beams at Position A (the same figure for Position B is shown in Supp. Mat. Figure S2). Table 5 presents the field sizes at 90% isodose for different collimators used at Position A and B. The UHDR beam profiles at Position A showed a maximum beam size of 4.2 and 3.8 cm at 90% isodose for the 6 and 9 MeV open fields, respectively. The profiles at Position B provide a maximum beam size of 6 cm at 90% isodose for both energies.

3.D. QA and references preparation

The QA tests were performed according to Table 2. The reference data were obtained from the experiments described in previous sections for the acceptance and the commissioning of the Mobetron.

4. DISCUSSION

Here we report on the acceptance, the reference dosimetry, the commissioning and the QA preparation of the Mobetron device for 6 and 9 MeV UHDR electron beam. The device is therefore dosimetrically validated for pre-clinical animal experiments and for clinical human protocols.

During the acceptance, we measured a linearity for different pulse numbers and different PW that was in line with what could be expected from a clinical device (less than 1.5% in any case). The reproducibility was less than 1% and therefore also compatible with clinical use. The PRF did not affect the delivered dose more than

2% except for PRF=90Hz. This level of PRF is an extension of the usual range of the Mobetron and remains subject to improvement with enhanced power supply in the near future. The other acceptance tests all fulfilled the company's specifications.

The reference dosimetry showed a good agreement within uncertainty. We found that the two detectors agree within 2.2%, meaning that our dosimetric validation based on redundant measurements can be considered adequate. For comparison, we found an agreement within 3% with the eRT6 for the radiobiological setups [13].

The short- and long-term stability observed in the UHDR mode is comparable to what is found in the CONV mode. Therefore, the device modifications made to provide the UHDR mode did not affect the stability within a 3-month period.

PDDs, profiles, and reference dosimetry were measured at Position A and B. Position A is where the dose rate is maximum, reaching 8.3 and 9.2 Gy per pulse for 6 and 9 MeV respectively. The cost of such a high dose rate is radiation contamination (head scatter) around the device head. As can be seen in Figure 3, compared to the expected PDD of a CONV beam, the elevated shallow dose deposition is a clear indication of a low energy contribution of the beam's energy spectrum. The dose rate at Position B is 3.0 and 3.3 Gy per pulse for 6 and 9 MeV resp., which is more representative of the dose rate that has been used in previous pre-clinical biological experiments and for the first patient. The open field PDDs is what is expected for electrons in clinical practice (Figure 3), which is due to the absence of radiation contamination from the head. However, the use of collimators at the water surface increases the surface dose, again due to scatter production. The commissioning of both positions provides validated set-ups for future biological experiments with higher dose per pulse than previously tested. Also, the aforementioned setups can be used for clinical trials and will provide irradiation conditions that have demonstrated the FLASH effect on animals. Obviously, the beam penetration is not large enough to irradiate deep-seated tumours.

When looking at the collimated beams, the beam size at 90% isodose roughly corresponds to the physical diameter of the collimator for all beams at Position A and for beams of 4cm and more at Position B. The reason why beam sizes of 2 and 3cm at Position B are not following that trend is probably due to the same reason that the output factors are lower for small fields as described in [21] (differential backscattering in the applicator).

These beam characteristics provide large enough beams for preclinical experiments and for human clinical trials.

When comparing the PDDs and profiles between the UHDR and the CONV mode, it is clear that they are consistent. This shows that adapting the clinical device to a UHDR mode did not affect either the dosimetric or geometric characteristics of the beams. Moreover, the PDDs produced by different PW or PRF (Figure 6) were all in agreement within uncertainties. This demonstrates that using variable beam production parameters does not affect the spectrum of the UHDR beams.

The variation of the output factors with the beam size (Figure 7) show a similar behaviour observed in other publications.[21,24] The different values for the output factors that we obtained compared to the other publications are explained by the difference in set-up configuration.

The QA reference tests were obtained according to AAPM recommendations on IORT of CONV mode beams and transposed to UHDR mode beams.

To date, there are only a few publications about the commissioning of an UHDR electron beam device [14-17,25]. The most comprehensive publication described the commissioning of the Oriatron eRT6 prototype (PMB Alcen, France)[14]. Another prototype was evaluated for preclinical studies[16] and other authors have also provided information about the commissioning of a modified conventional linear accelerator to produce UHDR (Elekta[15], Varian[17] or Novac7[25]). The main results concerning the commissioning of these devices are summarized in Table 5. The short- and long-term stability of the Mobetron (2% or less) showed results similar to the eRT6 and the Elekta device. The Mobetron had a superior linearity than the eRT6 (the linearity of the other devices was not reported). The variations in dose measurements observed when PRFs were changed were of the same order of magnitude or lower with the Mobetron than with the eRT6 (again, the studies on other devices did not provide information). The Mobetron and the eRT6 provided beam sizes up to 6cm in diameter at 90% isodose, which is compatible with clinical protocols. The other devices remain usable for pre-clinical experiments, but their beam sizes are too small for a clinical transfer. Note that none of these studies provided information about QA preparation for clinical use. When looking at the characteristics of available UHDR electron mean devices, the Mobetron appears to be a good candidate for the clinical transfer of FLASH RT.

A remaining question is the ability of independently counting and controlling the pulse number, that are important safety concerns. UHDR beams like the ones produced by the Mobetron are able to deliver high prescribed doses in only some pulses (typically less that 10). Therefore, a deviation of one pulse would lead to a dose deviation of several percent which would not be acceptable in clinical practice. This is the reason why the data provided in the present study give enough confidence for using the device for pre-clinical studies and clinical protocols only. The safety issues remain unsolved for a complete clinical use of UHDR beams. However, ongoing studies on instruments able to monitor the pulses (not being transmission chambers that are saturating at such dose rates) are promising. This would allow the monitoring of the beam and possibly the control of the pulse number by an independent counting linked to an electronic beam stop when something would go wrong. The time between two pulses being on the order of 10^{th} of ms would allow such kind of strategy for stopping the last pulse when needed.

5. Conclusion

We have provided a description of the acceptance, reference dosimetry, commissioning, and QA reference test of a modified Mobetron device operating with UHDR electrons of 6 and 9 MeV. The device is now commissioned in UHDR mode for the validation of the FLASH effect in preclinical biological experiments and will be used in the frame of a FLASH RT clinical trial in patients with dermatological tumors.

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In memoriam Cécile Crevoisier (11.6.1969 – 24.12.2020)

CONFLICTS OF INTEREST

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHORS CONTRIBUTIONS

All authors have made substantial contributions to conception and design of the study or acquisition of data or analysis and interpretation of data. They all have been involved in drafting the manuscript or revising it critically for important intellectual content; and have given final approval of the version to be published.

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Figure captions

Figure 1. Measurements configurations at the exit of the device (Position A) and with an additional cylindrical applicator of 20 cm length and 6cm diameter (Position B).

Figure 2. Linearity of the dose with pulse width (a) and at different frequencies (b). The error bars represent one standard deviation.

Figure 3. PDD of 6 and 9 MeV UHDR at Position A (a) and Position B (b).

Figure 4. 9 MeV PDD at Position A for UHDR and CONV modes.

Figure 5. PDD of the 9 MeV UHDR mode for different collimator sizes at Position A (a) and B (b).

Figure 6. PDD of the UHDR 6 MeV open field for 1 and 4μs PW (a) and PRF (b).

Figure 7. Output factor of 6 and 9 MeV UHDR beams at Positions A and B.

Figure 8. Profile of open field at R_{max} (a) and R30 (b) of 6 and 9 MeV UHDR, and 9 MeV CONV beams at Position A.

391 Table 1. Variable parameters in UHDR mode and their respective range.

Parameter	**Range**
Beam energy [MeV]	6 or 9
Pulse width (PW) [μs]	0.5 – 4
Number of pulses	1 – 200
Pulse Repetition Frequency (PRF) [Hz]	5 – 90
Maximum dose per pulse* [Gy]	> 8

392 * Obtained at Position A (See paragraph 2.A.3)

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394 Table 2. Tests and frequency of QA program (modified version of AAPM recommendations Nr 72[20]).

Test and frequency	Method	Tolerance	Remark
Daily			
Output constancy	Daily check set-up.	3 %	
Energy constancy	Daily check with 2cm additional water slabs.	2 mm shift in depth dose	
Door interlock	Run an irradiation in CONV mode and open the door (key, chain, door)	functional	In CONV mode
Mechanical motion	Manual and visual check	functional	In CONV mode
Docking system	Manual and visual check	functional	In CONV mode
Monthly			
Output constancy	Daily check set-up. Ten measurements per mode.	2%	
Energy constancy	Daily check with 2cm additional water slab. Ten measurement per mode	2mm shift in depth dose	
Flatness and symmetry constancy	Profile at maximum depth comparison	3%	
Annually			
Beam output: Definitive calibration	Reference dosimetry with alanine and films	2%	
Depth dose curve for all collimators	Same set-up as for commissioning	2%/2 mm	
Dose profiles: Extensive checks	Same set-up as for commissioning	3 %	2% for ref. collimator
Output factors	Same set-up as for commissioning	2-3%	
Linearity of the dosimetry system	Same set-up as for acceptance	1 %	

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Table 3. Reference dosimetry of 6 and 9 MeV UHDR beams at Positions A and B. Uncertainties represent one standard deviation.

Position	**A (PW: 4 μs; PRF: 60 Hz; 2 pulses)**		**B (PW: 4 μs; PRF 60 Hz; 7 pulses)**	
Energy [MeV]	**6**	**9**	**6**	**9**
Film dose [Gy]	16.9 ± 0.2	18.7 ± 0.1	20.9 ± 0.2	23.4 ± 0.4
Alanine dose [Gy]	16.6 ± 0.2	18.3 ± 0.1	20.9 ± 0.3	22.9 ± 0.2
Difference [%]	1.8	2.2	0	2.2
Dose per pulse [Gy]	8.3	9.2	3.0	3.3

401 Table 4. R90 and R50 (in mm) for both beam energies and each collimator at Position A and B.

			Collimator size [cm]				
		Energy [MeV]	**2**	**3**	**4**	**5**	**Open field (A) or 6 (B)**
Position A	R90	6	5	9	21	22	22
	R50		23	28	31	32	32
	R90	9	12	13	19	19	22
	R50		28	33	37	37	38
Position B	R90	6	6	7	11	12	21
	R50		23	26	28	29	31
	R90	9	4	7	13	17	25
	R50		24	29	33	36	37

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404 Table 5. Field size at 90% isodose of the 6 and 9 MeV UHDR and the 9 MeV CONV beams for different collimators
405 at Position A and B

	Position A					**Position B**				
Collimator [∅ cm]	**2**	**3**	**4**	**5**	**Open field**	**2**	**3**	**4**	**5**	**6**
6 MeV	1.9	3.0	4.0	4.4	4.2	1.6	1.8	3.9	4.9	6.0
9 MeV	1.9	3.0	4.0	3.7	3.8	1.6	2.0	3.9	5.0	6.0
9 MeV (CONV)	1.9	3.0	4.0	4.1	3.7	1.6	2.0	3.8	5.0	6.1

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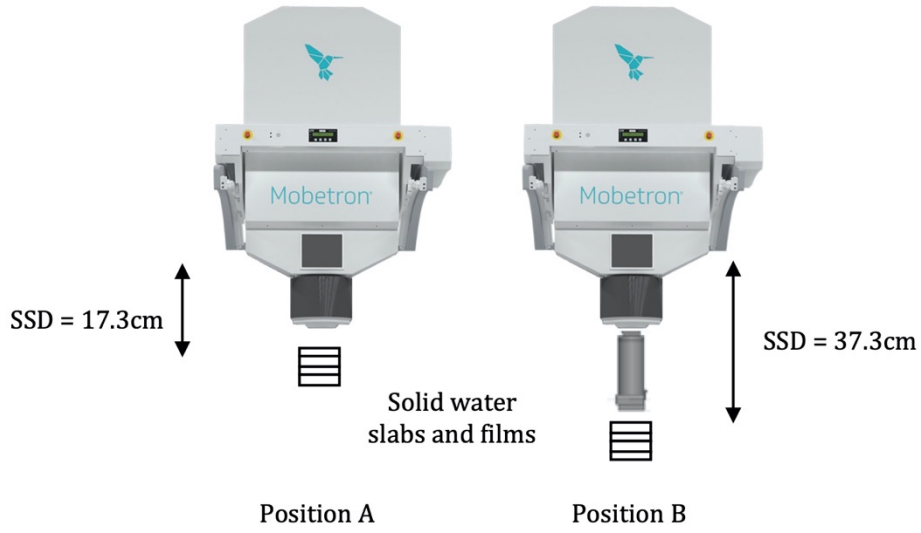
Table 5. Characteristics reported in the literature for electron UHDR devices.

Device	**Mobetron (IntraOp)**	**Oriatron eRT6 (PMB Alcen)**	**Kinetron (CGRMeV)**	**Modified Elekta**	**Modified Varian**	**Novac7 (Sordina)**
Reference	This publication	Jaccard [14] Petersson [26]	Lansonneur [16]	Lempart[15]	Schüler[8,17]	Felici [25]
Available beam energy [MeV]	6 and 9	6	4.5	10	9, 16 and 20	7
Maximum average dose rate [Gy/s]	> 700 @ 6 MeV > 800 @ 9 MeV	1000	NA*	≥ 300	74 @ 9 MeV 300 @ 16 MeV 200 @ 20 MeV	540
Maximum dose per pulse [Gy]	> 8 @ 6 MeV > 9 @ 9 MeV	10	1	1.9	1.67 @ 16 MeV 1.85 @ 20 MeV	18.2
Max. beam size @ max. dose rate [cm]	4 @ 90%	NA	NA	2 (5% flatness)	1 (90% isodose)	0.5 (FWHM)
Short term stability [%]	0.8	< 1	NA	1 to 4***	NA	NA
Long term stability	1.8 @ 6 MeV 2.3 @ 9 MeV	4.1%	NA	NA	NA	NA

* NA: data not available; ** during 10 mins; 7 to 11 for > 10 mins



410

411 Figure 1

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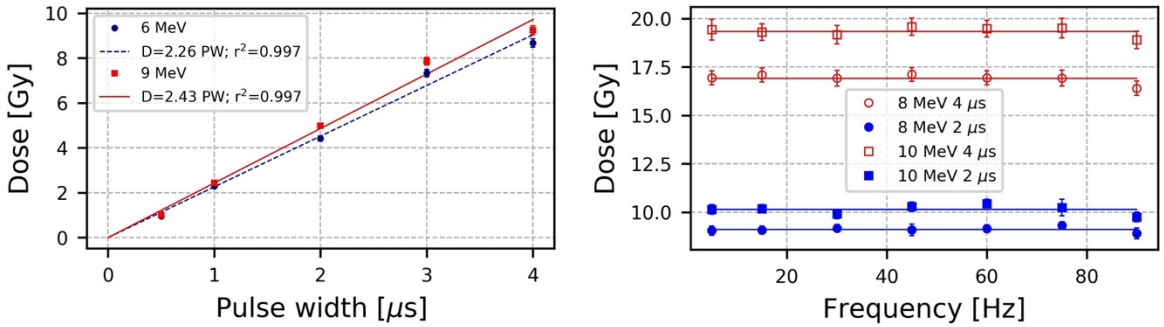

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414 Figure 2.

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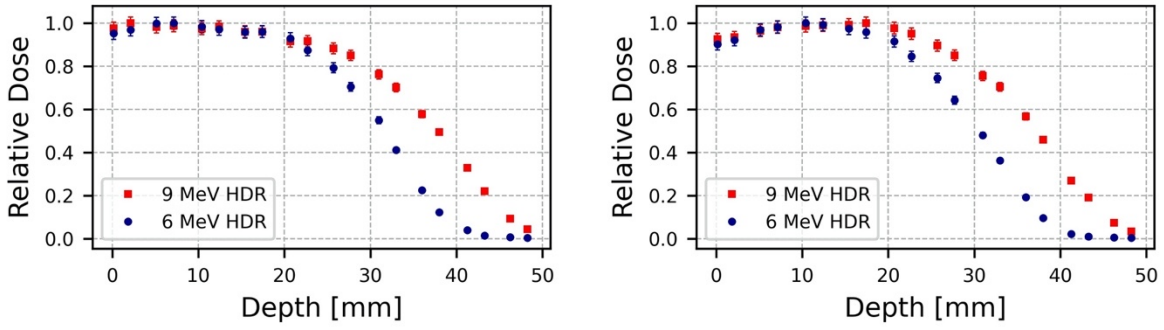

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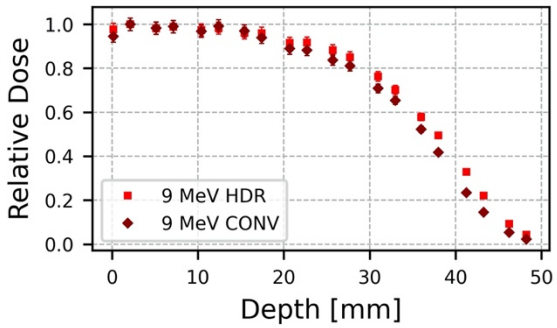
417 Figure 3.



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419 Figure 4.

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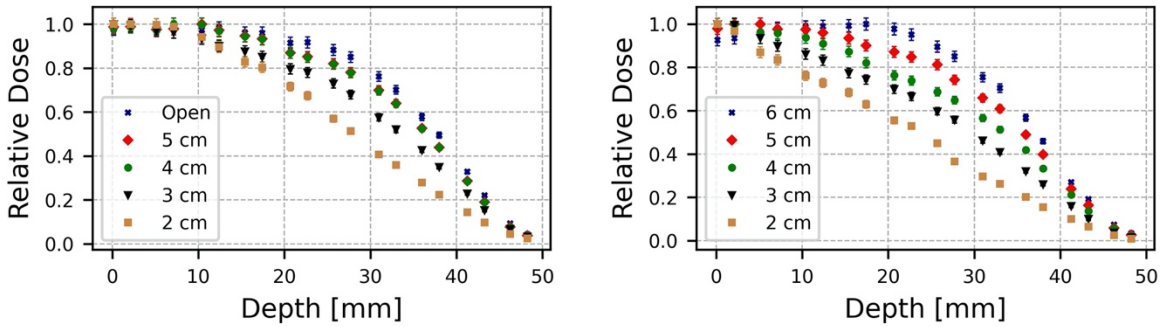

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422 Figure 5.

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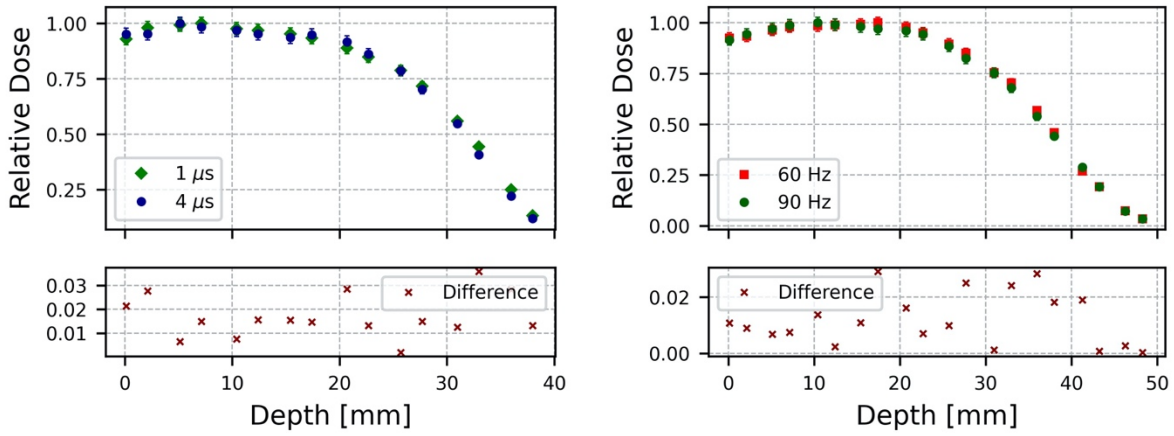

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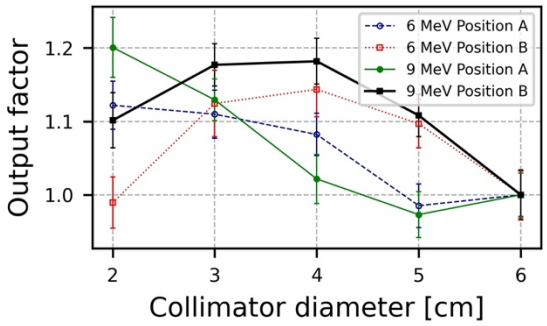
425 Figure 6.



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427 Figure 7.

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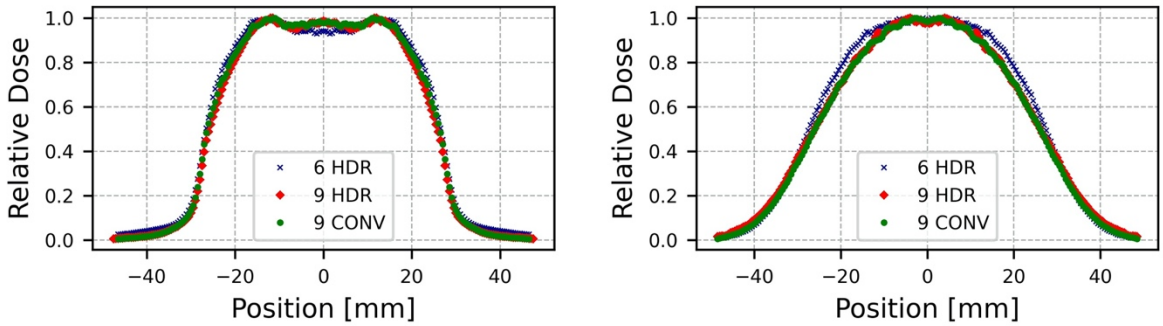

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430 Figure 8.

Supplementary file

Radiation protection survey

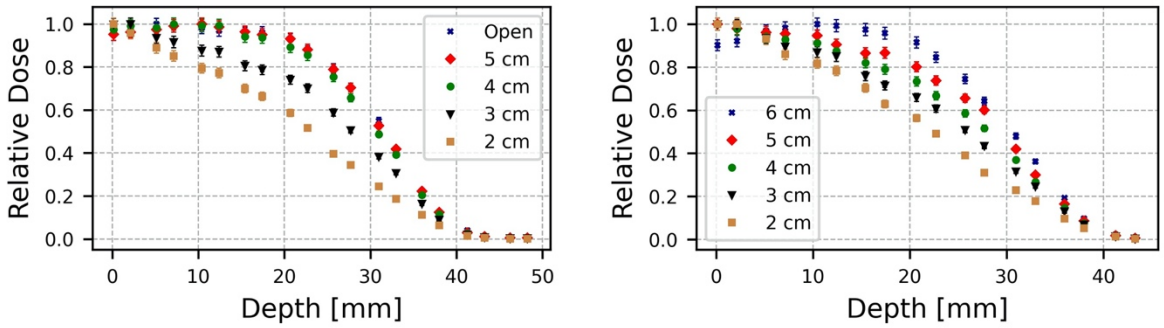
According to AAPM TG-72, the radiation survey is meant to verify that in any location outside of the room location of the IORT device and in the worst-case situation of possible clinical configurations of the units, the allowed weekly load is not exceeded[20]. It is also mentioned that the operational plan should account for all irradiation, being patients or commissioning. In our case we have set the weekly limit to 50 kGy.

The Mobetron was placed in a conventional bunker and its use for pre-clinical FLASH studies as well as FLASH clinical trials are planned in the same kind of environment (in opposition to a standard operating room for IORT). The measurements have been performed with an Atomtex AT1123 (Atomtex, Belarus) in "pulsed dose rate" mode. Additional passive dosimetry has been performed with TLD measurements during the whole commissioning process.

The results showed that the measured dose rates allowed the use of the device during 25 hours per week, whereas the weekly limit of 50 kGy could be reached in less than 1 hour. The passive dosimetry showed that the maximal weekly load measured reached a maximum 29% of the authorized load. In other words, in our case the allowed weekly load could have been reduced by a factor of three.

Obviously, these results are highly dependent on the type of room used for the device.

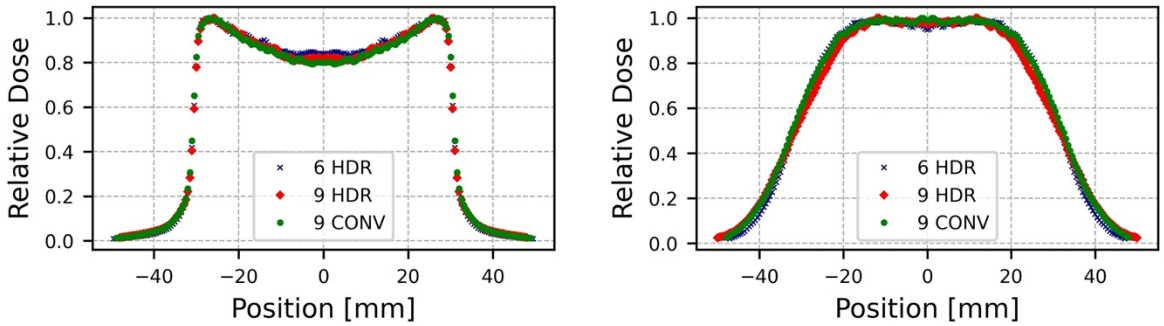
Additional PDD for & MeV in UHDR mode



(a) (b)

Figure S1. PDD of 6 MeV UHDR mode for different collimator sizes at position A (a) and B (b).

Additional profiles a Position B



(a) (b)

Figure S2. Profile of 6cm field at R_{max} (a) and R30 (b) of 6 and 9 MeV UHDR, and 9 MeV CONV beams at position B.