

# Challenges in dosimetry of particle beams with ultra-high pulse dose rates

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**Abstract.** Recent results from pre-clinical studies investigating the so-called FLASH effect suggest that the ultrahigh pulse dose rates (UHPDR) of this modality reduces normal tissue damage whilst preserving tumour response, when compared with conventional radiotherapy (RT). FLASH-RT is characterized by average dose rates of dozens of Gy/s instead of only a few Gy/min. For some studies, dose rates exceeding hundreds of Gy/s have been used for investigating the tissue response. Moreover, depending on the source of radiation, pulsed beams can be used with low repetition rate and large doses per pulse. Accurate dosimetry of high dose-rate particle beams is challenging and requires the development of novel dosimetric approaches, complementary to the ones used for conventional radiotherapy. The European Joint Research Project "UHDpulse" will develop a measurement framework, encompassing reference standards traceable to SI units and validated reference methods for dose measurements with UHPDR beams. In this paper, the UHDpulse project will be presented, discussing the dosimetric challenges and showing some first results obtained in experimental campaigns with pulsed electron beams and laser-driven proton beams.

## 1. Introduction

Radiotherapy (alone or in combination with other treatments) is currently used to treat over half of the patients diagnosed with cancer and it is responsible for approximately 60% of cancer survivals [1, 2]. However, therapeutic resistance to radiation can cause local disease progression and local recurrence for some malignancies. Moreover, radiotherapy can cause acute and chronic toxicities to the healthy tissues close to the tumour, which in some cases limit the delivered maximum radiation dose with evident consequences on the curative effect of radiation [3-7]. Therefore, innovative radiotherapy strategies are being developed, especially when dealing with radioresistant tumours, which might require larger doses of radiation for limiting the tumour progression [8].



The use of irradiation modalities characterized by ultra-high pulse dose-rates (UHPDR) has been found to decrease undesired side effects to healthy tissues whilst preserving the required tumour control, thanks to the so-called FLASH effect [9]. Moreover, advances in particle accelerators have led to the installation of a new generation of proton accelerators, such as synchro-cyclotrons, the development of alternative irradiation modalities, such as Very High Energy Electron (VHEE) radiotherapy, and novel pulsed sources, such as laser-driven beams, all of which further increase the interest towards irradiation with UHPDR beams.

Initial investigations of the FLASH effect have been carried out in several *in vivo* studies across a range of tissue types using electron beams accelerated by modified clinical LINACs or dedicated electron accelerators. These studies have demonstrated a remarkable reduction of normal tissue complication probability (NTCP) after irradiation at dose rates exceeding 40 Gy/s, whilst maintaining the same tumour control probability (TCP) as for conventional RT, suggesting that beams with UHPDR can sensibly widen the therapeutic window in radiotherapy [9-13]. Studies have been carried out using photon radiation [14, 15] and proton beams accelerated by conventional RF machines [16-18] as well as through laser-matter interaction, at which even higher dose-rate per pulse are achieved [19-23]. Recent *in vivo* studies with a dedicated apparatus for passively scattering clinical proton beams have more clearly demonstrated the FLASH effect with protons [24] and similar dedicated facilities have been developed in the perspective of exploring the potential of FLASH proton therapy [25].

FLASH-RT, VHEE-RT and laser-driven beams are promising radiation modalities under development that involve an almost instantaneous delivery of the prescribed radiation dose by only a few radiation pulses of ultra-high dose rate. Dosimetry for these modalities is challenging and accurate procedures to measure radiation doses at these ultra-high pulse dose rates are required before implementation in clinical practice.

## 2. The “UHDpulse” European Joint Research Project

The use of UHPDR beams implies the revision of protocols currently used for dosimetry of particle beams produced by conventional medical accelerators and the development of alternative approaches addressing the relevant metrological challenges for these beams. Indeed, the response of established active detectors for real time dosimetry can be strongly influenced by the high doses per pulse and/or the high dose rates. Ionization chambers are recommended by international protocols for clinical reference dosimetry but their response to UHPDR beams must be properly investigated. Indeed, ion recombination effects occurring at these regimes require large corrections for charge collection efficiency resulting in a large measurement uncertainty.

In the framework of the European Metrology Programme for Innovation and Research (EMPIR), the project “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates (UHDpulse)” has started in September 2019 with the aim of developing a measurement framework including validated methods for radiation dose measurements and reference standards traceable to SI units. Since its conception, the UHDpulse project aims to produce results over the course of 3 years that will be promoted to international agencies, standards organizations and users. The outcomes will also contribute to codes of practice and the development of detector systems for absolute and relative dosimetry as well as the characterization of stray radiation.

The UHDpulse project will be developed by a consortium composed of 16 leading institutes in the field of radiation dosimetry and detector development: five European National Metrology Institutes (NMI) (PTB – Germany, NPL – United Kingdom, CMI – Czech Republic, METAS – Switzerland and GUM – Poland), two academic hospitals (CHUV – Switzerland, and Institut Curie – France), three universities (PoliMi – Italy, QUB – United Kingdom, and USC – Spain), three national research institutes (IMB-CNM, CSIC – Spain, NPI – Czech Republic, and HZDR – Germany), one European research institute (ELI – Czech Republic) and two companies (ADVACAM – Czech Republic, and PTW – Germany). The main objectives of the project are: i) to develop a metrological framework, including SI-traceable primary and secondary reference standards and validated reference methods for dosimetry measurements for particle beams with UHPDR; ii) to characterise the response of available detector

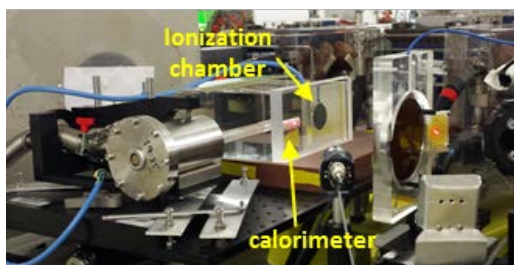
systems in particle beams with ultra-high dose per pulse or with ultra-short pulse duration; iii) to develop traceable and validated methods for relative dosimetry and for the characterisation of stray radiation outside the primary pulsed particle beams; iv) using the results, to provide the input data for future Codes of Practice for absolute dose measurements in particle beams with UHPDR.

The UHPDR project is composed of four technical work packages (WP). WP1 is devoted to the development and characterization of primary standard level instruments for UHPDR beams (Fricke dosimetry, water and graphite calorimetry); WP2 to the investigation of transfer methods of the dosimetry into clinical and preclinical UHPDR beam accelerators to enable a traceable measurement chain; WP3 to study of other detector types for absolute and relative dosimetry, such as: silicon microdosimeters, semiconductor pixel detectors and passive dosimeters (TLD and OSL) and WP4 to the development of traceable and validated methods for characterisation of stray radiation.

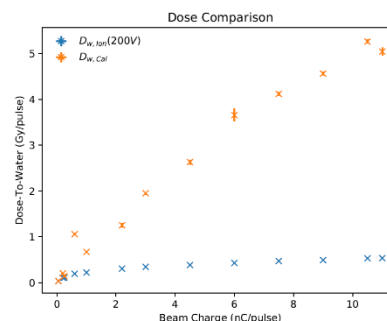
### 3. First results with VHEE and laser-driven proton beams

#### 3.1. Challenges of ionization chamber dosimetry in UHPDR VHEE beams

Most of the above-mentioned studies showing the FLASH effect have been carried out with UHPDR electron beams produced by linear accelerators with maximum energies up to 20 MeV, which, due to the low penetration depth at these energies, can be used only for treatment of superficial tumours. To overcome this limitation and with the aim of treating deep-seated tumours, VHEE beams with energy up to 250 MeV have been proposed as alternative RT modality. They are characterized by higher conformal dose distributions and lower integral dose, as compared to conventional RT [26-28]. VHEE beams can be produced using large RF accelerators or by laser-driven particle accelerators, with the latter delivering radiation pulses at extremely high dose rates (up to  $10^{10}$  Gy/s) [29]. With the perspective of a clinical translation of VHEE beams, accurate dosimetry must be performed, which requires addressing the challenges related to these very high dose rates.



**Figure 1.** The experimental setup used at the CLEAR facility at CERN.



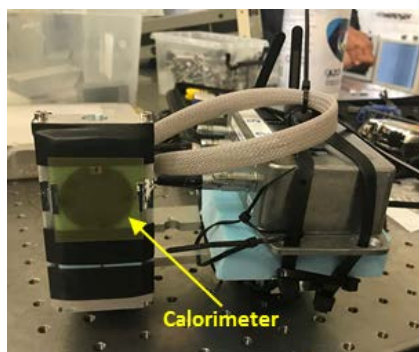
**Figure 2.** Cross-comparisons of the dose to water determined with the calorimeter and the dose to water that would be derived from an ionization chamber without applying any correction.

The response of plane-parallel ionization chambers to UHPDR VHEE beams at 200 MeV has been studied, as these chambers are recommended as secondary standard systems for clinical reference dosimetry of electrons. Experimental campaigns have been carried out at the CLEAR user facility at CERN [30], where charge measurements obtained with a PTW Roos Type-34001 chamber have been compared with the dose measured through a graphite calorimeter developed at the National Physical Laboratory (NPL, United Kingdom) (Figure 1) [31]. The doses per pulse (with pulse duration up to hundreds of ns), ranging from few cGy/pulse up to several Gy/pulse, have been measured with the calorimeter and compared with the response of the ionization chamber in order to determine the ion collection efficiency. The collection efficiency in the ionization chamber has been found to be less than 5% for the larger values of dose per pulse. From the ratio of the absolute dose determined with the

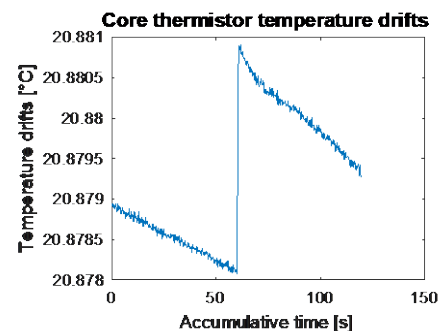
calorimeter and the response of the ionization chamber (Figure 2, for  $V = 200\text{V}$ ), the value of the recombination correction factor  $k_s$  has been determined for chamber collecting voltages ranging between 75 V and 600 V and for different dose-per-pulse values, exploring intra-pulse dose rates that as of yet, have never been tested in any dosimetric study [32]. Moreover, beyond the well-known two voltage method [33], the validity of analytical recombination models, respectively proposed by Boag [34] and De Martino [35], as well as of a logistic model proposed by Petterson [36] have been investigated. The results show that the recombination factor for a PTW Roos ionization chamber is strongly dependent on the dose-per-pulse at UHPDR, which implies the use of large correction factors, suggesting for the utilization of chambers with smaller sensitive volumes and higher electric fields.

### 3.2. First calorimetry measurements with laser-driven protons

Acceleration by intense, ultra-short laser pulses is an emerging technique, highly promising for the compact delivery of highly pulsed particle beams for both electrons and ions at energies of interest for medical applications [37, 38]. It is attracting an increased interest as a potential future radiation source for RT. In particular, acceleration of proton and ions up to several tens of MeV energies has been demonstrated in many experiments [39], with recent reports of near-100 MeV energies [40]. The pulse duration of laser-driven proton beams is very short (ps at the source – ~ns at a delivery site) and, with delivery systems demonstrated so far, the dose per single beam pulses can be as high as several Gy. This results in intra-pulse dose rates many orders of magnitude higher (up to  $10^9$ - $10^{10}$  Gy/s) than obtained using ion beams from RF accelerators. Dosimetry at these extreme dose rates is even more challenging than for FLASH proton beams. Moreover, the harsh experimental environment typical of high-power laser laboratories as well as the presence of large electromagnetic pulses (EMP) further complicates dose measurements with active dosimeters.



**Figure 3.** The SPGC prototype assembled in a dedicated holder for the measurement at the RAL facility.



**Figure 4.** Radiation induced temperature rise of the SPGC core thermistor for one of the laser shots.

A novel approach that has never been tested before has been proposed for dosimetry of laser-driven protons, which consists on the measurement of the absorbed dose using a small portable graphite calorimeter (SPGC), developed at NPL on the basis of a previous prototype used for low energy proton beams (Figure 3) [41]. The system was operated for the first time using the ultra-high dose-rate laser driven proton beam produced by the PetaWatt Vulcan Laser of the Central Laser Facility at the Rutherford Appleton Laboratory in the UK. Laser pulses of 600 J energy and ~500 fs duration were focused to intensities higher than  $10^{20}$  W/cm<sup>2</sup> onto 15  $\mu\text{m}$  Au targets, producing protons with energies up to 45 MeV spatially dispersed using a 0.9 T dipole magnet. Doses from 1 Gy up to 3 Gy per pulse were delivered in the calorimeter with an energy ranging from 15 MeV up to 40 MeV [42]. Despite the harsh experimental conditions, a very good signal-to-noise ratio was achieved in the SPGC (see temperature rise in Figure 4), with an average dose per pulse up to 3 Gy and a dose-rate reaching  $10^9$

Gy/s (pulse duration ~ 3 ns). This demonstrates the feasibility of calorimetry measurements in a laser environment.

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