Publishable Summary for 18HLT04 UHDpulse

Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Overview

Recently, in vivo radiobiological experiments have shown that irradiation with electron beams, with ultra-high dose per pulse, may dramatically reduce adverse side effects. However, pulses with dose rates higher than conventional radiotherapy present significant metrological challenges. The next generation of accelerators in radiotherapy will deliver extreme dose rates by laser-based accelerators. It will allow the development of more efficient therapeutic techniques and healthcare at a lower cost.

Need

According to the World Health Organisation, the estimated number of new cancer cases in Europe in 2018 is about 4.2 million. Approximately half of the European cancer patients receive radiotherapy. The therapeutic window, i.e. the range of dose which provides an effective cure, is limited by adverse side effects of the radiation on the healthy tissue surrounding the tumour.

Several animal studies demonstrated that delivering radiation dose in short bursts, i.e. with only a few beam pulses of ultra-high dose per pulse, may dramatically reduce adverse side effects. Due to this so-called FLASH effect, the prescribed dose could be increased, resulting in more effective tumour control. The future application of FLASH radiotherapy requires that its performance, safety and effectiveness are reliably measured and optimised. Accurate dosimetry is vital in delivering successful radiotherapy.
Additionally, laser-driven accelerators are considered the next generation of cost-effective accelerators for radiotherapy.

Both FLASH radiotherapy and laser-driven beams cause significant metrological challenges related to the ultra-high pulse dose rates, which need to be addressed to enable the translation of these advanced radiotherapy techniques to clinical practice. The complexity and the resources needed for research in advanced radiation therapy using particle beams requires wide, multidisciplinary scientific approaches that go beyond the capabilities of a single research institute. The project and the consortium are well suited to form a nucleus for a European network for long-term metrological support for modern and emerging forms of radiotherapy.

Objectives

The overall goal of the project is 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 are:

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. 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.

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

SI-traceable primary and secondary reference standards

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, will be developed, optimised, commissioned and compared against each other. This will make it possible to determine correction factors needed for Codes of Practice for FLASH radiotherapy as well as calibrate dosimetry systems for this new treatment modality.

Furthermore, different methods for a corresponding primary standard will be adapted, examined and compared against each other. The outputs of this project will provide 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 ultrahigh pulse dose rates (UHPDR) electron beams, will be investigated.

This project will contribute to the generation of roadmaps for the development of future primary standards suitable for novel laser-driven medical accelerators. It will allow for a cost-effective generation of very high energy electrons (VHEE) and will enable further alternative advanced treatment modality known as VHEE radiotherapy.

Detector systems

The capabilities of different existing and novel active dosimetric detectors for UHPDR particle beams will be investigated. Different types of custom-built detectors will be optimised or redesigned for UHPDR particle beams for primary beam as well as for the stray radiation field. It will be possible to determine the dose at UHPDR by using active instruments in real-time, i.e. in a much more efficient way than passive dosimeters.

Relative dosimetry and characterisation of stray radiation

The suitability of investigated detector systems for relative dosimetry in UHPDR electron beams will be studied resulting in recommendations for the necessary correction factors. Furthermore, validated methods of relative dosimetry in emerging pre-clinical laser-driven beams will be investigated and published.

Stray radiation causes parasitic doses to healthy tissue and critical organs. It consists of a mix of different types of radiation. Traceable and validated methods for characterisation of stray radiation outside the UHPDR primary particle beam will be developed. Active detection techniques will be developed by the optimisation of a custom-built detector type that will cope with short radiation pulses and distinguish and characterise radiation components. A custom-built detector type will be optimised to enable active measurement and precise dose determination of pulsed neutrons (unwanted at high-energy laser-driven proton beams). A Best Practice Guide for the characterisation of stray radiation outside UHPDR beams will be published.

Codes of Practice

A protocol, i.e. a validated formalism (preferably by extending an existing Code of Practice) for traceable absorbed dose measurement in ultra-high pulse dose rate electron beams under reference conditions will be drafted and published. Results will contribute to a future Code of Practice for dosimetry at FLASH radiotherapy or help with future update or revision of an existing Code of Practice.

Results

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 outcome. The project completed the optimization of the reference radiation fields for ultra-high dose per pulse electron beam. The accelerator allows generating a FLASH-like beam with dose-per-pulse reaching 3Gy/pulse. The setup for the determination of radiation chemical yield with Fricke dosimetry has been established. The PMMA phantom has been designed and used to carry out calorimetry measurements of VHEE beams. The first set of calorimetric exposures has been performed with a 200 MeV electron beam with dose-per-pulse ranging from 0.03 to 5.26 Gy/pulse. Partners used a small portable graphite calorimeter to perform the first calorimetry measurements in a laser environment and successfully tested it in a FLASH proton beam. An experimental campaign at Cincinnati Proton Center has been completed with 200 MeV FLASH proton beams. This work provided the US centre with traceability to NPL's primary standard proton graphite calorimeter.

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 the correction factors and mathematical models, several setups will be investigated. Several established dosimetry systems have been analyzed for their suitability to serve as a secondary standard in an ultra-high dose per pulse beams, namely Fricke-, Alanine- and film-dosimetry. These systems, after comparison, were found to be in good agreement, up to 1 Gy/pulse. The response of the detectors at higher doses per pulse was and is still thoroughly investigated. A solid phantom for the application in a VHEE beam was designed and made. It incorporated a common ionization chamber (secondary standard) and a calorimeter (transfer standard). Using this experimental setup, the absolute ion recombination factors for the Roos electron chamber have been investigated for a wide range of dose per pulse (from 0.03 to 5.6 Gy/pulse) and compared with the response of the chamber against graphite calorimeter. For the highest dose per pulse, the ion collection efficiency of the Roos chamber fell to approximately 10% when operating the chamber at 200V. The current analytical ion recombination models were lacking and cannot be used to predict the behaviour of the ionization chambers in these extremely high doses per pulse conditions. In addition, phantoms for relative dose measurements with alanine pellets or radiochromic films were developed and produced.
In order to make measurements of UHD pulses comparable, reference conditions have to be defined. These strongly depend on the medical requirements and the achievable parameters of the used machines. A table with all important parameters and their respective values was compiled. A more detailed analysis of the different parameters showed that some might easily be adapted from CoP for conventional radiotherapy. Others, like beam size, were more strongly influenced by the machine settings necessary for the production of electron beams with ultra-high dose per pulse. The list is continuously improved and supplemented throughout the entire task.

Detector systems
The semiconductor detector module based on a novel TimPIX3 chip was optimized for operation immersed in a water phantom. Its material composition was made of tissue equivalent to minimize disturbances of the measured radiation field. Several prototypes with various sensor materials and thickness were developed.
An initial measurement of stray radiation was performed at electron and proton beam with the optimized TimePIX3 detectors. Satisfactory behaviour was observed already at 2 cm from the beam of 220 MeV and dose rates exceeding 160 Gy/s. Various kinds of the sensor were tested and the most suitable appeared to be the silicon 100 µm.

Relative dosimetry
A monitoring system based on 2 ACCT detectors was installed and tested on the eRT6 at CHUV. It was found that the calibration wasn't universal (within 5 %) and it depended on beam parameters, such as pulse width or dose rate or collimators. Therefore, calibration procedures, tailored for specific beam parameters, were commissioned to keep uncertainties on calibration factors below 10 %.

Impact
The consortium published 8 open access papers in peer-reviewed scientific publications, such as Nature and Frontiers in Physics. In addition, partners presented in national and international conferences more than 20 papers and posters. An event, merging the 3rd FLASH workshop, the INSPIRE project workshop and the UHDpulse stakeholder workshop, has been planned and due to be delivered in October 2021.

Impact on industrial and other user communities
The project will provide the metrological tools needed by (medical) physicists and radiobiologists to perform traceable dosimetric measurements in clinical or pre-clinical UHPDR particle beams. This will improve ongoing and future 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 will allow ensuring that cancer patients who are treated by UHPDR particle beams receive the prescribed dose. The work carried out within the scope of this project already provided traceability of FLASH proton beam at Cincinnati Proton Centre to the UK's primary standard. This work enabled the US centre to receive the FDA approval to initiate the first worldwide clinical trial on FLASH proton RT. The first patient has been 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 results of this project, will allow 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 will enable manufacturers to develop the necessary devices for the safe clinical application of UHPDR particle beams in advanced radiotherapy. This will foster 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 are available (mainly water and graphite calorimeters), whose equivalency is regularly verified by international key comparisons organised by the BIPM (Bureau International des Poids et Mesures). Within this project, the dose-rate limits of application of existing primary standards will be extended and new prototype calorimeters applicable in UHPDR particle beams will be developed. Additional international dosimetry comparisons might become needed and can be undertaken based on the 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 will support the development and improvement of theoretical models of the response of dosimetric detectors (e.g. charge recombination of ionisation chambers). It will generally lead to a better understanding and adequate theoretical description of the response of dosimetric detectors in UHPDR particle beams.

Impact on relevant standards

Dosimetry in conventional radiotherapy is done based on nationally and internationally standardised Codes of Practice (CoP), which are currently not applicable in UHPDR particle beams. In this project, a metrological infrastructure and a validated formalism for dosimetry in UHPDR beams will be developed, which will contribute significantly to a future update or revision of the existing CoPs to extend their field of application. It will allow (medical) physicists and radiobiologists to perform dosimetric measurements in clinical or pre-clinical UHPDR particle beams at a level of uncertainty, which is comparable to the uncertainty achievable in conventional radiotherapy. The consortium's existing links with both national (IPEM, DIN) and international standardisation bodies (IAEA) provides an efficient route for the uptake of the results of this project in a future CoP for dosimetry in UHPDR particle beams. UHDpulse partners (Institut Curie, NPL, USC, PTW) joined the recently established new AAPM-ESTRO joint Task Group No. 359 - FLASH (ultra-high dose rate) radiation dosimetry (TG359) to embed the UHDpulse results in the recommendations, standards, and guides from this task group. The representative from the NPL is the official liaison between AAPM TG359 and UHDpulse. Furthermore, the close cooperation between hospitals, manufacturers of dosimetry equipment and national metrology institutes will enhance the uptake of such a CoP by the wider hospital community.

Longer-term economic, social and environmental impacts

Cancer incidence is expected to significantly increase due to the ageing of the European population. Approximately half of the cancer patients in Europe are treated by radiotherapy, the most cost-effective strategy in oncology. Therefore, innovation and clinical advancement in radiotherapy, such as FLASH radiotherapy, will 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 will 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 will promote future industrial developments of laser-driven irradiation facilities.

List of publications:

1. McManus, et al. *The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams*. Sci Rep 10, 9089 (2020). https://doi.org/10.1038/s41598-020-65819-y

2. F. Romano et al., *Challenges in dosimetry of particle beams with ultra-high pulse dose rates*, J. Phys.: Conf. Ser. 1662, 012028 (2020). https://doi.org/10.1088/1742-6596/1662/1/012028

3. Bourgouin A, et al (2020) *Calorimeter for Real-Time Dosimetry of Pulsed Ultra-High Dose Rate Electron Beams.* Front. Phys. 8:567340. https://doi.org/10.3389/fphy.2020.567340

4. A. Schüller et al., *The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates*, Physica Medica 80 (2020) 134-150. https://doi.org/10.1016/j.ejmp.2020.09.020

5. Kokurewicz K, et al (2020) *Dosimetry for New Radiation Therapy Approaches Using High Energy Electron Accelerators.* Front. Phys. 8:568302. https://doi.org/10.3389/fphy.2020.568302

6. Kranzer, R., et al (2021), *Ion collection efficiency of ionization chambers in ultra-high dose-per-pulse electron beams*. Med. Phys. https://doi.org/10.1002/mp.14620

7. Poppinga, D. et al 2021, *VHEE beam dosimetry at CERN Linear Electron Accelerator for Research under ultra-high dose rate conditions*, Biomed. Phys. Eng. Express 7 015012. https://doi.org/10.1088/2057-1976/abcae5

8. P. Chaudhary et al. *Radiobiology Experiments With Ultra-high Dose Rate Laser-Driven Protons: Methodology and State-of-the-Art*, Frontiers in Physics, 8 April 2021. https://doi.org/10.3389/fphy.2021.624963

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

Project start date and duration:	1 September 2019, 36 + 6 months	
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