FINAL PUBLISHABLE REPORT

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RMG: -		

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1 Overview

In vivo radiobiological experiments have shown that irradiation with electron beams and ultra-high doses per pulse leads to a dramatic reduction of adverse side effects. However, pulses with dose rates higher than conventional radiotherapy present significant metrological challenges. Most of the dosimetry detection systems used in electron and proton therapy beam monitoring, quality assurance, and commissioning had shown saturation effects or were unable to detect the entire radiation dose in such a short time of ultra-high dose delivery. The project investigated several technological challenges and state-of-the-art ideas for detector development, calibrations, and a metrological framework for traceable absorbed dose measurements. As a result, this project established metrology standards, traceability methods, and the development of new detection systems for beam monitoring and field characterisation. This includes i) a robust metrological framework, establishing SI-traceable primary and secondary reference standards and validated methods for dosimetry measurements in particle beams with ultra-high pulse dose rates, ii) characterised the response of available detector systems, iii) developed traceable and validated methods for relative dosimetry and characterisation of stray radiation outside the primary pulsed particle beams, ensuring safer and more effective treatments, and iv) provided essential input data for Codes of Practice for absolute dose measurements.

Overall, the project's achievements significantly enhanced the accuracy and reliability of dosimetry in ultra-high dose rate treatment techniques, empowering medical professionals and researchers to deliver more effective and safer radiotherapy. The project's outcomes have directly addressed the user's needs, enabling improved treatment, quality assurance, and commissioning in pre-clinical, clinical and research laboratories.

2 Need

According to the World Health Organisation, the estimated number of new cancer cases in Europe, in 2018, reached 4.2 million. Approximately half of the European cancer patients received radiotherapy. The therapeutic window, i.e. the range of dose providing an effective cure, was limited by adverse side effects of the radiation on the healthy tissue surrounding the tumour. Several animal studies have demonstrated that delivering radiation dose in short bursts, with only a few beam pulses of ultra-high dose per pulse (known as the FLASH effect), led to a dramatic reduction in adverse side effects. This promising effect allowed for the possibility of increasing the prescribed dose, resulting in more effective tumour control. However, the application of FLASH radiotherapy necessitated reliable measurement and optimisation of its performance, safety, and effectiveness. Accurate dosimetry plays a vital role in delivering successful radiotherapy. Ultra-high dose rate beams posed significant metrological challenges related to the high dose delivered in a short time. Addressing these challenges required wide multidisciplinary scientific approaches within a large consortium. The project and the consortium formed a recognised European network for metrological expertise, detector development, and support for modern and emerging forms of radiotherapy.

3 Objectives

The overall goal of the project was to provide the metrological tools needed to establish traceability in absorbed dose measurements of particle beams with ultra-high pulse dose rates (UHPDR), i.e., with ultra-high dose per pulse or with ultrashort pulse duration.

The specific objectives of the project were:

1. To develop a metrological framework, including **SI-traceable primary and secondary reference standards** and validated reference methods for dosimetry measurements for particle beams with ultra-high pulse dose rates.
2. To characterise the response of available **detector systems** in particle beams with ultra-high dose per pulse or with ultrashort pulse duration.
3. To develop traceable and validated methods for **relative dosimetry** and for the **characterisation of stray radiation** outside the primary pulsed particle beams.

4. To provide the input data for **Codes of Practice** for absolute dose measurements in particle beams with ultra-high pulse dose rates.
5. To facilitate the uptake of the project's achievements by the measurement supply chain, standards developing organisations (e.g., those associated with International Atomic Energy Agency (IAEA) and International Commission on Radiation Units (ICRU) reports) and end users (clinical and academic laboratories, hospitals and radiotherapy manufacturers).

4 Results

1. To develop a metrological framework, including **SI-traceable primary and secondary reference standards** and validated reference methods for dosimetry measurements for particle beams with ultra-high pulse dose rates **(WP1 & WP2).**

Relevance:
For conventional radiotherapy the metrological framework for traceable dosimetry is based on primary standards such as water calorimetry, graphite calorimetry and Fricke dosimetry. The traceability is disseminated via secondary standards such as ionisation chambers (IC), alanine and Fricke dosimetry. ICs are the most widely used and are also preferred in hospitals for reference dosimetry following the guidelines of accepted codes of practice (CoPs). In order to establish a metrological framework for FLASH radiation dosimetry, the existing primary and secondary standards need to be reviewed and, if necessary, further developed. To ensure comparability between the different standards at different facilities, precisely specified reference conditions must be determined, and reference methods must be established.

Primary standards:
The standard Fricke solution (1 mM Fe2+, 0.4 M H2SO4, air saturated) is well established at conventional dose rate for absorbed dose to water in MeV pulsed electron beams (with the pulse duration of the order of few µs) and nearly independent on the dose rate up to ~2 Gy per pulse. At METAS, sodium chloride (1mM NaCl) is added to the solution to desensitize the system to organic impurities. However, this increases the dose rate dependence of the radiation chemical yield on the dose per pulse (DPP). For an electron pulse duration of 3 µs and the Fricke composition used at METAS, the correction was found to be smaller than 1% up to 0.4 Gy per pulse while for 10 Gy per pulse a correction of 10% was determined. For higher DPP, this correction is increasing. For the realization of the primary standard for the UHDR pulsed electron beams, two steps were required. First, a monoenergetic electron beam of known particle energy and beam charge is totally absorbed in a large volume of Fricke solution, allowing the determination of the response of the Fricke dosimeter in relation to the energy deposited by the beam. Amongst others, this requires an absolutely calibrated beam charge measurement. At METAS, an Integrating Current Transformer (ICT) from Bergoz was used for this purpose. It was calibrated with a dedicated pulse generator provided by PTB. Second, small bags ($30 \times 30 \times 3$ mm^3) filled with the same Fricke solution as described above, were irradiated in the reference beam. The absorbed dose is determined by taking into account the previously derived response. The evaluated standard uncertainty 0.93%.

Following the establishment of reference, UHDR electron beams at PTB, enabling an operation of a beam with a DPP ranging from 0.13 Gy to 6.3 Gy at 2.5 µs pulse duration, the existing PTB's primary standard water calorimeter, was validated in that beam. The PTB calorimeter was used to disseminate the absolute dose to water for a range of total DPP (i) by modulating the instantaneous dose rate within a pulse and (ii) by modifying the pulse duration. The dose rate and field shape dependent correction factors, i.e., the heat transport correction factor and field perturbation and depth correction factors, were evaluated using thermal and Monte Carlo simulations, respectively. The results of the simulations have shown that the correction factors were comparable to the value found in the literature despite the very short delivery time and the non-conventional beam shape of the reference UHPDR beam. The largest impact of the very short total delivery time (few seconds), compared to the typical irradiation time required in conventional dose rate (>30 s up to 2 min), was on the analysis of the temperature-time trace used to determine the increase in temperature of the water. The combined correction factors for the water calorimeter used in the reference UHDR electron beam was found to be within 0.99 and 1.01. The final combined standard uncertainty was evaluated to be less than 0.5%.

To compare the respective primary standards of PTB and METAS in UHDR pulsed reference electron beam alanine dosimeters from the National Research Council of Canada (NRC) were used as a transfer standard. Both institutes (i.e. PTB and METAS) have irradiated NRC's alanine dosimeters in their reference UHPDR electron beam and compare the result to a known absorbed-dose-to-water measurement traceable to their respective primary standards. By including the third institute in this comparison, i.e. the NRC, a clear separation was obtained between the primary standards involved in this comparison, as the transfer standard, i.e. the alanie pellets, had an independent traceability route to the NRC's primary standard. The ratio between the dose delivered by a calibrated UHPDR electron beam using the METAS primary standard, Fricke dosimeter, and the dose delivered by a calibrated UHPDR electron beam using the PTB primary standard, water calorimeter, was shown to be 1.002(12).

GUM developed and characterized a portable graphite calorimeter as a primary standard for absorbed dose to water and tested it in PTB's ultra-high pulse dose rate reference electron beam. The first step included the development of Monte Carlo models of the research accelerator and generation of the IAEAphsp files using FLUKA. The next step involved determination of correction factors based on IAEAphsp files for GUM portable graphite calorimeter using Monte Carlo simulation in FLUKA code, which included:], which included: the impurity correction factor (k_{imp}), and the gap correction (k_{gap}), accounting for the presence of non-graphite components and vacuum gaps within the calorimeter, the water-to-graphite mass-stopping-power ratio ($s_{w,g}$), and the fluence correction factor (k_{fl}), correcting for the difference in fluence at water-equivalent depths between water and graphite. The correction for radial non-uniformity in water (k_{rn}) was also applied. The depth-dose curve obtained from the Monte Carlo simulation was used for the determination of heat loss correction factor using finite element method (FEM) in FreeFem++ environment. The average absorbed dose to the core was determined by multiplying the measured increase in temperature by the specific heat capacity of the core, which was determined experimentally after each series of measurements during electric calibration. The expanded uncertainty of the measured dose was 0.57%. The results of measurements were compared with results of PTB alanine dosimeters. The results are an agreement within 0.2% with combined standard uncertainty of 1 %.

NPL in support of implementation of the first in-human proton FLASH clinical trial at the Cincinnati Children's Hospital Medical Center performed measurements using the NPL primary-standard proton calorimeter (PSPC). Calorimetry measurements were performed in six rectangular fields developed for the treatment of symptomatic bone metastasis, according to the requirements of the FAST-01 cinical trial, with an averaged dose rate of ~63 Gy·s-1, using a 250 MeV mono-energetic scanned layer The average absorbed dose to the core was determined by multiplying the measured increase in temperature by the specific heat capacity of the core, which was determined experimentally at NPL. The absorbed dose to water was determined as a product of absorbed dose to calorimeter core and the necessary beam-dependent correction factors which were determined using Monte Carlo simulations. Those factors included: (i) the impurity correction factor, k_{imp}, and (ii) the gap correction, k_{gap}, accounting for the presence of non-graphite components and vacuum gaps within the calorimeter, respectively (iii) the water-to-graphite mass-stopping-power ratio, $s_{(w,g)}$, and (iv) the fluence correction factor, k_{fl}, correcting for the difference in fluence at water-equivalent depths between water and graphite.The numerical values of those factors are given in Table 1.

Table 1. Values of the specific heat capacity, c, as a function of temperature T in Kelvin, as well as the correction factors determined for the NPL PSPC for a field of 12×5 cm2 at a water-equivalent depth of 5.2 g·cm-2.

Parameter	Value
c (J·kg^{-1}·K^{-1})	651.57+2.74· (T-273.15)
k_{imp}	1.0016
k_{gap}	1.0029
$s_{\mathrm{w,g}}$	1.1210
k_{fl}	0.9713
$k_{\mathrm{z,cal}}$	1.0000

The overall uncertainty on the dose measured with the NPL's PSPC under proton FLASH conditions was 0.9% (k=1) which was in line with recommendations for reference dosimetry in clinical radiotherapy.

In summary, METAS, PTB, GUM and NPL adapted and validated their primary standard instruments for UHDR irradiations for pulsed electrons and proton beams which have been used within the scope of the UHDpulse project. The uncertainty for the disseminated quantity of interest, i.e. the absorbed dose to water for all of the standards was below 1% (k=1).

Secondary standards:

Secondary standards in radiotherapy allow determining the absolute dose delivered to water and they are directly linked to primary standards. They are used directly in hospitals or in reference laboratories of National Metrology Institutes (NMI) to calibrate working standards for application in clinics. The most widely established secondary standard in radiotherapy is the ionisation chamber in various forms. As part of the project, it was investigated whether these detectors are also suitable for use in UHDR beams. The studies were carried out for clinical electron beams (FLASH) on the one hand and for emerging pre-clinical beams (laser-driven proton and VHEE) on the other.

The main problem of ionisation chambers in ultra-high dose rate radiation is the dose rate dependent charge collection efficiency and it is is clearly visible in figure 1. The efficiency was measured with a parallel plate Roos chamber from PTW by PTB and it was simulated with numerical models by project partner USC. An individual saturation correction factor can thus be determined for each chamber.

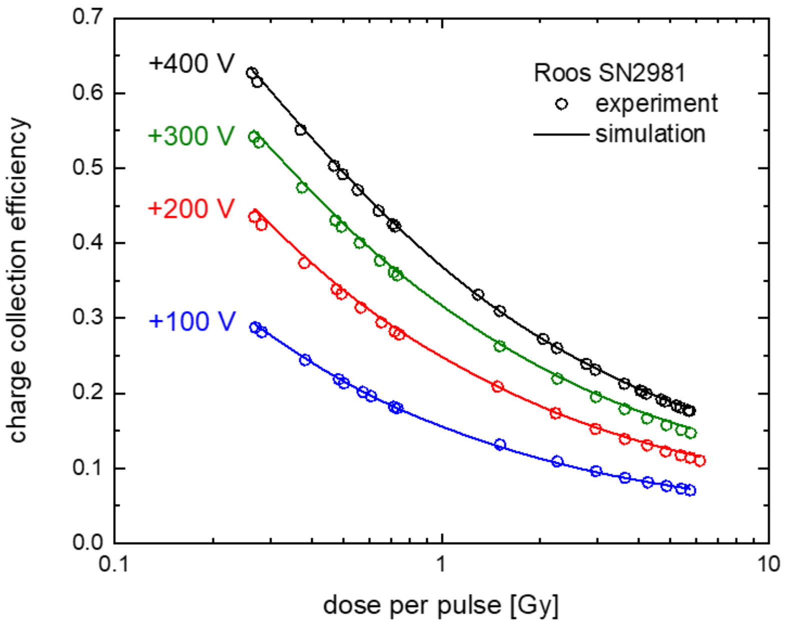

Figure 1: Charge collection efficiency of a parallel plate Roos chamber vs. dose per pulse in the UHDR regime.

In total, six different parallel plate IC-types were investigated in the modified Metrological Electron Accelerator Facility (MELAF) at PTB. The determination of the reference dose was done with alanine dosimetry and an integrating current transformer used as monitoring device. It was found that the electrode spacing in a parallel plate chamber plays a central role. USC then worked with PTW to develop an IC with an extra-small electrode gap. It could be shown that the charge collection efficiency is almost dose rate independent.

For the measurements with ionisation chambers in VHEE and laser-driven proton beams new setups had to be developed. Special PMMA phantoms containing ionisation chambers and small graphite calorimeters side by side in variable water depths were developed at NPL. Thus, the dose rate dependence of IC in VHEE beams could be determined at the CLEAR facility at CERN. The acquired data set was used to test the available ion recombination models for the PTW Roos chamber and has been published.

Fricke dosimetry is well suited as a secondary standard in conventional beams and has been used by METAS for a long time. It has long been known that the Fricke response is dose rate independent only up to a certain dose per pulse. It has been shown that the Fricke solution produced at METAS can be used without hesitation up to about 1 Gy per pulse (3 μs pulse). Above this, an empirically determined correction function must be applied. The dependence up to 10 Gy per pulse measured at METAS and at CHUV and the corresponding correction function is shown in Figure 2.

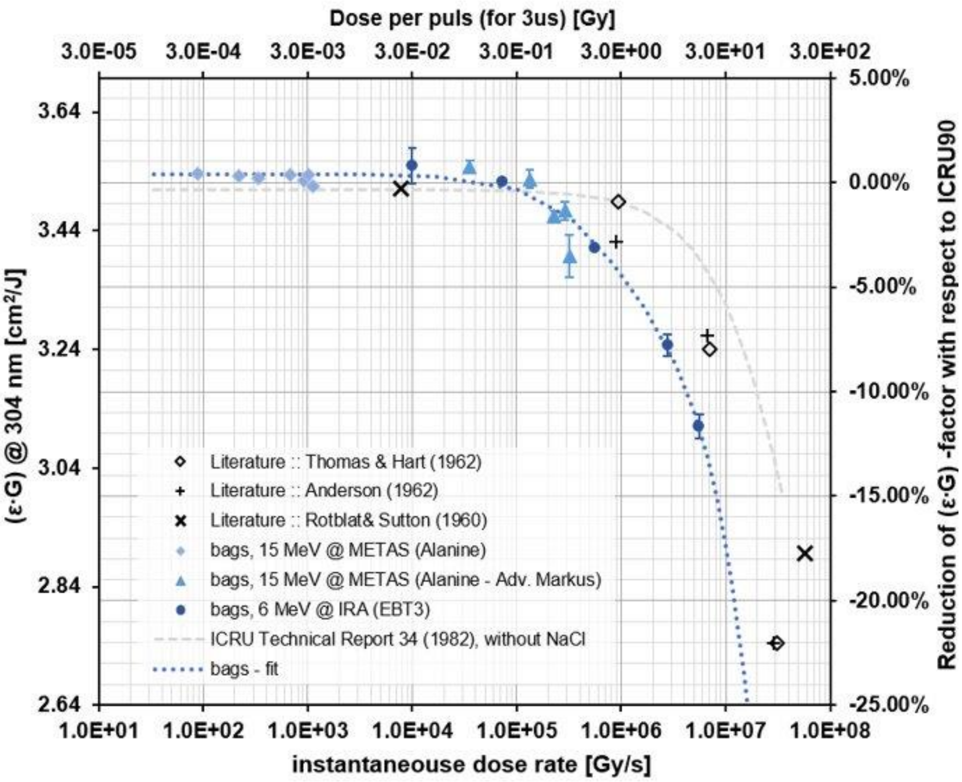

Figure 2: εG factor of Fricke dosimeter vs. instantaneous dose rate or vs. dose per pulse (in 3 μs pulse)

The alanine/ESR secondary standard dosimetry system of the PTB has been investigated in the characterised PTB reference UHPDR electron beam. Using the Monte Carlo model of the PTB research linac, the required correction factors for beam shape and beam quality were investigated. Finally, the relative response of the alanine/ESR secondary standard dosimetry system has shown a very close to linear relationship with the ICT charge measurements. The nonlinearity was found to be explained by a changing field size with dose per pulse. These results are reported in Deliverable D1. The alanine/ESR dosimetry system of the PTB was used to check and calibrate the detectors at METAS. It played also a very important role when investigating the dose rate dependence of Fricke dosimetry.

Solid state detectors have promising properties for use in UHDR beams. The project partners PTW and UHDpulse Collaborator URTV developed a special diamond detector specifically for this type of radiation. The flashDiamond was commercialised by PTW (flashDiamond Detector T60025) and extensively tested at PTB. A very linear response up to 10 Gy per pulse was found (see figure 3).

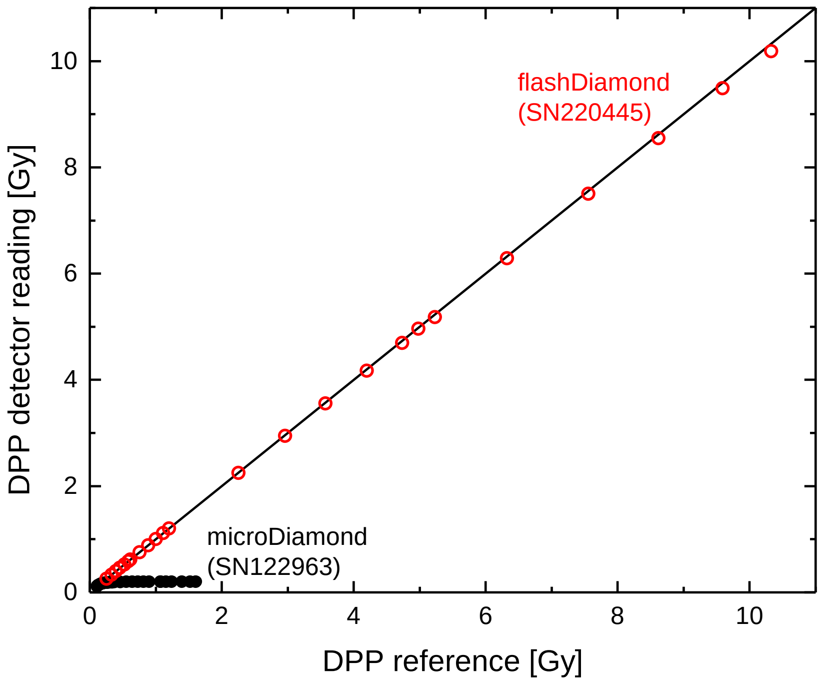

Figure 3: dose per pulse (DPP) measured with microDiamond and flashDiamond as function of actual DPP

The detailed investigations of various active detectors have shown that some are very well suited as secondary standards in certain dose rate ranges. However, the limitations of such systems were also clearly demonstrated. Measurements with parallel plate ionisation chambers at increasing dose rates must be strongly corrected for the decreasing charge collection coefficient. The project partners succeeded in applying and validating appropriate models for the correction. Fricke dosimetry can only be used in a certain dose rate range. Above this, an empirically determined correction of the measured value is necessary.

The specially developed solid-state detectors and novel ionisation chambers with very small electrode spacing behave most promisingly (see figure 3b) . In various measurement series, it could be shown that the linear range of the dose measurement could be shifted to ever higher dose rates with these detectors.

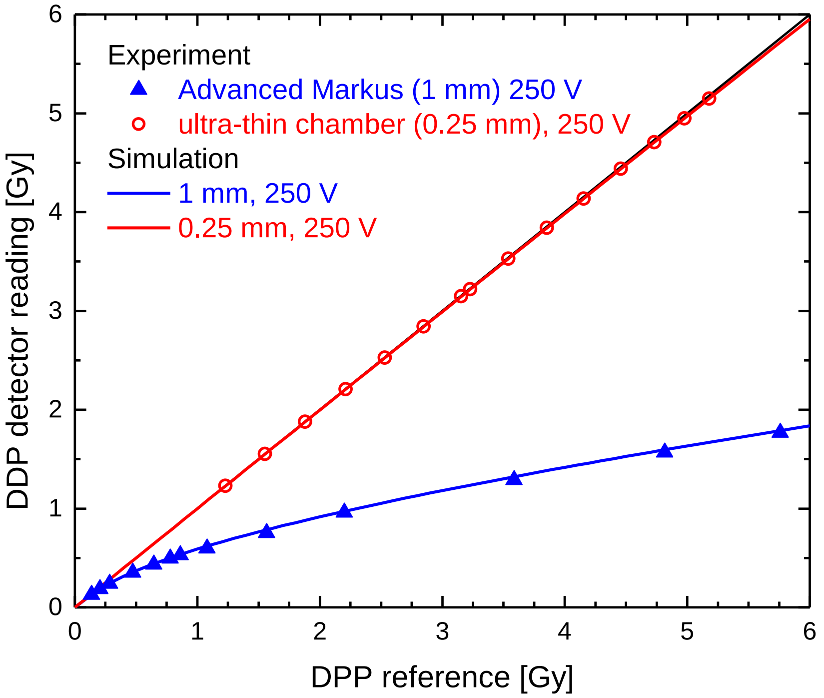

Figure 3b: dose per pulse (DPP) measured with Advanced Markus chamber and ultra-thin parallel plate ionization chamber as function of actual DPP

2. To characterise the response of available **detector systems** in particle beams with ultra-high dose per pulse or with ultra-short pulse duration **(WP2 & WP3).**

Relevance:
Detector systems for absolute dose measurement are of central importance for clinical and pre-clinical irradiation. Until now, dose has been determined mainly with passive systems such as film, TLD/OSL and alanine. In order to meet the requirement for comparability of experiments, the different systems must agree with small uncertainty. An overview of the different types of dosimeters and their applications in UHDR beams explored within the UHDpulse project is summarized in table 2 including the reference of the papers published as result of UHDpulse.

Table 2. The summary of devices and their applications in UHDR beams explored within the UHDpulse project.

Device/instrument	UHDR beam modality	energy [MeV]	DPP [Gy]	pulse dose rate [Gy/µs]	average dose rate [Gy/s]	pulse duration [µs]	pulse repetion rate [Hz]	standard uncertainty	references
Fricke dosimetry	electrons	15	0.1 - 10	0.033 - 3.3	1 - 10	3	10	0.93%	-
PTB's water calorimeter	electrons	20	0.1 - 10	0.04 - 4.0	1 - 50	1.2 - 2.8	5	0.49%	[15]
GUM's graphite calorimeter	electrons	20	0.1 - 10	0.04 - 4.0	1 - 10	2.5	5	0.57%	-
NPL's graphite calorimeter (PSGC)	protons	250	N/A	N/A	63	quasi continuous		0.90%	[28, 24]
aluminium calorimeter	electrons	50	0.2 - 1.8	0.1 - 0.7	1.5 - 9	2.5	5	-	[4]
small protable graphite calorimeter (SPGC)	laser-accelerated protons	15 - 40	1 - 3	1000	N/A	0.001	single pulse	-	[3]
ultra-thin ionization chamber (UTIC)	electrons	9 20	1 - 10 1.2 - 5.4	0.25 - 2.5 0.48 - 2.2	10 - 100 6 - 27	4 2.5	10 5	1.40%	[7, 21]
alanine	electrons	20	0.15 - 9	0.15 - 3.3	0.75 - 45	1.35, 2.5, 2.7	5	0.85%	[14]
flashDiamond	electrons	7, 9 20	0.3 - 26 0.2 - 10	0.5 - 6.6 0.15 - 3.3	up to 960 1 - 50	1 - 4 1.35 - 3	5 -245 5	1% @ 0.25 Gy/µs, 3% @ 2.5 Gy/µs	[11, 23]
silicon carbide (SiC) diode	electrons	20	0.4 - 11	0.7 - 6.6	2 - 55	2.9, 1.6, 0.6	5	5%	-
Aerrow graphite proble calorimeter	electrons	20	0.6 - 5.6	0.24 - 2.24	3-28	2.5	5	1.06%	[13]
commercially available ionization chambers	electrons	20	0.14 - 6.2	0.352 - 2.48	0.7 - 31	2.5	5	2.5% up to 10% *	-
	protons (PBS)	227	4.3, 17.5, and 38.1	4x10^-6 - 3.85x10^-3	4 - 385	1x10^6, 99x10^3	single pulse (PBS)	1.5%**	[34]
beam current transformer (BCT)	electrons	4 - 10	0.005 - 100	0.0017 - 35	0.05 - 100	1	10	1.00%	[18, 19]

Passive dosimeter such as gafchromic films, alanine/ESR have been tested in validation and routine protocol measurements. They were found to provide a reliable and accurate evaluation of the absorbed dose to water. No saturation effects could be recorded. The main drawback of passive dosimetry consists of the slow throughput and the delayed results delivery.

In conventional radiotherapy, ionization chambers are used as secondary standard dosemeters. However, the recombination effect in the chambers limits the usability in ultra-high pulse dose rate applications. To investigate this effect, seven different types of chambers have been investigated and the best suited commercially available plane parallel ionization chamber (Advanced Markus) was studied in more details.

3. To develop traceable and validated methods for **relative dosimetry (WP2)** and for the **characterisation of stray radiation** outside the primary pulsed particle beams **(WP4)**.

Relevance:

The goal of this objective was to establish a reliable and accurate method for measuring the dose of radiation in a given location and comparing it to a known standard. This ensured that measurements can be repeated and compared across different detection systems use, for example active detectors based on the Timepix3 chips and passive detectors TLD and OSL and film dosimetry and beam current monitors.

Stray radiation:

The characterisation of stray radiation outside the primary pulsed particle beams was carried out within the WP4. This stray radiation can cause unwanted dose to surrounding tissues and can have an impact on the overall effectiveness of the therapy. The goal is to develop reliable and accurate methods for measuring stray radiation levels, so that they can be minimized and kept within safe limits. In this work, selected active and passive detectors for the measurement of scattered and secondary radiation produced in a water or water-equivalent phantom, air, and the treatment room by UHPDR primary proton and electron beams were used. The overall results point out the best practice guide in using each type of investigated detectors either inside or outside of a phantom.

ADVACAM developed high-granularity active pixel detector Timepix3 in a customized MiniPIX-Timepix3 FLEX configuration. This detector was used for characterization of stray radiation in proton and electron beams in a wide range of dose rates up to UHDR levels. The suitability of Timepix3 detector for measuring the deposited energy, dose and Linear energy transfer (LET) in UHPDR proton beam was tested. A linear response of measured deposited energy in the Si sensor of a Timepix3 chip operated in frame mode was obtained when delivering DR ranging from ~0.2 Gy/s up to ~270 Gy/s in the entrance region of the depth-dose curve.

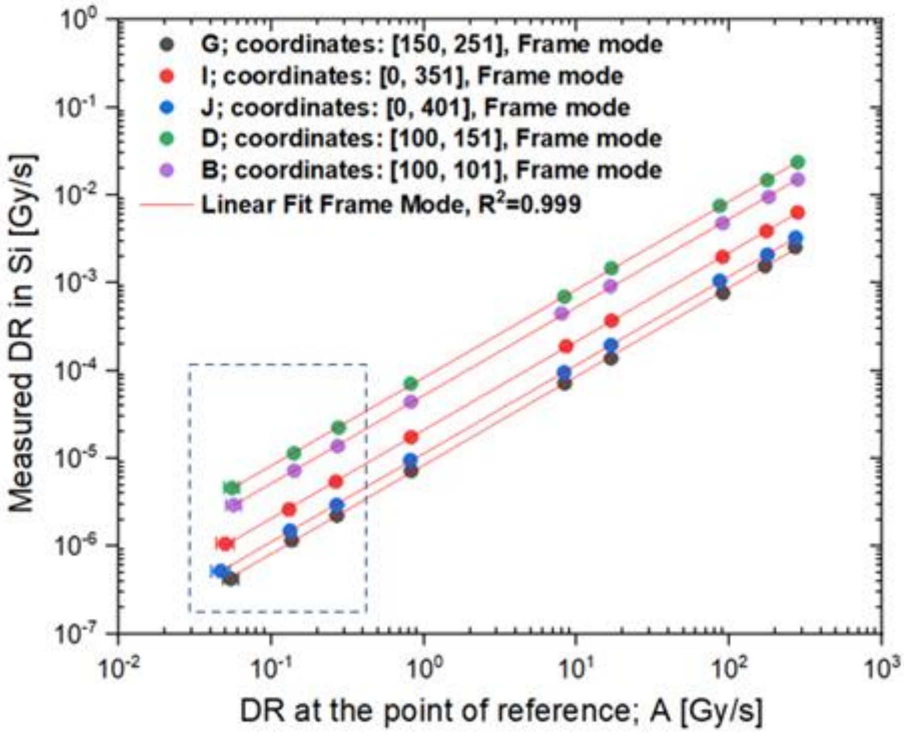

Figure 4: Measured dose rate in the Timepix3 detector with a silicon sensor of 500 µm (Y axis) in a wide range of delivered dose rates (X axis) at the reference point. Results given for out-of-field locations both conventional and UHDR regions (left and right regions along the X axis) (Oancea et al., 2023).

The LET spectra display the same shapes regardless of the DR and the field composition at certain location does not change when increasing the DR from conventional to UHDR levels. Therefore, to quantify these values either conventional or UHDR beams can be used depending on the irradiation facility or the position of the detector inside the water phantom.

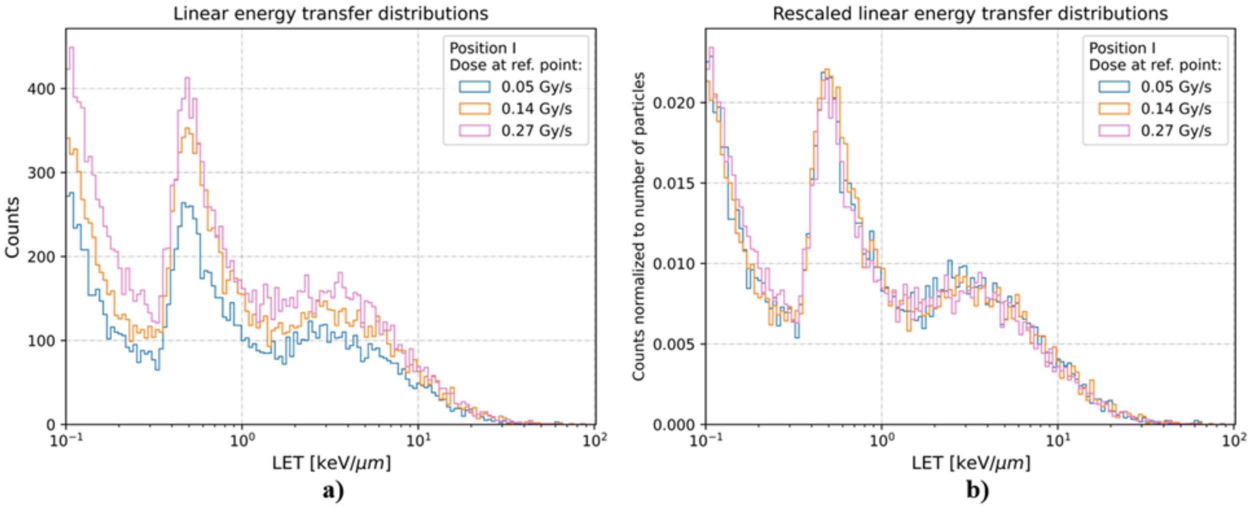

Figure 5: LET spectra measured by Timepix3 behind the Bragg peak at coordinates [0, 263], position I, for data collected in data-driven mode at low-intensity field, corresponding to max $D_{ref.\ point}$ of 0.270 Gy/s. The a) absolute distribution of LET in Si is shown b) normalized by the measured number of particles (Oancea et al., 2023).

In addition, a method for enhanced detection, imaging, and measurement of the thermal neutron flux created by 20 MeV electron beam at PTB. For this purpose, a semiconductor pixel detector Timepix3 with a silicon sensor partially covered by a 6LiF neutron converter was used to measure the flux, spatial, and time characteristics of the neutron field. To provide absolute measurements of thermal neutron flux, the detection efficiency calibration of the detectors was performed in a reference thermal neutron field. Neutron signals are recognized and discriminated against other particles such as gamma rays and X-rays. This is achieved by the resolving power of the pixel detector using machine learning algorithms and high-resolution pattern recognition analysis of the high-energy tracks created by thermal neutron interactions in the converter. The resulting thermal neutrons equivalent dose was obtained using conversion factor (2.13(10) pSv·cm2) from thermal neutron fluence to thermal neutron equivalent dose obtained by Monte Carlo simulations. The calibrated detectors were used to characterize scattered radiation created by electron beams. The results at 12.0 cm depth in the beam axis inside of the water for a delivered dose per pulse of 1.85 Gy (pulse length of 2.4 µs) at the reference depth, showed a contribution of flux of 4.07(8)×103 particles·cm-2·s-1 and equivalent dose of 1.73(3) nSv per pulse, which is lower by ~9 orders of magnitude than the delivered dose.

Passive BeO-OSL and LiF TL dosimeters were also prepared by FZU and UJF CAS and tested at stray radiation of FLASH electron and UHDR proton beam, resulting in precision on the absorbed dose of a few percent, if proper preparation and the readout procedure.

Four different measurement systems of NPL, PoliMi and PTB dedicated specifically for neutron spectrometry and dosimetry outside of a water or water-equivalent phantom have been tested and compared in the stray neutron fields of a medical linac and a FLASH electron accelerator. Their capabilities and limits of operation in the pulsed mixed fields were investigated. An overall good agreement of the results in terms of derived neutron fluence and neutron dose was achieved, given the systems are completely independent and based on different neutron detection principles.

Best Practice Guide for the characterization of stray radiation outside the UHPDR primary particle beam was created and published. This document describes and provides recommendations on the use of selected active and passive detectors for the measurement of scattered and secondary radiation produced in a water or water-equivalent phantom, air, and the treatment room by UHPDR primary proton and electron beams. The overall results point out the best practice guide in using each type of investigated detectors either inside or outside of a phantom.

Relative dosimetry:

Relative dosimetry is used for beam monitoring and for measuring the 3D dose distribution. The former is done either with a transmission ionisation chamber or a beam charge/current monitor. An AC current transformer (ACCT) from Bergoz attached to the beam exit of the clinical electron accelerator Mobetron at CHUV is shown in figure 6. At METAS' and PTB's research electron accelerators, integrating current transformers (ICTs) also from Bergoz were used to monitor the FLASH beams. METAS and CHUV calibrated their transformers with a reference charge source from PTB for absolute charge measurement. For beam monitoring, however, the beam current monitors must be calibrated for dose measurement. Such a calibration is shown in Figure 6. For this purpose, the charge measurement with the ACCT was related to the dose measurement with film at CHUV at ultra-high dose rate. Similar measurements were also made at PTB and METAS with their respective ICTs, except that the dose was determined using alanine or Fricke dosimeters.

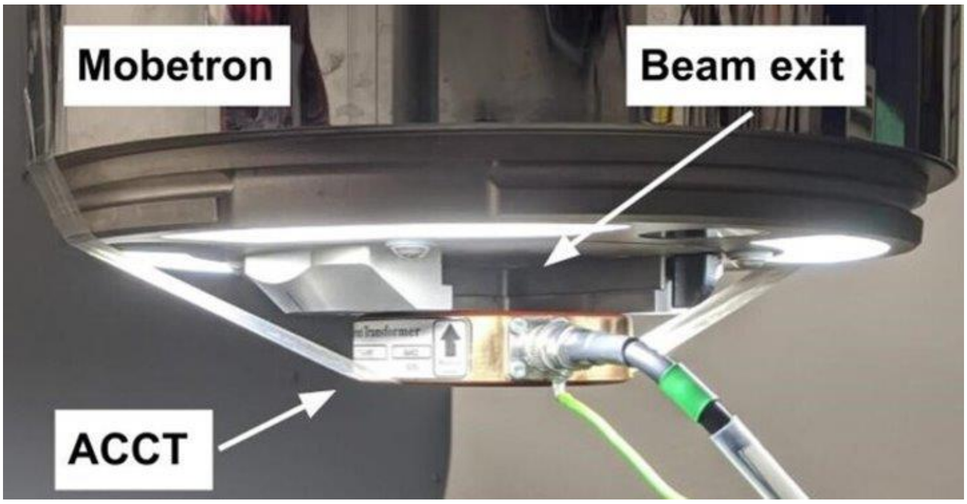

Figure 6: An ACCT attached to the beam exit of the Mobetron at CHUV

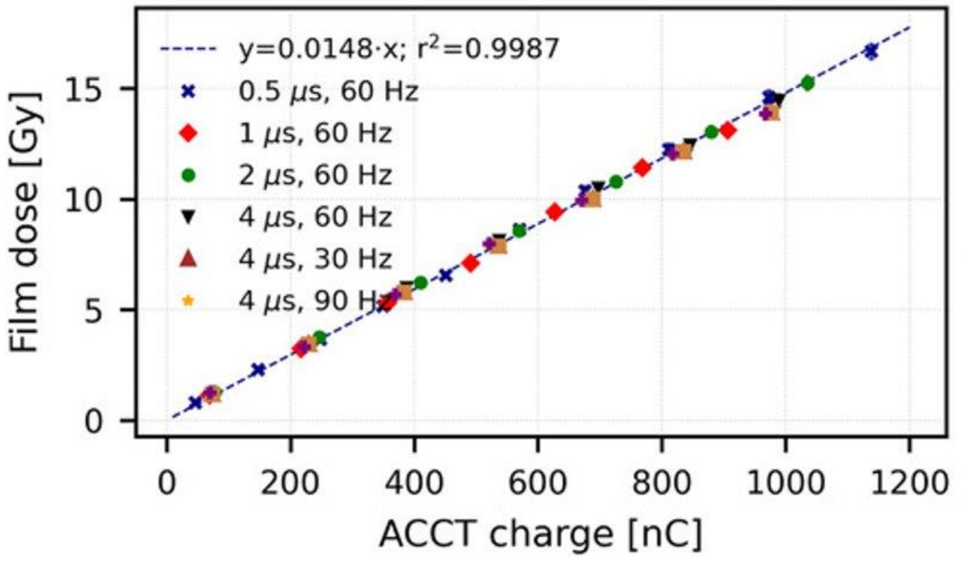

Figure 7: ACCT charge measurement vs. dose measurement with film dosimetry

The 3-dimensional (lateral and depth dose) dose distribution had to be carefully determined in the emerging pre-clinical beams from laser-driven proton accelerators and VHEE facilities using film and Alanine dosimetry. A setup for relative depth dose measurements in the VHEE beam at CLEAR facility is shown in figure 7. The measured 2-dimensional dose maps at different depths are depicted in figure 8. Excellent agreement with results from Monte Carlo simulations was found.

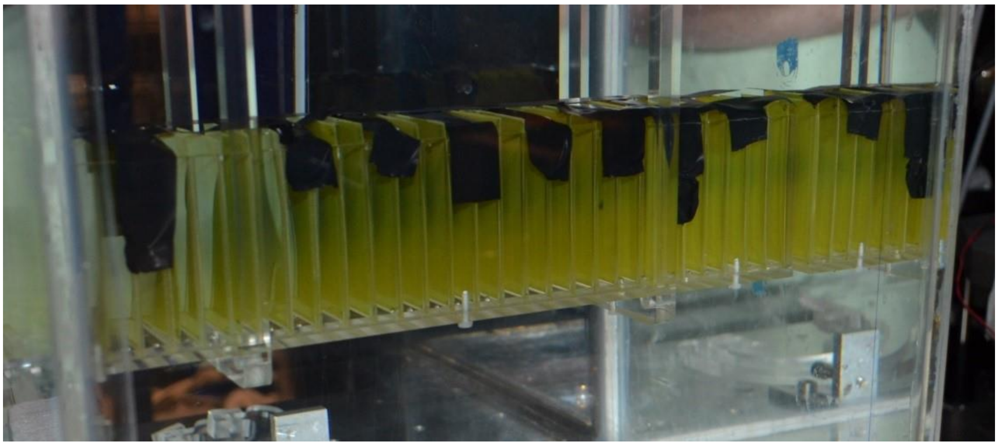

Figure 7. Setup for relative depth dose measurements with radiochromic films in a water tank

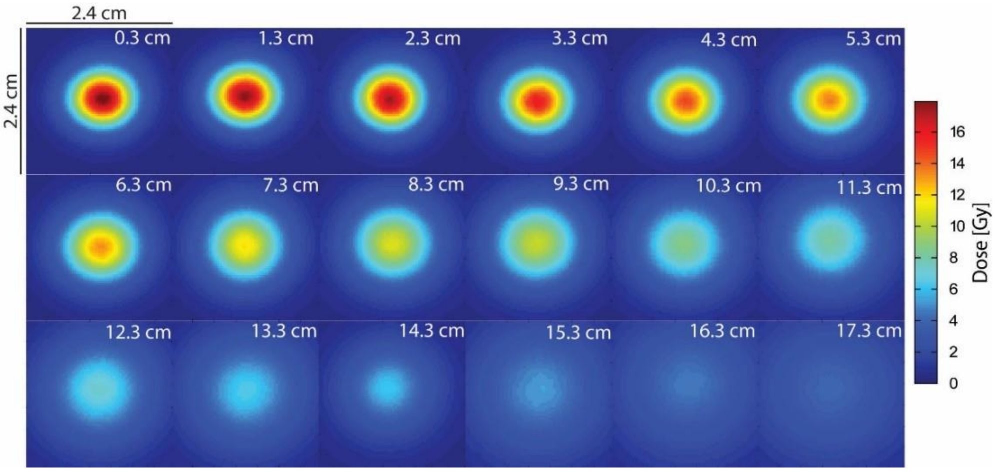

Figure 8. Two-dimensional dose maps captured on EBT-type film for the 165 MeV electron beam in planes normal to beam central axis at different depths (given in cm in the corner of each film) in the water phantom

4. Using the results from objectives 1-3, to provide the **input data for Codes of Practice** for absolute dose measurements in particle beams with ultra-high pulse dose rates **(WP2 & WP3)**.

Relevance:

Clinical and pre-clinical experiments with FLASH rely on precise and comparable dose determination. This can only succeed if the measurement is carried out according to uniform protocols. Within the framework of Objective 4, such protocols were extended and further developed for the use of dosimetry in UHDR beams. Care was taken to use established protocols (IPSM, DIN 6800-2, AAPM TG-51 and TG-25, and IAEA TRS-398 and TRS-381) as a basis. Fundamental questions such as: What are the characteristics of FLASH radiation? and What are the beam parameters of existing FLASH facilities? had to be answered first. Recommendations for a dosimetry protocol (Code of Practice) for traceable absorbed dose measurement in ultra-high pulse dose rate electron beams under reference conditions were summarized in Deliverable D8. It is a collaborative work with contributions and data from CHUV, Curie, NPL, PTB, PTW and USC.

Reference conditions:

For a reliable and comparable dose determination, reference conditions are needed under which the measurements should be carried out. A summary of the relevant parameter that are different from the ones used in conventional RT is given in the following.

- Dose and dose rate: The dose should be defined in terms of dose per pulse (total dose delivered within one pulse), DPP, rather than dose rate (total dose delivered in a defined time unit) as this parameter seems to be more relevant for dosimetry in UHDR.
- Beam energy/quality: The beam quality index remained the half-value depth of the depth-dose profile in water R_{50}. The following protocol is for beam energy ranging between 3 MeV to 50 MeV. The standard reference conditions for electron beams at conventional dose rate cannot be fulfilled in general by UHDR electron beams and thus the approximation of the relationship between the R_{50} value and the energy of the beam at phantom surface, E_0, will be less accurate.
- Pulse repetition frequency, length, and shape: The Pulse Repetition Frequency (PRF) should be reported. The following protocol is for a range of PRF between 5 Hz to 500 Hz. The pulse length should be systematically reported for any publication. The following protocol is for a range of pulse width between 1 µs to 10 µs.
- Field size, flatness, and symmetry: The field size is defined to be the FWHM of the radial beam relative dose profile (along a perpendicular direction to the beam axis). The field size should be at least of 5 cm diameter (for circular beam) or a 5 cm by 5 cm square. The flatness should be evaluated at the depth of measurement (z_{ref}). The absorbed dose variation due to the beam delivery should be smaller than 5.0 % in the detector sensitive volume and the radial beam profile correction factor (P_{rp} in TG-51 addendum) [2], or volume averaging correction factor, due to beam fluence non-uniformity should be smaller than 2.5 %.

Relative measurements:

The relative measurement, such as depth dose curve and profile measurement, should be performed with detectors that are shown to not have dose per pulse (DPP) dependence such as FLASH diamond, calorimeter, EBT3 film or any other detectors with verified dose-response linearity up to the maximum DPP to be measured. Relative measurements can be performed with an ionization chamber with additional precaution. The charge collection efficiency (CCE) can change drastically throughout the depth-dose curve and profile, especially for ionization chambers with large electrode space. The ionization chamber raw charge measurement must be corrected ksat before normalizing the measurements to the maximum (for PDD) or the beam centre (for profile).

Absolute measurements:

The use of a commercially available ionization chamber as a secondary standard in UHDR electron beams to determine the absorbed-dose to water is at the moment not recommended as the charge collection efficiency is greatly reduced in UHDR electron beam. This led to an increase in the uncertainty achievable using such a dosimeter, exceeding the 1 % level required in the clinic. The use of Alanine pellets, Calorimeter or Fricke dosimeter to evaluate the absolute dose to water would be more advisable at the moment. However, as most research institutions do not have access to such detectors, and pre-clinic research does not always need to reach an uncertainty below 1 %, the consortium prepared a corresponding protocol. A further development of ionisation chamber, the so-called Ultra-Thin Ionization Chamber (UTIC) have a typical electrode separation of 0.25 mm which corresponds to a compromise between low ion recombination effect, signal size, assembly reproducibility and mechanical robustness. The use of these chambers should follow the existing recommendations except for the saturation effect evaluation.

Alanine dosimetry has been shown to be largely dose rate independent. The biggest challenge to establish alanine dosimetry as a secondary standard for UHDR electron beam in research, pre-clinical and clinical institutions is therefore the required expertise, specialized equipment (EPR spectrum system) and time to achieve high accuracy and low uncertainty on the preformed measurements. However, another option is to take advantage of a mail alanine dosimetry service such as the ones provided by NPL or NRC, which could serve as reliable dosimetry assessment for UHDR electron beams.

It has been known for some time that radiochromic film is dose rate independent. That is why many of the FLASH experiments to date have relied on dose determination with this system. Radiochromic films can be preferred for their tissue equivalency, energy and beam quality independence, high spatial resolution, and thin and flexible structure. They are particularly favoured in pre-clinical experiments that use small fields and/or small scattering volumes and often need skin dosimetry.

The findings from the project provide direct input to the work of the American Association of Physics in Medicine Task Group No. 359. Several members of the project consortium belong to the AAPM TG 359.

5 Impact

The consortium published 38 open-access papers in peer-reviewed scientific publications, such as Scientific Reports, Frontiers in Physics, Physica Medica, Medical Physics, and Physics in Medicine and Biology. In addition, partners participated in national and international conferences with 91 oral presentations and 29 posters. An event, that merged the 3rd FLASH workshop, the INSPIRE project workshop, and the UHDpulse stakeholder workshop, was held in December 2021. The COVID-19 lockdown in Austria a week before the event forbade participation on-site. However, a full online event was a great success with more than 700 participants from over 40 countries and 30 contributions from the project partners. The final UHDpulse workshop for stakeholders was organised in January 2023 in the Czechia.

Impact on industrial and other user communities

The project provided the metrological tools needed by (medical) physicists and radiobiologists to perform traceable dosimetric measurements in clinical or pre-clinical Ultra-High Pulse Dose Rate (UHPDR) particle beams. This has improved radiobiological, pre-clinical, or clinical studies on the effect of UHPDR irradiations by ensuring better comparability between studies carried out in different facilities as well as with conventional radiotherapy treatment modalities. Ultimately, it ensured that cancer patients who were treated by UHPDR particle beams received the prescribed dose. The work carried out within the scope of this project had already provided traceability of the FLASH proton beam at Cincinnati Proton Centre to the UK's primary standard. This work enabled the US centre to receive FDA approval to initiate the first worldwide clinical trial on FLASH proton RT. The first patient was treated in November 2020.

The definition of reference conditions for dosimetry in UHPDR particle beams together with the availability of well-characterised and optimised irradiation facilities, as a result of this project, allowed manufacturers of detector and measurement equipment to characterise and calibrate existing and novel detectors for dosimetry of UHPDR particle beams. The increased knowledge gained in the project related to methods for precise measurement of absorbed dose to water in such beams enabled manufacturers to develop the necessary devices for the safe clinical application of UHPDR particle beams in advanced radiotherapy. This fostered the competitiveness of European manufacturers of radiotherapy and dosimetry equipment.

Impact on the metrology and scientific communities

For reference dosimetry in conventional radiation therapy, several types of primary standards for absorbed dose to water were available (mainly water and graphite calorimeters), whose equivalency was regularly verified by international key comparisons organised by the Bureau International des Poids et Mesures (BIPM). Within this project, the dose-rate limits of application of existing primary standards were extended, and new prototype calorimeters applicable in Ultra-High Pulse Dose Rate (UHPDR) particle beams were developed. Additional international dosimetry comparisons might have become needed and could have been undertaken based on facilities and primary standards adapted for UHPDR beams in this project.

The data and information obtained in this project related to the behaviour of secondary standards as a function of dose rate supported the development and improvement of theoretical models of the response of dosimetric detectors (e.g., charge recombination of ionisation chambers). It generally led to a better understanding and adequate theoretical description of the response of dosimetric detectors in UHPDR particle beams.

Impact on relevant standards

In conventional radiotherapy, dosimetry was traditionally based on nationally and internationally standardised Codes of Practice (CoP), which were not directly applicable to Ultra-High Pulse Dose Rate (UHPDR) particle beams. However, within this project, a metrological infrastructure and a validated formalism for dosimetry in UHPDR beams were developed, contributing significantly to a future update or revision of existing CoPs to extend their field of application. This advancement allowed (medical) physicists and radiobiologists to perform dosimetric measurements in clinical or pre-clinical UHPDR particle beams with a level of uncertainty comparable to that achievable in conventional radiotherapy.

The consortium's established connections with national standardisation bodies (IPEM, DIN) and international standardisation bodies facilitated the smooth incorporation of the project's results into a future CoP for dosimetry in UHPDR particle beams. Additionally, UHDpulse partners (Institut Curie, NPL, USC, PTW) actively participated in the newly formed AAPM-ESTRO joint Task Group No. 359 (TG359) - FLASH (ultra-high dose rate) radiation dosimetry to integrate the UHDpulse findings into the recommendations, standards, and guides of this task group. The NPL representative served as the official liaison between AAPM TG359 and UHDpulse.

Furthermore, the close collaboration between hospitals, dosimetry equipment manufacturers, and national metrology institutes fostered the widespread adoption of the CoP among the broader hospital community. Recent efforts involved presenting consortium activities and research results to various organisations, such as EURAMET TC-IR, European Federation of Organisations for Medical Physics (EFOMP), and European Radiation Dosimetry Group (EURADOS), further promoting the significance and impact of the project's findings in the field of dosimetry.

Longer-term economic, social and environmental impacts

Cancer incidences are expected to significantly increase due to the ageing of the European population. Approximately half of the cancer patients in Europe were treated by radiotherapy, the most cost-effective strategy in oncology. Therefore, innovation and clinical advancement in radiotherapy, such as FLASH radiotherapy, were expected to significantly contribute to the quality of life by increasing long-term cancer survival (especially important for children) and reducing the occurrence and severity of early and late complications affecting normal tissue.

The research done in this project contributed and will continue to contribute to the definitive demonstration of the feasibility of using laser-driven beams for therapeutic purposes, providing a large group of European patients with faster access to more advanced, more cost-effective, and safer radiotherapy treatments. In addition, this project promoted future industrial developments of laser-driven irradiation facilities.

6 List of publications

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