Publishable Summary for 18HLT04 UHDpulse
Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

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.

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.

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).

Progress beyond the state of the art

Within the UHDpulse project, reviews about the recent advances of the state of the art were published (see https://doi.org/10.1259/bjr.20220560 and https://doi.org/10.1002/mp.15649 . In this project, for the first time, reference radiation fields for electron beams with ultra-high dose per pulse, comparable to fields used for FLASH radiotherapy, were developed, optimised, commissioned, and compared against each other. Correction factors, needed for Codes of Practice for FLASH radiotherapy, were determined, and novel dedicated dosimetry systems for this new treatment modality were calibrated. Furthermore, different methods for a corresponding primary standard were adapted, examined and compared against each other. The outputs of this project provided a calibration chain up to an adequate primary standard for FLASH radiotherapy both for treatment with electrons and with protons. The suitability of different commercially available detector systems, as a secondary standard for UHPDR electron beams, was also investigated. This project contributed to the generation of roadmaps for the development of future primary standards suitable for novel laser-driven medical accelerators.

The project also investigated the capabilities of different commercially available dosimetry systems as well as novel active detectors, such as PTW's flashDiamond or ultra-thin parallel plate ionisation chamber for dedicated dosimetry at UHPDR particle beams. Further types of custom-built detectors (e.g. active pixel detectors) were optimised or/and redesigned for UHPDR particle beams for the primary beam as well as for the stray radiation field. The suitability of investigated detector systems for relative dosimetry in UHPDR electron beams has been thoroughly studied, leading to valuable recommendations for necessary correction factors. Additionally, comprehensive research was conducted to establish traceable and validated methods for relative dosimetry in emerging pre-clinical laser-driven beams. Moreover, significant efforts were made to develop robust methods for characterising stray radiation outside the UHPDR primary particle beam. This involved implementing active detection techniques through the optimisation of a custom-built detector capable of handling short radiation pulses and accurately characterising radiation components. Specifically, a custom-built detector, based on Timepix3 chips, was fine-tuned to enable active measurement of single pulses of electrons/protons and enable field characterisation (including identification of scattered particle components).
To ensure standardised practices and guidelines, a Best Practice Guide was created, providing recommendations and guidelines for characterising stray radiation outside the UHPDR primary proton and electron beams using selected active and passive detectors.
Additionally, the project created a validated formalism for traceable absorbed dose measurement in ultra-high pulse dose rate electron beams under reference conditions protocol. The results of this project directly contribute to a future Code of Practice for dosimetry at FLASH radiotherapy, which AAPM TG-359 is working on.

Results

Objective 1: SI-traceable primary and secondary reference standards

The document reviewing FLASH beam parameters has been generated, with the most relevant parameters grouped according to associated biological outcomes. METAS and PTB optimised their UHPDR electron beams which were used for further characterisation of devices within the project. The technical details for both beamlines and their characteristics were included in the report describing the new reference beams for dosimetry in electron beams with UHPDR. Both METAS and PTB established their primary standards, i.e. Fricke dosimetry and water calorimetry, respectively for the UHDR pulsed electron dosimetry. Subsequently, both standards were compared through an independent route using NRC's (National Research Council of Canada) alanine dosimetry system traceable to NRC's primary standard. The agreement between these two standards was 1.002 ± 0.012.

GUM developed and characterised a portable graphite calorimeter as a primary standard for absorbed dose to water, tested it at PTB's ultra-high pulse dose rate reference electron beam, and compared the measurements against the PTB's alanine dosimetry system. The 0.2% agreement was reached with a combined standard uncertainty of 1 %. NPL evaluated their portable graphite calorimeter for dosimetry of UHDR proton beams and provided traceability to the Cincinnati Children's Hospital Medical Center for the implementation of the FAST-01 clinical trial. The measurements were provided with an uncertainty of 0.9% (k=1). The report including the details on the traceability of these measurements has been published. The calorimetric measurements have been completed for 200 MeV very high energy electron beam and associated Monte Calculations have been carried out to calculate graphite to water conversion factor and relevant correction factors for the experimental conditions used. This work was essential to evaluate Roos chamber ion recombination correction factors which were evaluated in the project for the VHEE beam. Additionally, a small portable graphite calorimeter (SPGC) was used to perform the first calorimetry measurements in a laser environment.

In general, in conventional radiotherapy, ionisation 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 were investigated up to 6.2 Gy per pulse at a pulse length of 2.5 ms. The commercially available plane-parallel ionisation chamber "Advanced Markus" was studied in more detail. Several detectors of this type were compared and showed intra-type variations of up to 10%. Further dosimetry systems were analysed for their suitability to be used in absolute dosimetry in ultra-high doses per pulse beams. The Fricke solution in small bags can be used for absolute dosimetry up to 1 Gy/pulse. Beyond that, an empirical correction function needed to be applied, which was determined in this project. The PTB's Alanine/ESR dosimetry system was studied in the characterised PTB reference UHPDR electron beam. The required correction factor for beam shape and beam quality was studied using the Monte Carlo model of the PTB research linac. The relative response of the Alanine/ESR secondary standard dosimetry system has shown a very close to linear relationship with the beam charge measurements by means of a current transformer (ICT). However, the ICT to alanine/ESR ratio depends on the geometry and a dedicated calibration of the ICT remains necessary. For film dosimetry, linearity against a few pulses (i.e., total dose) and against pulse duration (i.e., dose-per-pulse), repeatability of optical density measure, reproducibility of the total dose measurement process (irradiation, optical density reading and dose conversion), as well as ageing dynamics were assessed in FLASH mode up to a total dose of 30 Gy and a dose-per-pulse of 3 Gy per pulse. Diamond detectors were also of central importance. During the project, the flashDiamond was developed and showed a linear behaviour of up to 26 Gy per pulse. This detector was commercialised by PTW. An overview of the different systems is given in a recently submitted review paper.

NPL developed a 20 cm × 20 cm × 10 cm PMMA phantom. The setup allowed the incorporation of the Roos chamber to accommodate the IMRT calorimeter at a specific water equivalent thickness (WET) and allowed side-by-side measurements. The characterisation of the PTW Roos chamber as a function of dose-per-pulse was carried out at the VHEE CLEAR facility at CERN from 0.03 to 5.6 Gy per pulse. For the highest dose per pulse, the ion collection efficiency of the Roos chamber fell to approximately 10% when operating the chamber at 200 V. The acquired data set was used to test the available ion recombination models for the PTW Roos chamber and was published. Finally, a report on relative dosimetry for VHEE and laser-driven beams using radiochromic films was written and published. To make measurements of UHD pulses comparable, reference conditions have been defined. Starting from IAEA TRS-398, a table containing a set of relevant parameters was prepared and was continuously amended by the collaborators. A beam specifier, an empirical quantity accessible by measurements, had to be found. The combination of the three independent values Dose-per-pulse (DPP), Pulse duration/length (PL) and Pulse Repetition Frequency (PRF) was identified. Furthermore, the reference conditions depend on the medical requirements and the beam parameters achievable by the existing FLASH machines. These findings were compiled in a conventional protocol, that was mainly based on the available electron beam Codes of Practice (CoPs). It included the required modification for the particularity related to the Ultra-High Dose (UHD) rate electron beam. Further work towards a UHDR beam code of practice was not possible due to the lack of maturity of the field. Radiobiological experiments did not identify a FLASH effect metric and it remains the first goal to achieve before defining an accepted code of practice. In the meantime, the UHDpulse participants have reported their experiments using the identified beam specifier.

In summary, the objective to develop SI-traceable primary and secondary reference standards and validated reference methods for dosimetry measurements for particle beams with ultra-high pulse dose rates was achieved, however, the establishment of these methods still requires further work.

Objective 2 – Characterisation of the response of available detector systems

For the following detector systems, the response in particle beams with ultra-high pulse dose rates was investigated: ionisation chambers, as PTW Roos, PTW Advanced Markus, IBA PPC05, IBA PPC40, IBA NACP02, IBA Razer Nano, Sun Nuclear SNC350p, and different ultra-thin plane-parallel ionisation chamber prototypes, solid state detectors as PTW microDiamond, PTW flashDiamond, PTW microSilicon, Sun Nuclear EDGE detector, CSIC's silicon carbide diode, and semiconductor pixel detectors based on Timepix3 read-out chip with and without a silicon sensor, calorimeters, as NPL's SPGC calorimeter, NRC's aluminum calorimeter, GUM's graphite calorimeter, and Sun Nuclear's Aerrow graphite problem calorimeter, as well as passive dosimetry systems as, Alanine, TLD, OSDL, Gafchromic EBT3, and EBT-XD. Numerous publications describe the obtained results.

In summary, the objective to characterise the response of available detector systems in particle beams with ultra-high pulse dose rates was achieved.

Objective 3 - Methods for relative dosimetry and for the characterisation of stray radiation

i. Methods for relative dosimetry

A monitoring system based on current transformers (2 ACCT detectors) was installed and tested on the eRT6 (PMB-Alcen), the electron accelerator for FLASH RT at CHUV. It was found that the calibration wasn't universal (within 5 %) and it was dependent on beam parameters, such as pulse width, dose rate or collimators. Therefore, calibration procedures, tailored for specific beam parameters, were commissioned to keep uncertainties on calibration factors below 10 %. In addition, the current transformer system was tested on the commercially available FLASH accelerator “IntraOp Mobetron” and showed great use and reliability within the known limitations. Following these investigations, commercial companies are now offering inductive monitoring as upgrades (such as IntraOp) and are integrating such systems in their products (SIT, PMB-Alcen). Lately, a new system with a larger dynamic range was implemented to develop further the system. The first tests were successful and will lead certainly to the adoption of such systems in the future. In addition, many detectors were developed in the framework of the project, which have a strong potential for relative dosimetry. Customised diamond detector prototypes were designed, realised and validated in ultra-high DPP conditions. Silicon carbide (SiC) diodes suitable for ultra-high DPP real-time dosimetry were also designed and fabricated.

ii. Characterisation of stray radiation

The semiconductor pixel detector module based on a novel TimePIX3 chip was optimised for operation immersed in a water phantom. Its material composition was made of graphite fibre substrate to minimise disturbances of the measured radiation field. Several prototypes with various sensor materials and thicknesses were developed. Firstly, the suitability of this detector for measuring the deposited energy, dose, Linear Energy Transfer spectra (LET), and thermal neutron fluence in the UHDR proton beam was tested. A linear response of measured deposited energy in the Si sensor of a Timepix3 chip 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. In conclusion, it can be stated that the customised Minipix Timepix3 detectors can be successfully used inside water phantoms for the characterisation of stray and secondary radiation fields generated by UHDPR beams.

Secondly, the Timepix3 detectors were used to characterise stray radiation in UHDR electron beams at the PTB facility. Secondary particles such as thermal neutron interactions were identified and discriminated against background radiation. Characteristic tracks created by the interaction of thermal neutrons with a 6LiF converter positioned above part of the pixel detector resulted in the emission and detection of alpha and tritium particles. The reaction products were selectively identified thanks to the detector's high granularity and per-pixel spectral response. The results at 12 cm depth in the beam axes inside of the water phantom for a delivered dose of 1.85 Gy and pulse length of 2.5 µs showed a contribution of thermal neutron flux of 814 ± 15.80 particles cm-2 per pulse and equivalent dose of 1.70 ± 0.03 nSv per pulse at the detector position. In conclusion, the Timepix3 detector with a thermal neutron converter is suitable for measuring the flux and equivalent dose created by thermal neutrons in both electron and proton beams. This serves to examine and characterise the stray radiation and estimate the impact of thermal neutrons on healthy tissue surrounding the tumour. On the other hand, the measurements performed in electron beam at the Microtron facility with a delivered dose-per-pulse of 0.09 Gy/pulse at a frequency of 423 Hz allowed for a more detailed particle type classification resolving individual electrons and photons, in addition to the thermal neutrons. Passive BeO-OSL and LiF TL dosimeters were used in a similar setup to characterise the absorbed dose created by stray radiation in UHDR electron and proton beams.

In addition to the above-mentioned active and passive detectors, 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.
The output of this objective was summarised in a document entitled “Best Practice Guide for the characterisation of stray radiation outside the UHPDR primary particle beam”. In this document were described recommendations on the use of selected active and passive detectors for the characterisation of scattered and secondary radiation produced in a water or water-equivalent phantom, air, and treatment room by UHPDR primary proton and electron beams. The overall results point out the best practice guide in using each type of investigated detector either inside or outside of a phantom.

In summary, the objective to develop traceable and validated methods for relative dosimetry and for the characterisation of stray radiation outside the primary pulsed particle beams was achieved.

Objective 4 – Codes of Practice

A document with recommendations for a dosimetry protocol for traceable absorbed dose measurement in ultra-high pulse dose rate electron beams under reference conditions was drafted. It would be mainly based on the available electron beam Code of Practice with modification for the ultra-high dose rate electron beam. It is recommended to keep using the current protocols in place in the clinic and apply the modification proposed. Recommendations include reference conditions, phantoms and electrometers, dosimetry using commercially available ionisation chambers and ultra-thin ionisation chambers, alanine dosimetry, film dosimetry, as well as dosimetry using flashDiamond. These recommendations were provided to AAPM Task Group No. 359 "FLASH (ultra-high dose rate) radiation dosimetry" for the TG359 guidelines.

In summary, the objective to provide the input data for Codes of Practice for absolute dose measurements in particle beams with ultra-high pulse dose rates was achieved.

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.

List of publications:

1. M. McManus et al. The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams, Scientific Reports, https://doi.org/10.1038/s41598-020-65819-y
2. Andreas Schüller et al. The European Joint Research Project UHDpulse - Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates, Physica Medica: European Journal of Medical Physics, https://doi.org/10.1016/j.ejmp.2020.09.020
3. Francesco Romano et al. Challenges in dosimetry of particle beams with ultra-high pulse dose rates, Journal of Physics: Conference Series, https://doi.org/10.1088/1742-6596/1662/1/012028
4. Alexandra Bourgouin et al. Calorimeter for Real-Time Dosimetry of Pulsed Ultra-High Dose Rate Electron Beams, Frontiers in Physics, https://doi.org/10.3389/fphy.2020.567340
5. Karolina Kokurewicz et al. Dosimetry for New Radiation Therapy Approaches Using High Energy Electron Accelerators, Frontiers in Physics, https://doi.org/10.3389/fphy.2020.568302
6. Daniela Poppinga et al. VHEE beam dosimetry at CERN Linear Electron Accelerator for Research under ultra-high dose rate conditions, Biomedical Physics & Engineering Express, https://doi.org/10.1088/2057-1976/abcae5

7. Rafael Kranzer et al. Ion collection efficiency of ionization chambers in ultra-high dose-per-pulse electron beams, Medical Physics, https://doi.org/10.1002/mp.14620
8. Pankaj Chaudhary et al. Radiobiology Experiments With Ultra-high Dose Rate Laser-Driven Protons: Methodology and State-of-the-Art, Frontiers in Physics, https://doi.org/10.3389/fphy.2021.624963
9. Cristina Oancea et al., Stray radiation produced in FLASH electron beams characterized by the MiniPIX Timepix3 Flex detector, Journal of Instrumentation, https://doi.org/10.48550/arXiv.2201.13171
10. Michael McManus et al. A Geant4 Fano test for novel very high energy electron beams, Physics in Medicine and Biology, https://doi.org/10.1088/1361-6560/ac3e0f
11. Marco Marinelli et al. Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry, Medical Physics, https://doi.org/10.1002/mp.15473
12. Alexandra Bourgouin et al., Characterization of the PTB ultra-high pulse dose rate reference electron beam, Physics in Medicine and Biology, https://doi.org/10.1088/1361-6560/ac5de8
13. Alexandra Bourgouin et al. The probe-format graphite calorimeter, Aerrow, for absolute dosimetry in ultra-high pulse dose rate electron beams, Medical Physics, https://doi.org/10.1002/mp.15899
14. Alexandra Bourgouin et al., Absorbed-dose-to-water measurement using alanine in ultra-high-pulse-dose-rate electron beams, Physics in Medicine and Biology, https://doi.org/10.1088/1361-6560/ac950b
15. Alexandra Bourgouin et al., The PTB water calorimeter for determining the absolute absorbed dose to water in ultra-high pulse dose, Physics in Medicine and Biology, http://dx.doi.org/10.1088/1361-6560/acce1d
16. Rafael Kranzer et al. Response of diamond detectors in ultra-high dose-per-pulse electron beams for dosimetry at FLASH radiotherapy, Physics in Medicine & Biology, https://doi.org/10.1088/1361-6560/ac594e
17. Michael McManus et al., Determination of beam quality correction factors for the Roos plane-parallel ionisation chamber exposed to very high energy electron (VHEE) beams using Geant4, Physics in Medicine & Biology, https://doi.org/10.1088/1361-6560/ac5a94
18. Patrik Gonçalves Jorge et al., Technical note: Validation of an ultrahigh dose rate pulsed electron beam monitoring system using a current transformer for FLASH preclinical studies, Medical Physics, https://doi.org/10.1002/mp.15474
19. Roxane Oesterle et al., Implementation and validation of a beam-current transformer on a medical pulsed electron beam LINAC for FLASH-RT beam monitoring, Journal of Applied Clinical Medical Physics, https://doi.org/10.1002/acm2.13433
20. Marco Cavallone et al., Determination of the ion collection efficiency of the Razor Nano Chamber for ultra-high dose-rate electron beams, Medical Physics, https://doi.org/10.1002/mp.15675
21. Faustino Gómez et al., Development of an ultra-thin parallel plate ionization chamber for dosimetry in FLASH radiotherapy, Medical Physics, https://doi.org/10.1002/mp.15668
22. Jaroslav Šolc et al., Monte Carlo Modelling of Pixel Clusters in Timepix Detectors Using the MCNP Code, Physica Medica: European Journal of Medical Physics, https://doi.org/10.1016/j.ejmp.2022.08.002
23. Gianluca Verona Rinati et al., Application of a novel diamond detector for commissioning of FLASH radiotherapy electron beams, Medical Physics, https://doi.org/10.1002/mp.15782
24. Eunsin Lee et al., Ultrahigh dose rate pencil beam scanning proton dosimetry using ion chambers and a calorimeter in support of first in-human FLASH clinical trial, Medical Physics, https://doi.org/10.1002/mp.15844

25. Rafael Kranzer et al., Charge collection efficiency, underlying recombination mechanisms, and the role of electrode distance of vented ionization chambers under ultra-high dose-per-pulse conditions, Physica Medica: European Journal of Medical Physics, https://doi.org/10.1016/j.ejmp.2022.10.021
26. Jose Paz-Martín et al., Numerical modeling of air-vented parallel plate ionization chambers for ultra-high dose rate applications, Physica Medica: European Journal of Medical Physics, https://doi.org/10.1016/j.ejmp.2022.10.006
27. Patrik Gonçalves Jorge et al., Design and validation of a dosimetric comparison scheme tailored for ultra-high dose-rate electron beams to support multicenter FLASH preclinical studies, Radiotherapy and Oncology, https://doi.org/10.1016/j.radonc.2022.08.023
28. A. Lourenco et al., Absolute dosimetry for FLASH proton pencil beam scanning radiotherapy, Scientific Reports, https://doi.org/10.1038/s41598-023-28192-0
29. P. Stasica et al., Single proton LET characterization with the Timepix detector and artificial intelligence for advanced proton therapy treatment planning, Physics in Medicine and Biology, https://doi.org/10.1088/1361-6560/acc9f8
30. Pankaj Chaudhary et al., Cellular irradiations with laser-driven carbon ions at ultra-high dose rates, Physics in Medicine and Biology, https://doi.org/10.1088/1361-6560/aca387
31. O. McCusker et al., Multi-species ion acceleration from sub-ps, PW interactions with ultra-thin foils, Plasma Physics and Controlled Fusion, https://doi.org/10.1088/1361-6587/aca1dc
32. Pankaj Chaudhary et al. Development of a portable hypoxia chamber for ultra-high dose rate laser-driven proton radiobiology applications, Radiation Oncology, https://doi.org/10.1186/s13014-022-02024-3
33. Valeriia Istokskaia et al., A multi-MeV alpha particle source via proton-boron fusion driven by a 10-GW tabletop laser, communications physics, https://doi.org/10.1038/s42005-023-01135-x
34. A.M.M. Leite et al., Ion recombination correction factors and detector comparison in a very-high dose rate proton scanning beam, Physica Medica: European Journal of Medical Physics, https://doi.org/10.1016/j.ejmp.2022.102518
35. Samuel Flynn et al., Development of CMOS dosimetry in proton minibeams for enhanced, Journal of Instrumentation, https://doi.org/10.1088/1748-0221/18/03/P03014
36. Anna Subiel and Francesco Romano, Recent developments in absolute dosimetry for FLASH radiotherapy, The British Journal of Radiology, https://doi.org/10.1259/bjr.20220560
37. Francesco Romano et al., Ultra-high dose rate dosimetry: Challenges and opportunities for FLASH radiation therapy, Medical Physics, https://doi.org/10.1002/mp.15649
38. Marco Marinelli et al., A diamond detector based dosimetric system for instantaneous dose rate measurements in FLASH electron beams, Physics in Medicine & Biology, https://doi.org/10.1088/1361-6560/acead0

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

<table>
<tr><td colspan="2">Project start date and duration:</td><td>1 September 2019, 42 months</td></tr>
<tr><td colspan="3">Coordinator: Andreas Schüller, PTB, Tel: +49 531 592-6209 E-mail: andreas.schueller@ptb.de
Project website address: http://uhdpulse-empir.eu/</td></tr>
<tr><td>Internal Funded Partners:
1. PTB, Germany
2. CMI, Czechia
3. GUM, Poland
4. METAS, Switzerland
5. NPL, UK</td><td>External Funded Partners:
6. ADVACAM, Czechia
7. CHUV, Switzerland
8. CSIC, Spain
9. Curie, France
10. FZU, Czechia
11. PoliMi, Italy
12. QUB, UK
13. UJF CAS, Czechia
14. USC, Spain</td><td>Unfunded Partners:
15. HZDR, Germany
16. PTW, Germany</td></tr>
<tr><td colspan="3">RMG: -</td></tr>
</table>