New horizon in therapy & treatment
FRPT FLASH RADIOTHERAPY & PARTICLE THERAPY
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E-Poster Discussion and E-Poster Viewing

E-Poster Discussion Abstracts

EPD001 / #76

ZEBRAFISH EMBRYOS: A HIGHTHROUPUT MODEL TO CHARACTERIZE BEAM PARAMETERS ABLE TO TRIGGER THE FLASH EFFECT

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: The FLASH effect is characterized by antitumor effect and reduced normal tissue toxicity. In this project, wt zebrafish (AB) embryos were used as an high throughput and integrated physiological model, to dissect the beam parameters (dose rate, frequency…) leading to Normal tissue protection after irradiation at UHDR.

Methods: 4 hours post fertilization zebrafish embryos (n>20) were irradiated in egg water without methylene blue at 10 Gy. Irradiations were performed with electron beam eRT6 (5.5MeV) at various dose rates (0.1 to $5.6.10^6$ Gy/s), pulse widths (0.7 to 4µs) and frequencies (100 – 250Hz). Dosimetry at eRT6 was performed as described (Jorge, 2019). Survival and development of zebrafish were monitored 5 days post-fertilization.

Results: For a dose of 10 Gy, the higher was the dose rate ($5.6.10^6$ Gy/s), the better the development of zebrafish embryo was preserved. Interestingly, a dose rate escalation (from 0.1 to $5.6.10^6$ Gy/s) identified 100Gy/s, 100 Hz and 10 pulses of 1.8 µs as the threshold parameters to obtain protection of zebrafish embryo. Interestingly, these parameters are the one described in mice after whole-brain-irradiation (Montay-Gruel, 2017) (correlation coefficient > 0.94). Assays with modified pulse width and frequency are ongoing.

Conclusions: The good correlation obtained with zebrafish embryos and mouse models enabled identification of critical parameters to trigger normal tissue protection. They are above 100 Gy/s, below 10 pulses of 1.8 µs at 100 Hz for an irradiated volume below 1cc and 5.5 MeV electron beam. These results support the use of zebrafish embryos as a rapid and accurate model for parametrization.

EPD002 / #296

WORLDS FIRST AUTOMATED HYPOXIA END-STATION FOR IN VITRO PROTON IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: The PRECISE group at the University of Manchester and the Christie NHS Foundation Trust, in collaboration with Don Whitley Scientific (DWS) and Thermo Fisher Scientific (TFS), have developed the world's first automated hypoxia end-station for proton irradiation of cells in vitro.

Methods: The custom environmentally controlled cabinet from DWS allows us to vary oxygen concentrations between 0.1% to 20% and maintain these levels throughout the experiment, giving confidence that the cells we irradiate are under the exact conditions we expect. This is especially important for experiments investigating the FLASH effect, as it is expected to only occur within a certain range of oxygen concentrations. A thin 125 µm Kapton beam window of 20 x 20 cm enables beam extraction into the hypoxia cabinet, compatible with proton beam scanning, enabling dose-distribution patterns to be scanned onto the sample. The addition of a 6-axis robotic arm, supplied by TFS, enables us to quickly and repeatably irradiate up to 18 samples of T75 flasks or 96-well plates with no physical human intervention required. Should more samples be required, the hotel can be manually rotated by 180 degrees, giving access to a further 18 samples without compromising the cabinet environment. The Hypoxia end-station integrates a Well Wash Versa (TFS) for automated application of fixative agents at controllable time points.

Results: First experiment delivered a total of 90 Gy to 18 T75 flasks in approximately an hour.

Conclusions: Full automation enables accurate, high-throughput, repeatable experiments, alongside rapid processing of samples at timepoints where sample activation would preclude human handling.

EPD003 / #295

PLATFORM FOR STEP-AND-SHOOT ELECTRON FLASH IRRADIATIONS

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Currently, we are suffering from technological limitations, which forbid a systematic investigation of the beam characteristics necessary to trigger the FLASH effect. In particular, it is challenging to achieve large, clinically relevant UHD radiation fields. One way to circumvent this hurdle is to use a spot scanning strategy. As a first step, we want to evaluate the feasibility of simulating a scanning beam using our FLASH validated eRT6 linac.

Methods: We have constructed a motorized system scanning a narrow slit across the beam. We designed irradiation schemes to generate scanned beam configurations equivalent to a single field lateral and percentage dose profile (PDD).

Results: We systematically recorded the beam lateral and PDD profiles, total absorbed dose to water, and beam flatness to characterize the radiation field obtained by slit scanning. We found the bias to remain under 5 % for all selected metrics between the open and the slit-scanned fields.

Conclusions: We have been able to simulate equivalent irradiation fields using a step-and-shoot strategy. Therefore, we can now study the relevance of the beam scanning for the FLASH effect using our system. This future study has great potential to foster a quick clinical translation.

EPD004 / #136

POSSIBILITY TO ENHANCE FLASH EFFECT WITH SINGLE PULSE OF PROTONS

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: To study the role of dose rate, we irradiated with 209MeV protons tumor cells HT29 and HCT116 and normal cells - fibroblasts (ADSC). Depending on mean dose rate $\dot{D}_m$, we used three modes: the conventional mode with $\dot{D}_m$<3Gy/s, the flash mode with $\dot{D}_m$~60Gy/s, and the single-pulse flash ("splash") mode with $\dot{D}_m$>30000Gy/s.

Methods: We irradiated almost 200 dishes and plates in two experiments, both in the SOBP and in the plateau. Dosimetry was provided with EBT films. The sparing factor (SF) is defined as the ratio of apoptosis levels in tumor and normal cells under the same conditions. We calculated the ratio R = SF(splash)/SF(flash) to study the flash effect enhancement. To estimate statistical effects, we calculated the p - value for the two sets of SF, splash and flash.

Results:

Cells	HT29	HT29	HT29	HCT116	HT29+ HCT116	HCT116	HCT116	HT29	HCT116	overall
position	bragg	bragg	bragg	bragg	bragg	bragg	bragg	plateau	plateau	overall
run #	1	2	1+2	1	1	2	1+2	2	2	1+2
R	2,67	1,75	2,05	3,47	3,28	2,52	2,65	1,35	1,86	2,04
p	0,0171	0,193	0,0902	0,0188	0,0338	0,0297	0,00179	0,393	0,217	0,00153

Preliminary results: the flash effect for HCT116 works in flash and splash modes, but for HT29 - only in splash mode; the flash effect in the plateau weakens compared to SOBP (this statement, however, has large p-values and must be confirmed).

Conclusions: The main conclusion - the sparing factor is significantly increased in the single-pulse mode compared to the flash mode (overall p<0.002), at least in vitro.

EPD005 / #190

CALIBRATION OF THE ZEBRAFISH EMBRYO MODEL FOR RADIOTHERAPY WITH TESTING ON FLASH PROTONTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: A great challenge of FLASH-RT is to identify the parameters allowing protection, such as radiation type or dose rate. In this regard, there is a strong need for a biological model that offers ease of use for testing multiple conditions in a timewise and reproducible manner. The zebrafish embryo (ZE) is a non-autonomous transparent organism which allows rapid, cost-friendly testing of large numbers of individuals, thereby achieving high statistical power. FLASH protection has been demonstrated on ZE length using electron accelerators. However, several conditions must be met to measure adequate responses, such as dose and larval stage.

Methods: In this study, we calibrated the dose and stage-dependent RT response of ZE for ultimately testing FLASH protontherapy. Survival, embryo length and curvature were determined as experimental readouts.

Results: The optimal doses to produce length and curving effects while maintaining survival of >80% were 6-8 Gy at 4 hpf and 30-40 Gy at 28 hpf. No statistical difference was found between 225 kV photons and 68 MeV protons. Additionnally, we found that spending time in a closed tube impacts ZE response to irradiation, leading to increased RT-induced curvature and viability. This was associated with decreased oxygen level. Yet, 28 hpf embryos placed in these conditions exhibited similar effects in conventional (0.25 Gy/sec) and FLASH (7.5 kGy/sec, one pulse) protontherapy.

Conclusions: These data provide valuable ressources for designing ZE irradiation in a reproducible manner across different laboratories. No protective effect of ultra-high dose rate protontherapy was observed.

EPD006 / #33

TOWARD SINGLE DOSE RADIOTHERAPY: DREAM OR REALITY?

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: The capability to safely generate high energy beam modalities, characterize beam time signatures, perform accurate dosimetry and deliver image-guided treatment plans has been the cornerstone of the field. Radiotherapy has been reliant on interdisciplinary contributions from physics, chemistry and biology, but has moved forward conservatively, but constrained by the very technologies that have now ushered in precision driven stereotactic approaches.

Methods: Recently, ultra-high dose rate FLASH radiotherapy (FLASH-RT), overlooked for over 40 years, has triggered a renaissance in the field, aimed at evaluating if/how dose rate modifications can be garnered for therapeutic gain. This so called “FLASH effect” has been defined and validated in vivo, and provides a heretofore unforeseen capability to minimize normal tissue complications while maintaining isoefficient tumor control. Multiple pre-clinical models have now been studied, and suggest that older, more traditional views of radiobiology may not be valid under FLASH conditions.

Results: The potential promise of affording curative, dose escalation via FLASH-RT was immediately recognized, and in this regard, photon and particle FLASH radiotherapy have the potential to transform healthcare, and dovetail nicely into current trends toward hypofractionation and possibly single dose therapy. This talk will highlight the known and possible physico-chemical and biological mechanisms that might help us realize these goals.

Conclusions: Here the endgame lies within the science, and will dictate whether FLASH may eradicate multi-fraction treatment plans. If/how that laudable goal can be accelerated or even achieved through forthcoming advancements in FLASH-RT remains to be seen, but this intriguing technology has captured the imagination of radiation science.

EPD007 / #184

MONTE CARLO MODELLING OF PIXEL CLUSTERS IN TIMEPIX DETECTORS USING THE MCNP CODE

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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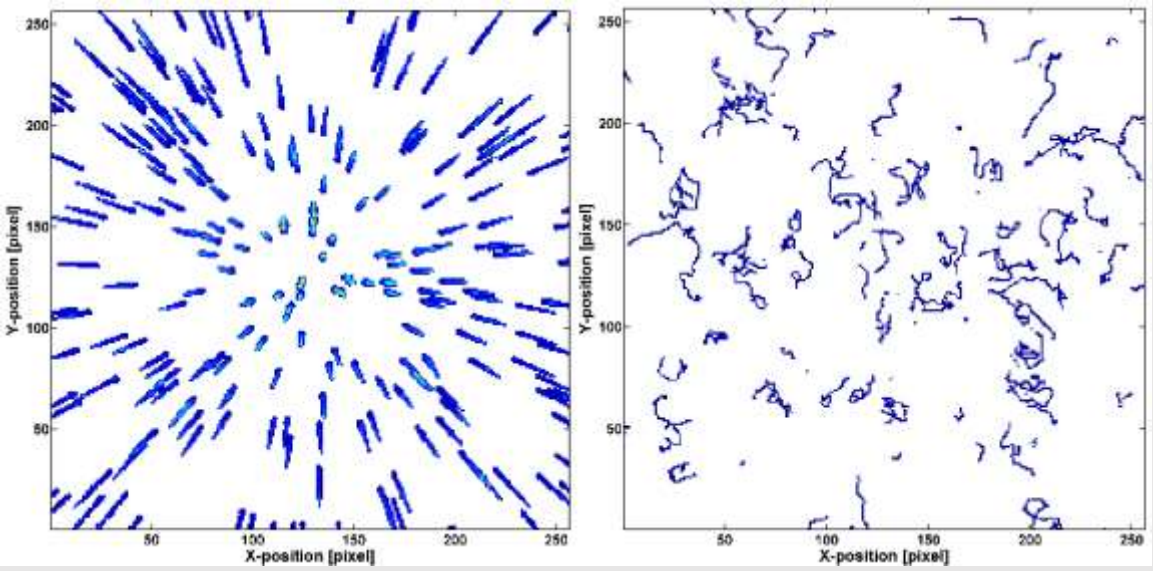
Background and Aims: Main goal of ADVACAM and Czech Metrology Institute (CMI) in the project UHDpulse is to develop methods for measurement of absorbed dose-to-water using Timepix3-based pixelated spectrometric radiation detector, both inside and outside of the pulsed beams with high dose-per-pulse (UHD beams).

Methods: Due to the complexity of the mixed radiation field generated by most UHD beams, the MC simulations are used to determine the response of Timepix detector to particular particle types, energies, and incidence angles which are not possible to measure separately. The MC model is pixel-level detailed (256×256 pixels, 55×55 μm^2 pixel size) and includes an analytical model of charge diffusion which allows for a precise modelling of so-called clusters of adjacent hit pixels observed in measured data due to charge diffusion and drift processes. MC model validation was performed by comparison of selected cluster types with measurements performed with standard radionuclide gamma-emitting sources and in proton beams. Figure: Simulated tracks of 250 MeV proton (left) and 3 MeV electrons (right) originating 1 cm from CdTe sensor.



Results: The MC model validation allowed to select the optimal cluster parameters for differentiation between various particle types and their energies and clarified the sensitivity of the MC simulation results to detector setting, e.g. energy threshold and bias voltage.

Conclusions: The validated MC model will be used to support the development of methods for particle qualification and quantification aiming to determine absorbed dose-to-water in UHD beams with Timepix detectors. This work resulted from the project 18HLT04 UHDpulse which received funding from the EMPIR programme.

EPD008 / #199

FRONTIER SOLID-STATE TECHNOLOGIES: A POSSIBLE ACE UP YOUR SLEEVE FOR FLASH BEAM MONITORING?

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Current radiotherapy beam monitors, such as ionization chambers, are unable to check the beam parameters during FLASH irradiations. This work shows the best cards of frontier solid-state solutions as transmission beam monitors in high dose-rate regimes, comparing their expected characteristics and performances.

Methods: Based on literature studies, preliminary simulations and possible configurations allowed by the manufacturing technology, several parameters, such as radiation hardness, dose-rate linearity and spatial resolution have been evaluated for ultra-thin segmented and highly polarized silicon sensors, diamond detectors and silicon carbide (SiC) sensors.

Results: Preliminary simulations of the interaction of 6 MeV electrons with thin silicon/diamond/SiC sensors result in an average energy released per electron of approximately 0.33 keV/μm in silicon, 0.44 keV/μm in SiC e 0.49 keV/μm in diamond. This lead to a charge of around 50 pC for an instantaneous dose-rate of 10^5 Gy/s in a 5 μs beam pulse in a silicon of 100×100 μm^2 x 20 μm thickness, as an example. Considerations on the sensor technology and geometry have been performed in order to envisage the most promising choices in dealing with such an amount of released energy, fulfilling at the same time the beam monitoring requirements.

Conclusions: This study does not hold all the cards, but it deepens the knowledge about the expected performances of solid-state detectors as monitors to online control FLASH irradiations, and it will help identifying the most promising technologies among silicon sensors, diamond detectors and SiC sensors.

EPD009 / #176

DIAMOND DETECTORS IN ULTRA-HIGH DOSE-PER-PULSE PROTON BEAMS WITH DIFFERENT PULSE LENGTHS

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: In FLASH radiotherapy ultra-high dose rate (UHDR) electron as well as proton beams in continuous and pulsed configurations are used. This creates new requirements for dosimetry and the use of diamond detectors appears beneficial. The aim of this work is to investigate the linearity of synthetic PTW microDiamond detectors in ultra-high dose rate pulsed proton beams with different pulse lengths.

Methods: Three different diamond detectors were investigated at PTB's cyclotron facility with a 10 MeV proton beam. DC-currents between 90 and 2250 nA were pulsed with lengths of 2.6, 6.3 and 13 µs using an electrostatic deflection system.

Results: Two detectors showed a linear response to the instantaneous dose rate, which was independent of the beam pulse length. One detector showed a saturation already at the lower dose rates, which was strongly pulse length dependent.

Conclusions: In principle, microDiamonds are suitable for dosimetry of UHDR proton beams, especially for short (µs) pulses. However, the dose rate range above which saturation occurs depends on the specific design of the detector. The results demonstrated that the commercially available microDiamond can be improved for use in UHDR proton beams. This project 18HLT04 UHDpulse has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.

EPD010 / #37

PARTICLE DOSIMETRY FOR PULSED ULTRA-HIGH PEAK DOSE RATES: THE I-BEAT DETECTOR

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Accurate dosimetry is key for precise clinical treatments and pre-clinical research. However, ultra-high peak dose rates typical for FLASH therapy which could be achieved with laser-driven ion beams are a challenge to conventional particle detection systems.

Methods: These demanding issues can be overcome by measuring the acoustic signals of pulsed particle bunches depositing their energy in water, referred to as Ion-Bunch Energy Acoustic Tracing (I-BEAT). The I-BEAT detector consists of a water volume surrounded by up to four ultrasound transducers, is fully online evaluable and radiation hard.

Results: While the ability of I-BEAT to determine complex energy spectra was already demonstrated, recent experimental campaigns at different conventional and laser-driven ion beams exhibit the possibility of a three-dimensional dose measurement. The I-BEAT detector was irradiated with more than 10^7 protons within a few tens of nanoseconds corresponding to 10^8 Gy/s, and also much higher particle numbers are expected to be measurable. Thereby the detector is sensitive to the deposited amount of dose and is thus suitable for absolute dosimetry.

Conclusions: I-BEAT is a simple and innovative monitoring solution that currently serves for particle bunch characterisation in three dimensions at ultra-high peak dose rates. Its potential for online dosimetry of individual bunches is on the horizon. This work was supported by the German Research Foundation (DFG) within the Research Training Group GRK 2274. FB acknowledges financial support by the BMBF under the project 05P18WMFA1.

EPD011 / #171

THE LINE FOCUS X-RAY TUBE – AN X-RAY SOURCE FOR FLASH AND SPATIALLY FRACTIONATED RADIATION THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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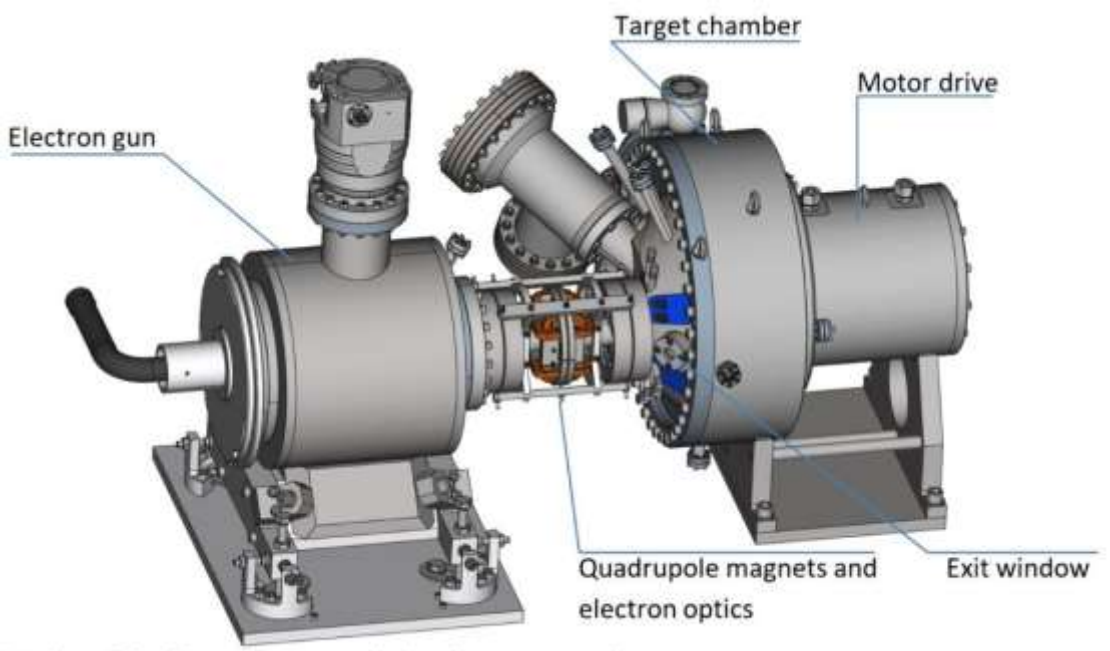
Background and Aims: FLASH and spatially fractionated radiation therapy (SFRT) demonstrated reduced side effects at equal tumour control compared to conventional radiotherapy. Currently only large synchrotrons may facilitate clinical x-ray FLASH or SFRT treatments. We are constructing a prototype of an innovative, table-top x-ray source that will allow FLASH and SFRT treatments. The source is based on the line focus x-ray tube (LFxT) concept and will eventually deliver dose rates of up to 200 Gy/s.

Methods: We designed a thermionic electron gun that generates a low-emittance, high-current electron beam at 300 keV. Two quadrupole magnets focus the electrons onto a 50 µm wide focal spot on a tungsten-molybdenum target that spins at 250 Hz. We assessed the radiation field, temperature and mechanical stress conditions with finite-element and Monte Carlo simulations. The separation tube equipped motor drive and liquid metal bearings fit for operation in ultra-high vacuum. We developed a high-voltage supply based on modular multi-level converter (MMC) technology for increased power in a future clinical source.

Results: Finite element simulations showed an operation of the LFxT in the heat capacity limit permitting substantially enhanced dose rates at small focal spot sizes. Thermal and mechanical stresses are tolerated by the target design. An MMC based DCDC converter with 320 battery-powered units can store enough energy to supply the source with 2 MW electrical power in a duty cycle of 2%.



Design of the first prototype of a line focus x-ray tube

Conclusions: The LFxT is an x-ray source concept that may soon enable FLASH and SFRT in a hospital environment.

EPD012 / #195

EFFECTIVENESS OF ULTRA-HIGH DOSE RATE PROTON CELL KILLING IN 2D AND 3D GLIOBLASTOMA

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Recent advances in laser technology have allowed the delivery of ultra-high dose rate (UHDR) to study radiation-induced biological effects. So far, studies employing laser-driven UHDR protons have mostly used cells growing in 2D monolayers. Since existing data indicate a differential response in 3D models associated to changes in the microenvironment, an assessment of the radiobiology of laser-driven ions in 3D systems is therefore important for any future application of UHDR proton beams.

Methods: Patient-derived glioblastoma stem-like cells (GSCs) were irradiated as 2D monolayers or 3D neurospheres with doses ranging from 0 to 8 Gy, using 35 MeV protons, delivered in a single ultra-short pulse of ~700 picoseconds, at a dose rate of ~10^{10} Gy/s. The UHDR protons were generated using the Vulcan laser system at the Rutherford Appleton Laboratory, UK. After irradiation and seeding, the cells were incubated for 2 weeks to allow visible macroscopic colony formation. Comparative exposures used conventional 30 MeV protons, at 4 Gy/min (INFN, Catania, Italy), or reference 225 kVp X-ray source (Queen's University Belfast, UK).

Results: We have observed similar cell-killing response to UHDR laser-driven protons in 2D monolayers and in 3D neurospheres ($DMF_{SF=0.5}$=0.95±0.26). Additionally, the data suggest increased cell killing efficacy in the 3D configuration ($RBE_{3D,SF=0.5}$=1.23±0.34) and increased survival in 2D ($RBE_{2D,SF=0.5}$=0.88±0.17) at UHDR, compared to X-rays.

Conclusions: Our results show the effectiveness of UHDR protons in inducing cell death irrespective of the microenvironment of the cells, whereas 3D neurospheres are radioresistant to X-rays and conventional protons.

EPD013 / #142

A COMPACT MULTI-ION LINAC WITH FLASH CAPABILITY

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Hadron therapy offers improved localization of the dose to the tumor and much improved sparing of healthy tissues, compared to traditional X-ray therapy. Combined proton/carbon therapy can achieve the most precise dose confinement to the tumor. Moreover, recent studies indicated that adding FLASH capability to such system may provide significant breakthrough in cancer treatment. However, this capability is beyond cyclotrons and synchrotrons presently available.

Methods: The Advanced Compact Carbon Ion Linac (ACCIL) is a conceptual design for a compact ion linac based on high-gradient accelerating structures operating in the S-band frequency range. Thanks to this innovation, the footprint of this accelerator is only 45 m, while its capabilities are well beyond the current state of the art for hadron therapy machines and include: operation at 1000 pulses per second, pulse to pulse energy variation to treat moving tumors in layer by layer regime and compatibility with FALSH therapy.

Results: ACCIL is capable of accelerating all ions with mass-to-charge ration A/q ~ 2 to a full energy of 450 MeV/u, and that includes protons, helium, carbon, oxygen and neon. With very short beam pulses of ~ 1 μs and high instantaneous dose delivery, ACCIL is capable of delivering FLASH-like doses (>100 Gy/sec) for most ion species.

Conclusions: In close collaboration between Argonne and Radiabeam, we have and are developing different design options and prototypes of the high-gradient structures needed for ACCIL. Following an overview of the ACCIL design and its capabilities, the most recent results from the high-gradient structure R&D and future plans will be presented and discussed.

EPD014 / #29

FIRST THEORETICAL DETERMINATION OF RELATIVE BIOLOGICAL EFFECTIVENESS OF VERY HIGH ENERGY ELECTRONS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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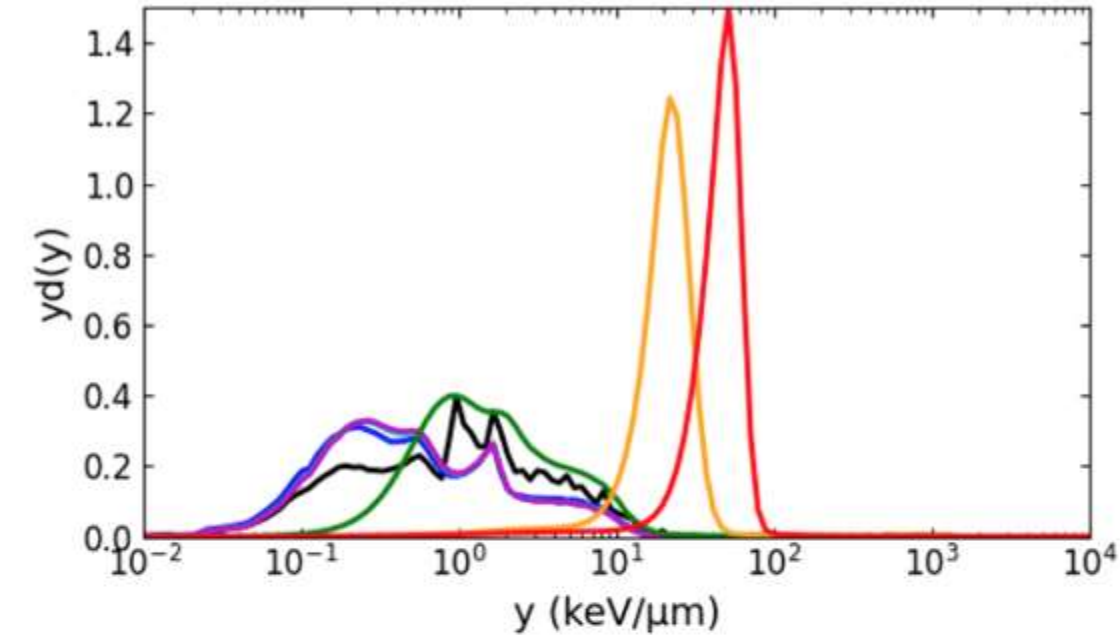
Background and Aims: Very high energy electrons (VHEEs) present promising clinical advantages over conventional beams, such as their improved practical range for targeting deep-seated tumors, relative insensitivity to tissue heterogeneities, and their capability to be electromagnetically scanned. In conjunction with advancements in laser wakefield accelerator technologies, VHEEs have the potential to augment emerging radiation modalities such as spatial fractionation or FLASH. In order to tackle the current lack of radiobiological data, this study characterises different VHEE beams against clinically available beams by making use of Monte Carlo (MC) based numerical simulations to compare their macro- and microdosimetric properties.

Methods: All simulations were performed in GATE. A water phantom was irradiated by beams of: electrons (5 to 300 MeV), photons, protons, ^{12}C ions, and ^{20}Ne ions. Macroscopically, the dose averaged LET (L_d) was calculated. Microscopically, the dose-mean lineal energy y_d was calculated using a tissue equivalent proportional counter (TEPC). Finally, the modified microdosimetric kinetic model (MKM) was used to calculate the cell survival curves.

Results: The macrodosimetric results suggest an enhanced biological effectiveness for VHEEs due to their increased L_d. This, however, is in contrast to the microdosimetric results which conclude that there is no increased biological effectiveness of VHEEs over clinical photon/electron beams.



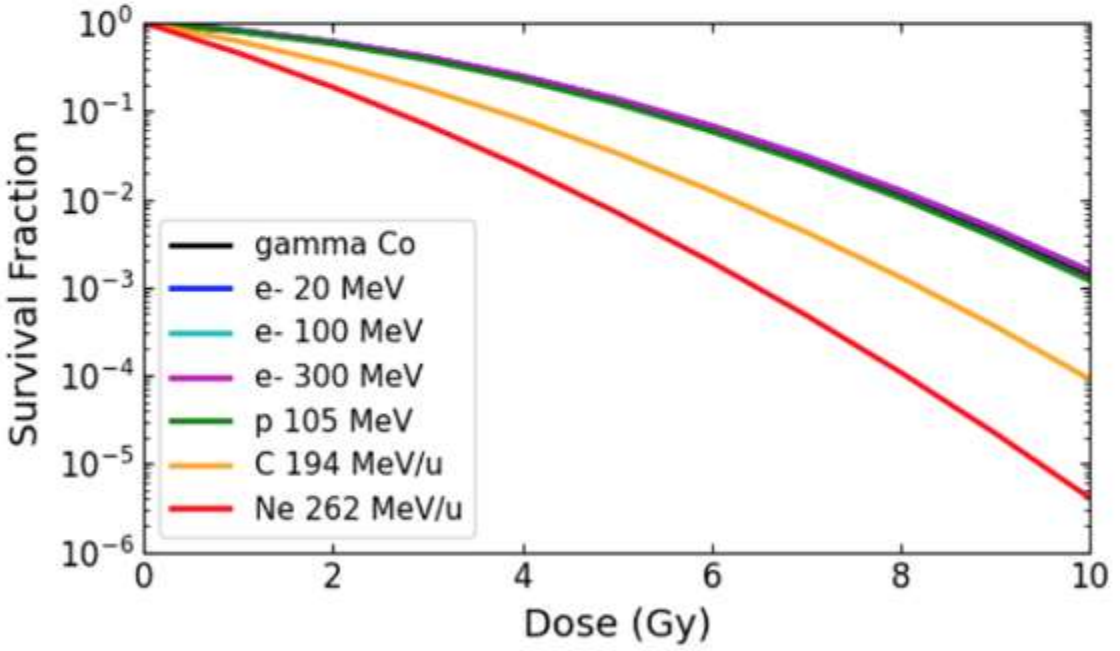


Figure 1: Comparison of microdosimetric spectra yd(y) for beams of photons, electrons, protons, carbon and neon ions (upper panel), and corresponding cell survival curves obtained with the MKM (lower panel), calculated at a depth of 4 cm in water (plateau region for ions).

Conclusions: This study represents the first step towards a full evaluation of the biological efficacy of VHEE beams. It highlights the difference between a macro- and microdosimetric approach, and the biologically relevant information obtained from these theoretical MC simulations could be used to complement further experiments which explore the radiobiological response to VHEEs.

EPD015 / #72

PROTONTHERAPY THERAPEUTIC WINDOW WIDENING BY PBCT AND FLASH MODALITIES

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: There has been a renewed spark of interest in the so-called FLASH dose-rates (generally – above 40 Gy/s) recently proposed for the treatment of cancer. While the exact mechanisms are still elusive, the results observed so far, in terms of sparing of healthy tissue, are very promising, pushing the research forward. In our study, we focus on improving biological effectiveness of accelerated protons by exploiting a novel binary nuclear approach: proton Boron Capture Therapy (pBCT), where incident protons react with B-11 atoms, releasing three highly DNA-damaging alpha particles. This modality has not yet been studied with protons under FLASH regimes and could improve the protons' ability to eradicate radioresistant cancers while even further lowering the healthy tissue complications due to the FLASH effects. This would result in a widening of protontherapy therapeutic window.

Methods: Human lung cell lines are used in this study: radioresistant cancer line A549 and MRC-5 as representative of normal tissue. Irradiation was conducted at the Orsay Proton Therapy Center (France), using modified IBA Proteus Plus machine – exposing cell cultures to protons at approximately 150 Gy/s in a scanned beam. Along with clonogenic survival, radiation-induced senescence, and induction of DSBs (observed in the form of γH2AX and 53BP1 foci) were studied.

Results: Preliminary results show the pBCT modality effects on cancer cells under irradiation regimes never tested before. In addition, FLASH effects on normal lung cells are discussed.

Conclusions: This approach provides novel insights into the possibility of simultaneously enhancing clinical protons' ability of tumor killing and healthy tissue sparing.

EPD016 / #77

LASER-DRIVEN ION ACCELERATION BEAMLINE AT THE CENTRE FOR ADVANCED LASER APPLICATIONS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Laser-driven ion sources can provide particle bunches with high charge in ultra-short timescales (ps-ns), achieving single bunch peak dose rates much higher than in conventional accelerators. In the last years progress was made to improve ion energy and stability. Further development of the ion source, transport, and suitable instrumentation is ongoing and promises controlled experiments with increasing ion energy in radio-biological applications.

Methods: At the Centre for Advanced Laser Applications (CALA) in Garching near Munich the ATLAS-3000 laser system is used to achieve focus intensities of more than 10^{20} W/cm^2 and accelerate energetic ion bunches in a suitable target. This setup is used for target, transport and diagnostic development to improve the ion source. Furthermore, an application platform for irradiation experiments in air has been established.

Results: During the commissioning phase protons were accelerated from sub-micron thin plastic foil targets. Stable production and transport of >12 MeV protons towards the application platform was demonstrated. Dose rates of several Gy per shot with ns bunch duration were observed.

Conclusions: Along with development of the source and instrumentation, CALA will provide an experimental platform for bio-medical sample irradiation with laser-driven ion bunches at ultra-high peak dose rates in individual bunches. This is of particular interest in the context of unraveling the microscopic mechanisms that are responsible, for example, for the emerging FLASH ion-therapy modalities. FB acknowledges the support of the BMBF within project 05P18WMFA1. LD acknowledges the support of the DFG within project FOR 2783/1, SG within Research Training Group GRK 2274.

EPD017 / #200

TIME DYNAMICS OF THE DOSE DEPOSITED BY RELATIVISTIC ULTRA-SHORT ELECTRON BEAMS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Laser plasma accelerators are routinely used to produce ultra-relativistic electron beams as short as 1 fs, leading to very high dose rates. Very high Energy Electrons (VHEE) Radiotherapy is one of the key applications envisioned for laser-plasma accelerators due to the compact footprint.

Methods: In this work, we investigate by means of Monte Carlo simulations the time dynamics of the dose deposited by ultra-short electron beams with energy in the range of VHEE. The simulations have been done with the FLUKA, Geant4, and Phits codes.

Results: In this work, we show that the dose is deposited in a time scale larger than the fs duration of the electron beam, leading to a reduced peak dose rate.

Conclusions: Moreover, the dose deposition time is found to be dependent on the electron beam energy, on the depth inside the water phantom target, and on the radial distance from the electron beam axis. This work was supported by the European Regional Development Fund, ADONIS (CZ.02.1.01/0.0/0.0/16 019/0000789).

EPD018 / #155

MODIFICATION OF COMMERCIAL RADIOTHERAPY SYSTEM FOR ULTRA-HIGH DOSE RATE ELECTRON BEAM IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Because electron generation in X-ray mode needs to be about 1000 times more than electron beam mode, modifying commercial radiotherapy system make it possible to irradiate with ultra-high dose rate. This study aimed to show the feasibility of ultra-high dose rate irradiation using a commercial linear accelerator.

Methods: Removing targets and flattening filters, adjusting source-surface-distance (SSD), and controlling RF driver and electron gun were performed in Simens Oncor® and Varian Clinac iX® radiotherapy system. The irradiation time was adjusted in microseconds through the Arduino-based gating system, and dose rate was confirmed with EBT3 and EBT-XD films.

Results: In 6 MV X-ray mode of Siemens® system, 100.9±3.78 Gy/s electron beam was irradiated at SSD of 60cm. After modifying 10MV X-ray mode in Varian® radiotherapy system, dose rate was 43.1Gy/s at SSD of 100cm. By manually controlling the parameters of the RF driver and electron gun, 318 Gy/s rate of electron beam was irradiated within 15 x 15 cm^2 of irradiation field at SSD of 100cm. Acquired ultra-high dose rate electron beam exhibits the following characteristics at SSD of 100cm with full opened jaw irradiation: R_{50} 4.1cm, W_{80} 9.8cm (vertical) and 9.3cm (horizontal).

Conclusions: We confirmed that FLASH irradiation was feasible by modifying a commercial radiotherapy system, which made further research possible.

EPD019 / #126

A MECHANISTIC MODEL OF FLASH-DOSE-RATE RADIOTHERAPY BASED ON TIME-DEPENDENT DNA DAMAGE COMPLEXITY, REPAIR AND OXYGEN TENSION

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Recent FLASH studies are conducted under vastly different experimental conditions and circumstances i.e. investigated biological endpoint, radiation quality and environmental oxygen level, complicating the investigation of FLASH phenomena and assessment of clinical applicability.

Methods: To address this issue, we present a dynamic (time-dependent) extension of the mechanistic "UNIfied and VERSatile bio-response Engine" (UNIVERSE), incorporating fundamental temporal mechanisms necessary for dose-rate effect prediction, i.e. DNA damage repair kinetics (DDRK), oxygen depletion and re-oxygenation during irradiation. Model performance in various experimental conditions is validated based on in-vitro and in-vivo data from the literature and impact of dose, dose-rate, oxygen tension, tissue-type, beam quality and DDRK is analyzed.

Results: UNIVERSE adequately reproduces dose-, dose-rate and oxygen tension-dependent influence on cell-survival. For the studied systems, results indicate that the extent of cell/tissue sparing effect, if present at all, strongly depends on DDRK and beam quality used for reference conventional irradiation. A mechanistic framework for predicting clinically relevant end-points comparing conventional and FLASH high-dose-rate effect has been successfully established, relying on time-dependent processing of radiation-induced damage classes taking into account variable oxygen tension.

Conclusions: Highlighted by UNIVERSE itself, the multi-dimensional nature of this relative sparing effect using high dose-rate radiation compared to conventional means underlines the importance of robust quantification of biophysical characteristics and consistent/well-documented experimental conditions both in-vitro and in-vivo prior to clinical translation. To further elucidate underlying mechanisms and appraise clinical viability, UNIVERSE can provide reliable prediction for biophysical investigations of radiotherapy using ultra-high dose-rate. The possibility to extend the prediction to high-LET radiation is explored.

EPD020 / #282

FLASH OXYGEN DEPLETION EFFECTS DEPEND ON TISSUE VASCULATURE STRUCTURE – A SIMULATION STUDY ON SMALL ANIMAL PROTON FLASH EXPERIMENT

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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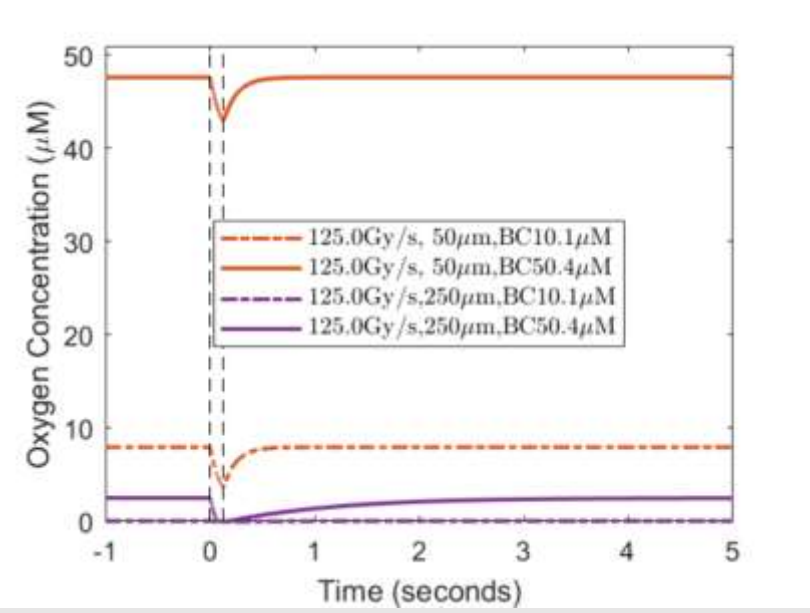
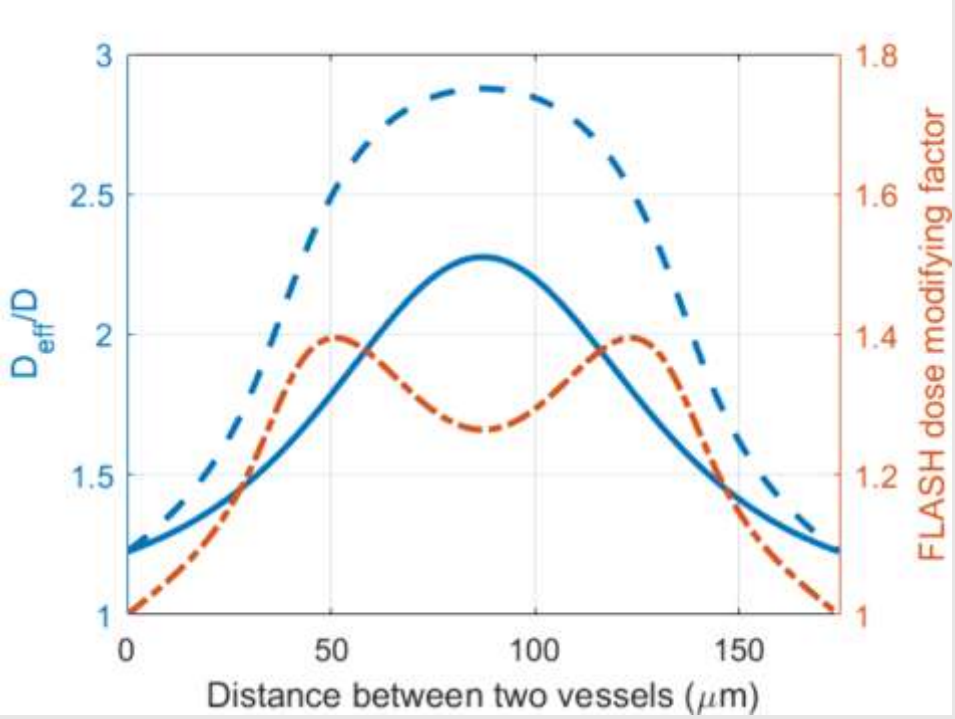
Background and Aims: Radiation-induced oxygen depletion is assumed as a significant contributor to the FLASH sparing effects. We investigated the proton oxygen depletion in a simulation approach to derive the proton FLASH effective dose modifying factor with local vasculature information.

Methods: The dose and LET of a small animal proton irradiator were simulated with MC simulation. We deployed a parabolic PDE to account for the dose-oxygen depletion, tissue oxygen diffusion, and metabolic processes. Various dose and dose rate levels, LET, vasculature spacing and blood oxygen supplies were considered. Using the particle oxygen enhancement ratio (OER), the FLASH modifying factor was derived as the ratio of the cumulative effective dose to the delivered.

Results: Oxygen dynamic equilibrium between diffusion and tissue metabolism can result in hypoxic region in healthy vasculature prior to irradiation. Comparing 15Gy delivered at 0.5 and 125Gy/s, 63.5% of the tissue exhibits >20% FLASH modifying factor at 175 mm vasculature spacing and 18.9 mM oxygen supply boundary condition. This percentage reduces to 38.9% and 0% for 8 and 2Gy deliveries. Poor oxygen supplies of 5.4 mM at the same vasculature spacing will display less FLASH effect in only 32% tissue. This differential effect remains at larger vasculature spacing and increases at higher dose rate.



Higher proton LET does not appear to alter the FLASH effects.



Conclusions: In this radio-biological model, we derived the proton FLASH effective dose modifying factor related to the dose delivery and the local tissue vasculature information. The simulation provides a measure that can be potentially validated in small animal experiments.

EPD021 / #69

MODELING OF THE FLASH EFFECT FOR ION BEAM RADIATION THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: FLASH (extremely high dose-rates) irradiation have shown interesting normal tissue sparing. Their potential clinical application is being investigated for various types of particles including photon, electron, proton, and carbon ion. However, it is unknown how to quantify the FLASH effects for various types of particles. Assuming oxygen depletion in the FLASH effect, the aim of this work is to develop simple prediction model of the FLASH effects for ion beam radiation therapy.

Methods: We used the linear-quadratic and the Alper-Howard-Flanders model to describe the radiosensitivity during high dose-rates irradiation. The oxygen kinetic equation was integrated to the model to incorporate oxygen depletion. The FLASH sparing effectiveness (FBE) was defined as the ratio $FBE=D_{conv} / D_{FLASH}$ where D_{conv} is a reference absorbed dose delivered with conventional dose rate and D_{FLASH} is the one with high dose-rates. The characteristics of this model were explored in terms of linear energy transfer (LET).

Results: The developed model predicted the alpha (Gy^{-1}) and beta (Gy^{-2}) values depending on dose-rates and LET. Thus we were able to calculate FBE with 0.1 Gy/s conventional dose-rate as reference. According to our calculations for a carbon ion spread-out Bragg peak at clinically relevant intermediate oxygen levels (0.5-10 mmHg), the advantage of FLASH effect might be relatively moderate, with FLASH effect values about 2-15% smaller than for proton.

Conclusions: We proposed a simple model to quantify the FLASH effect in a practical way and provides the potential to optimize biological dose in FLASH treatment planning.

EPD022 / #41

MODIFIED LETHAL AND POTENTIALLY LETHAL MODEL FOR CELL SURVIVAL IN CONVENTIONAL AND FLASH RADIOTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: To incorporate intracellular environmental factors, e.g., oxygen tension, into Curtis' Lethal and Potentially Lethal (LPL) model to make it applicable to FLASH radiotherapy (RT).

Methods: We introduce two modifications to the LPL model: 1) adding a prelesion state to its state diagram. The radiation-induced prelesions on DNA strains in cells are the predecessor to LPL lesions. 2) due to the oxygen effect, transition rates from prelesions to LPL lesions are assumed proportional to the oxygen enhancement ratio (OER). We use ordinary differential equations (ODEs) to describe the kinematics of the states. The survival fraction (SF) of irradiated cells is linked to the total number of LPL lesions through Poisson statistics. We use analytical analysis and numerical simulation to study the SF for both conventional- and FLASH-RT.

Results: Our model degenerates to the original LPL model mathematical structure with fast prelesion repair shortly after cell irradiation starting. Except now, the production rates per unit dose for both LPL lesions are proportional to OER. Due to this difference, the new model can produce the differential effect on SF between hypoxic cells (typically found in tumors) and aerated cells (routinely inside normal tissues) in FLASH-RT under radiation-induced oxygen depletion. For fixed intracellular oxygen tension, our model is identical to the LPL model applicable to conventional RT. The introduction of prelesions state can also help us understand the oxygen effect beyond cell irradiation.

Conclusions: Our modified LPL model can provide kinetic information on cell survival following FLASH-RT. Future quantitative studies are necessary to validate the new model.

EPD023 / #253

HYDROGEN PEROXIDE PRODUCTION AFTER IRRADIATION WITH PROTON BEAM AT VARIOUS DOSE RATES

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: While the FLASH effect (Kacem et al., 21) has been primarily studied in the context of electron beams, proton delivery at high dose rates has been shown to produce the same radiobiological effect (Diffenderfer et al., 20; Cunningham et al., 21). To investigate the initial physico-chemical mechanisms underlying the FLASH effect, we determined radiolytic yields (G-values) of hydrogen peroxide after irradiation at various dose rates with protons.

Methods: Transmission 230MeV proton irradiations at 0.1, 1, 100 and 1400Gy/s (continuous cyclotron beam), with fractional dose of 5-30Gy. RBE were delivered on Gantry 1 at PSI to ultra pure water equilibrated with 4%O_2. Dosimetry was performed as described previously in (Nesteruk et al., 21). Amplex Red fluorescent reaction was used to quantify the amount of H_2O_2 produced.

Results: The concentrations of hydrogen peroxide produced after the irradiation at various dose rate were measured and G-values determined as depicted in Figure1. We found that the differential radiolytic H_2O_2 production showed dose and dose-rate dependency, and we are currently performing experiments to estimate the primary G-values of hydrogen peroxide.

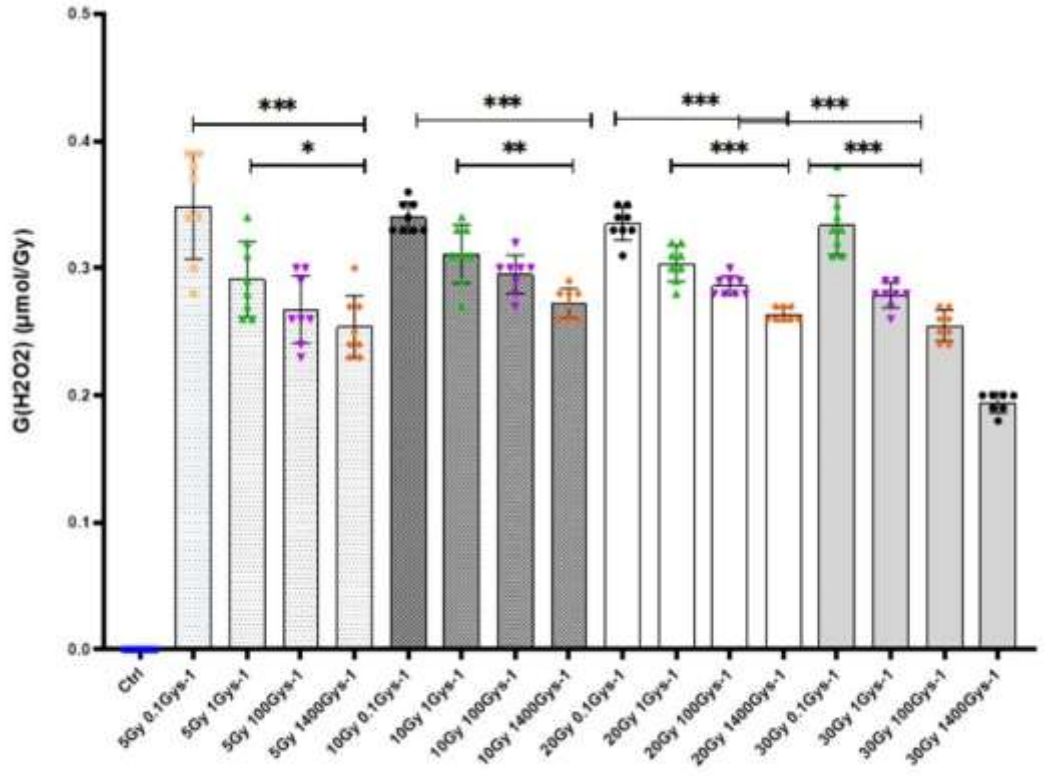

Figure 1-G(H2O2) as function of increased doses and dose rates protons performed in water samples equilibrated at 4% to mimic physiological conditions.

Conclusions: Consistent with results obtained with electrons at UHDR, the production of H_2O_2 several minutes after irradiation is inversely proportional to the dose rate. Investigations are ongoing to understand the significance of these observations as downstream biological cascades can be modified. In addition, the lower production of H_2O_2 at high dose rates might be the result of altered radical-radical reactions. Acknowledgement : funded by an industrial grant from Varian Medical Systems Inc. (Palo Alto, CA, USA)

EPD024 / #203

A COMPUTATINAL ANALYSIS OF IN VIVO OXYGEN KINETICS DURING ELECTRON FLASH IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Recent results of animal studies of FLASH effect have revived interest in the potential of FLASH radiotherapy to spare normal tissue with no compromise of tumor control. Our group recently measured oxygen depletion in vivo by 10 MeV electron FLASH, and the data has yet to be quantitatively analyzed. A computational analysis is presented to describe the in vivo oxygen kinetics during FLASH irradiation.

Methods: In vivo oxygen kinetics were measured using a phosphorescence quenching method with the water-soluble molecular probe Oxyphor 2P. The proposed time-dependent model combines the concentration-independent interaction rate and oxygen diffusion through the tissue to describe the oxygen kinetics during and after FLASH irradiation based on our previous in vitro and in vivo data.

Results: The chemical depletion yield per unit dose (G-values) for oxygen consumption is ~0.1 mmHg/Gy for normal tissue upon FLASH irradiation. After the initial FLASH irradiation reduction, the oxygen recovers at the rate of 0.15-0.2 mmHg/s with resupply of oxygen diffusing in from capillaries.

Conclusions: This study shows that the in vivo oxygen kinetics are related to total dose, instantaneous dose rate, repeat rate and oxygen recovery rate. Oxygen consumption and recovery rates differ during FLASH therapy as opposed to conventional radiation where the consumption and re-oxygenation are nearly equivalent, such that no oxygen change is detected during conventional irradiation.

EPD025 / #146

DEVELOPING A COMPUTATIONAL MODEL FOR FLASH RADIOTHERAPY CONSIDERING INTRACELLULAR CONTENTS WITH CPU-GPU COUPLING INDEPENDENT REACTION TIMES MODULE IN MONTE CARLO SIMULATION CODE NASIC

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Monte Carlo simulation of the radiolytic species in nanometer scale is an effective tool to analyze the reactions after irradiation due to the non-uniform distribution of species. Concentration of species at the end of chemical stage provides primary state of the diffusion-reaction equation, which is used to analyze long time chemical and biological processes.

Methods: To simulate the reactions in the intracellular medium, we implemented the organic molecules and related reactions to chemical module in our nanodosimetric Monte Carlo simulation code NASIC. The organic molecules are regarded as scavengers of radicals. Organic radicals, which are generated from the reactions, are simulated in the following reactions. The independent reaction time (IRT) method is utilized to improve the performance of chemical module. The method is further accelerated with CPU-GPU coupling method. The NASIC code is used to study the oxygen depletion hypothesis in FLASH radiotherapy. The radiolytic oxygen consumption rate values in the water are calculated when the dose rate is 10^6-10^{12}Gy/s for primary oxygen concentrations of 0.3%-21%. The effect of time structure of pulses generated by a linear accelerator is analyzed to evaluate the real reaction. A typical dose of 30Gy is simulated to study the oxygen depletion.

Results: The results considering the organic molecules are compared with results calculated in water medium. Results show great difference attributed to intracellular medium.

Conclusions: Based on this simulation which considered the time structure of linear accelerator, it indicated that the 30 Gy FLASH radiation cannot deplete the oxygen in normoxic cells.

EPD026 / #158

UNDERSTANDING THE TRANSITION TO FLASH

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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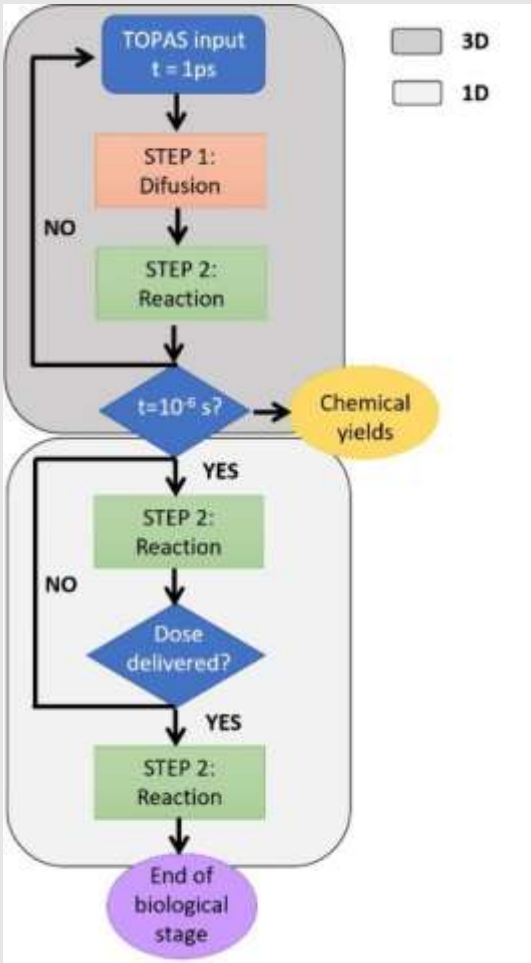
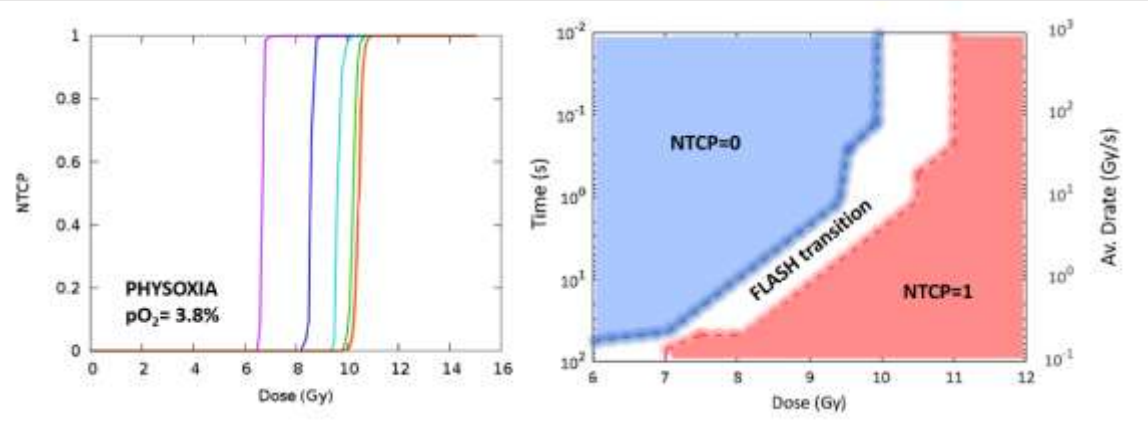
Background and Aims: In vitro and in vivo studies have shown that oxygen plays a key role in the FLASH effect. However, the exact mechanism behind this process is still far to be well understood. Since experimental data is scarce, simulations of the radiolysis of water in oxygenated conditions at ultra-high dose irradiation can shed some light on this issue. In this work, we present a new simulation framework aiming to study dose rate effects in the production of radical species in water and biological media.

Methods: The physical stage is simulated using the Monte Carlo track structure code TOPAS-nBio, whereas the chemical stage is based on a nonlinear reaction-diffusion model implemented in GPU. This approach allows us to consider the oxygen and other substances, without compromising the global computational time of the simulation. To cover the biological stage, simulations are extended over a longer period (~100 s) assuming a homogeneous distribution of radicals.



Results: In normoxic conditions the increase in ROO· radicals shows a FLASH transition for doses ranging in the 7-14 Gy range delivered in times below 100 ms. The influence in ROO· yields of other other beam parameters such as intrapulse dose rate and pulse frequency, according to the simulations, is below 4% in all cases.



Conclusions: The results obtained in organic matter media support enhanced radical recombination rather than transient radiolytic oxygen consumption and average dose rate as the main drivers of the FLASH effect.

EPD027 / #32

MODELLING THE EFFECTS OF INTER-SPUR INTERACTIONS AT FLASH DOSE RATES

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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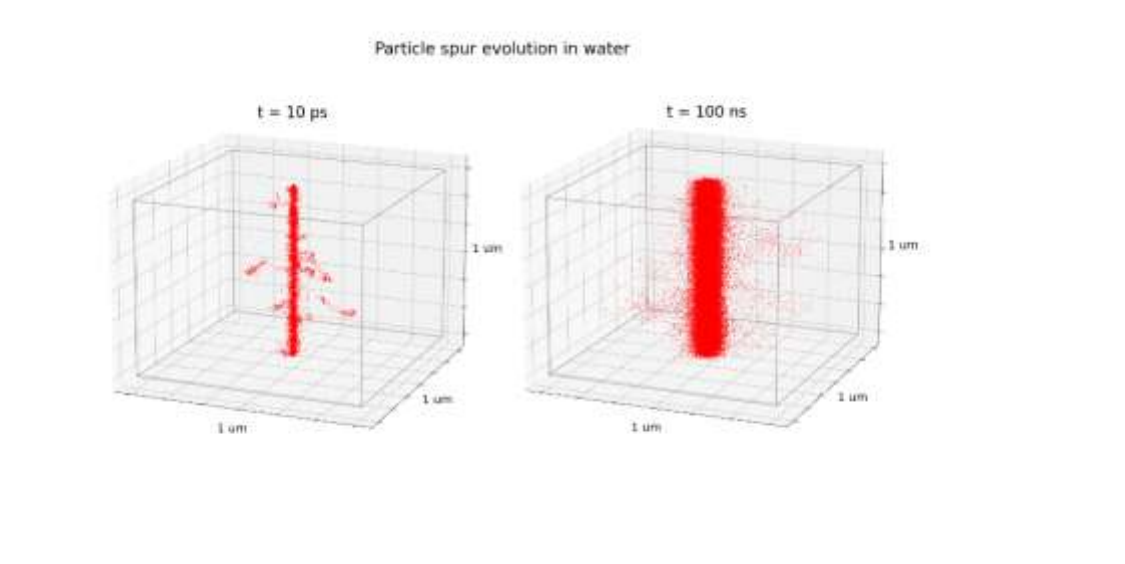
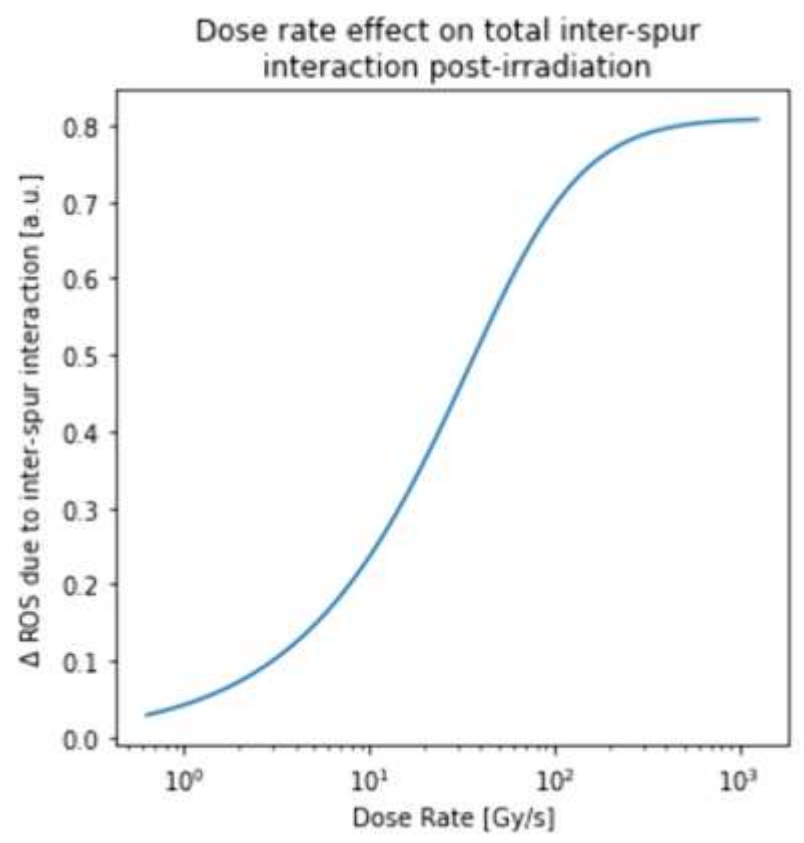
Background and Aims: Understanding the mechanisms contributing to the FLASH effect remains a critical challenge to FLASH radiotherapy research and clinical development. One hypothesis suggests that ultra-high dose rates lead to altered ROS radiochemistry. The interactions of particle spurs, the collection of radiochemical species produced along the track of an ionizing particle through biological material, with themselves (intra-spur) and other particle spurs (inter-spur) may play a vital role in causing this altered radiochemistry. We therefore investigate the amount of inter- and intra-spur interaction as a function of beam parameters with reaction-diffusion modelling.

Methods: The spatiotemporal evolution of the radiochemical species distributions that constitute each spur is modelled with a reaction diffusion system with one linear reaction (consumption) term which describes ROS scavenging. The spurs themselves are modelled as straight and homogeneous along the beam axis, spread spatiotemporally across the simulated target surface as dictated by the initial beam parameters. The amount of interaction within and between spurs is measured with the rate equation. Theoretical expectation values of the average amount of intra- and inter-spur interaction over time are validated with a computational implementation of the model.



Results: Our model allows for calculation of the amount of intra- and inter-spur interaction over time as a function of beam parameters, both over the irradiation time and post-irradiation.



Conclusions: Our model provides a framework to investigate alterations of ROS radiochemistry at FLASH dose rates depending on beam parameters. Future work will include varying oxygen concentrations and the full reaction diffusion system of different ROS species.

EPD028 / #264

FORMATION OF EARLY, TRANSIENT, STRONGLY ACIDIC SPIKES IN THE PROTON RADIOLYSIS OF WATER AT ULTRA-HIGH (FLASH) DOSE RATES.

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: FLASH radiotherapy is a new irradiation method that uses ultra-high dose rates (>40 Gy/s) to deliver large doses of radiation to tumors almost instantly (<100 milliseconds). Healthy tissue is spared using this method without compromising tumor control, resulting in a markedly increased therapeutic index compared to conventional radiation delivery at much lower dose rates (~0.03 Gy/s). The underlying mechanism(s) behind this effect remains unknown.

Methods: Monte Carlo track chemistry simulations of the low linear energy transfer (LET) radiolysis of water by multiple, simultaneously interacting proton tracks were used along with an “instantaneous pulse” irradiation model to quantify the early, transitory, acidic response of the irradiated volume, as previously predicted by our group. Simulations were carried out for 300-MeV irradiating protons (LET ~ 0.3 keV/μm) under deaerated and aerated conditions at 25 °C.

Results: Our calculations show that the formation of H3O+ temporarily renders the irradiated volume very acidic. The “acid spike” effect is observed immediately after the energy release and is greatest for times shorter than ~1 μs. In this time period, the pH remains nearly constant, decreasing sharply as a function of dose rate, from ~6 for low-dose-rate irradiation to about 3 at 5 × 109 Gy/s. These values remain little dependent on the presence or absence of oxygen.

Conclusions: Confirming our previous work, this study raises the question of the importance and role of these spikes of acidity in the current radiobiological puzzle that seeks to explain the underlying mechanism(s) behind the FLASH effect.

EPD029 / #281

MICROSCOPIC SIMULATIONS OF OXYGEN ENHANCEMENT ON DNA DAMAGES IN FLASH CONDITIONS

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Oxygen depletion is one popular hypothesis to explain the FLASH effect, which leads to redced oxygen enhancement ratio (OER) in normal tissue. We previously revealed that oxygen depletion is unlikely to happen due to a reduced oxygen consumption rate along with increased dose rate and decreased oxygen concentration. In this work, we extended our in-house developed high-performance microscopic Monte Carlo (MC) simulation package, gMicroMC, to include the oxygen fixation role into the FLASH effect study.

Methods: We applied gMicroMC to simulate the DNA damage under different oxygen concentrations. A step-by-step diffusion and mutual reaction of oxygen molecules with radicals and DNA was simulated for a proton radiation pulse of 100 ns. The proton is 79.7 MeV and with a dose rate of 10^8 Gy/s. The dose deposition is considered at the Bragg peak region. We grouped the DNA damage sites into DNA double strand break (DSB). The OER between 0% and 2% is determined as the ratio of the DSBs at these two levels.

Results: We determined that w/o oxygen fixation, strand break probabilities from a damage site were 0.28 and 0.08, respectively, from simulations for x-ray cases. Applying these parameters in the proton case, the relative OER was 2.01 for the single pulse FLASH mode comparing cases with PO2=2% and PO2=0 while it was 2.8 for the conventional mode.

Conclusions: The lower OER indicates reduced damage to normal tissue compared to tumor considering their oxygen concentration. More studies on other oxygen levels, other FLASH dose rates and beam delivery scenarios are under investigation.

EPD030 / #297

DOSIMETRIC COMPARISON SCHEME FACILITATING MULTI-CENTER FLASH-RT PRE-CLINICAL STUDIES

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: FLASH radiotherapy (FLASH-RT) showed the promises of reduced normal tissue toxicity and equivalent tumor response. At a practical and routine level, FLASH-RT preclinical studies suffer from significant metrological challenges. FLASH irradiations are currently performed using ultra-high dose-rates (UHDR) irradiations, which remain outside the internationally recommended framework. In this context, a comparison scheme using passive dosimeters was designed and validated in order to bring rapidly a dosimetric consensus.

Methods: IRA has been piloting multiple inter-laboratory comparisons in the field of radiation protection, nuclear medicine, radionuclide metrology and radiotherapy. In external beam RT, phantoms are used to ease the comparison process and improve repeatability. Tailored for the FLASH preclinical studies, a mouse phantom containing passive dosimeters was designed and validated.

Results: We evaluated the dosimeters in light of previous results obtained using our UHDR beams. Three types of passive dosimeters were selected: Thermoluminescent Dosimeters (TLDs), EBT3 Gafchromic films, and alanine pellets. The comparison process was optimized taking into account as many factors of influence as possible. The standard deviation of dosimeters within a single phantom remained below 3% and the measured dose from each dosimeter was always compatible with the target dose.

Conclusions: The mouse phantom and passive dosimeters were successfully validated using 3 linacs on 2 sites. The target dose was chosen approximatively exactly at 15 Gy and conventional as well as UHDR were used. This work resulted from the project 18HLT04 UHDpulse which received funding from the EMPIR programme and by NIH program project grant PO1CA244091.

EPD031 / #232

A NEW DOSIMETRIC SYSTEM FOR RELATIVE AND ABSOLUTE DOSIMETRY OF PROTON BEAMS WITH DOSE RATES UP TO 230 GY/S

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Currently, no well-established absolute calibration protocols for dosimetry of extremely high dose-rate charged particle beams are established. Moreover, the establishment of an accurate and reliable absolute dosimetry of ultra-intense proton/ion beams, able to fulfil the specific requirements and tolerances needed for clinical applications, is an ambitious task that also requires the development of innovative detectors, methods and procedures. In this work, we will present a solution for real-time absolute and relative dosimetry under FLASH irradiation conditions. The system was designed and successfully developed and tested at the INFN-LNS (Catania, Italy) with pulsed proton beams up to 230 Gy/sec.

Methods: The proposed approach is based on the use of dose-rate independent detectors (Faraday Cup and Radiochromic Films) coupled to a specifically designed dual-gaps, in-transmission ionization chamber, able to correct the recombination effects. A secondary electron emission monitor was also employed to online measure the proton beam flux.

Results: The overall absolute dose estimation accuracy, in terms of the relative mean difference between the dose measured with the different detectors, was found to be less than 5%.

Conclusions: Recently, a new relative dosimeter, based on a stack of Silicon Carbide detectors to reconstruct the incident proton energy spectra was additionally realized. The detector, named PRAGUE (Proton Range Measure Using Silicon Carbide) was funded by the H2020 in the framework of the MSCA-IF program and by the INFN. The entire dosimetric system, including the PRAGUE detector, was designed to work also with proton bunches (up to hundreds of nanoseconds) typically produced by the laser-plasma interaction.

EPD032 / #93

THERMOACOUSTIC RANGE VERIFICATION DURING PENCIL BEAM DELIVERY OF A CLINICAL PLAN TO AN ABDOMINAL IMAGING PHANTOM

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: High dose rate ion therapy will increase risk due to range errors - and maximize thermoacoustic emission amplitudes. We achieved submillimeter accuracy of thermoacoustic range estimates in an abdominal phantom during delivery of a hypofractionated clinical plan.

Methods: A single-field 12-layer proton pencil beam scanning (PBS) treatment plan prescribing 6 Gy/fraction was delivered by a superconducting synchrocyclotron to a triple modality (CT, MRI, and US) abdominal imaging phantom. Data was acquired by four acoustic receivers rigidly affixed to an ultrasound array. Acoustic receivers (transducer + amplifier) tuned to this application provided 15-25 dB amplification relative to 1 mV/Pa over 10-100 kHz. Receivers 1-2 were located distal to the treatment volume, whereas 3-4 were lateral. Receivers' room coordinates were computed relative to the ultrasound image plane after co-registration to the planning CT volume. For each prescribed beamlet, a Monte Carlo simulation of the energy density provided initial pressure from which simulated emissions were computed. To overcome the diffraction limit, range estimates were computed by comparing measured to simulated emissions.

Results: Shifts were small for high-dose beamlets that stopped in soft tissue. Signals acquired by channels 1-2 yielded -0.2+/0.7 mm shifts relative to Monte Carlo simulations for high dose spots (~40 cGy) in the second layer.

Conclusions: Shifts were small for high-dose beamlets that stopped in soft tissue. Signals acquired by channels 1-2 yielded -0.2+/-0.7 mm shifts relative to Monte Carlo simulations for high dose spots (~40 cGy) in layer two. FLASH particle therapy could benefit from online range verification based upon the first few beamlets delivered.

EPD033 / #75

AN ION CHAMBER ARRAY FOR EASY ASSESSMENT OF FLASH PROTON FIELDS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Accurate dosimetry is a key issue for understanding the mechanism of FLASH. There is a need for an easy to handle, two-dimensional QA solution capable of measuring dose profiles at FLASH dose rates. Here, we characterize a prototype of a commercially available and potentially 'FLASH-ready' ionization chamber (IC) array with an extended dose rate range.

Methods: The OCTAVIUS 1600 XDR detector (PTW) was tested in a 250 MeV proton FLASH beam at a Varian ProBeam facility (DCPT, Denmark). The array consists of 1521 air filled ICs (0.0125 cm3) with a chamber-to-chamber distance of 5/2.5 mm in a 15/6.5 cm square area. Evaluation of the prototype array was performed for nozzle currents from 20 nA to 215 nA and included reproducibility, dose linearity, recombination and dose rate dependence tests.

Results: The array shows a linear dose response with reproducibility of average dose better than 0.1%. The functional dose limit is approximately 9 Gy. Higher doses might lead to saturation depending on field parameters and proton current. Dose rate dependence is smaller than 1% for all tested proton currents.

Conclusions: The OCTAVIUS 1600 XDR prototype IC array is suited for QA of FLASH fields (< 15 cm) for doses up to 9 Gy. It is a commercially available solution easy to implement in a clinical routine.

EPD034 / #169

DOSIMETRY IN PULSED PHOTON FIELDS WITH DOSEPIX

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: In this contribution, we will present measurements of personal dose equivalents for photons in continuous and pulsed fields. The investigations were carried out in cooperation with the Erlangen Centre for Astroparticle Physics and the German National Metrology Institute PTB.

Methods: We use a setup of three Dosepix photon-counting hybrid pixel detectors equipped with 0.3 mm thick pixelated silicon sensors individually covered by specific filter-caps. The filters in front of the pixel detectors are necessary to extend the energy range for correct dosimetry as Compton scattering starts to dominate interactions in silicon for photon energies above 60 keV. The dose calculation principle is entirely linear and supplies $H_p(10)$ and $H_p(0.07)$ with the same data set.

Results: We will demonstrate the independence of the measured dose from pulse duration down to 2 ms short pulses and a dose rate capability up to 700 Sv/h in an RQR8 reference photon field. The normalized response shows a maximum deviation to 1 of 20% and is therefore within IEC 61526 limits for the energy dependence ($H_p(10)$: 12 keV to 1.3 MeV, $H_p(0.07)$: 25 keV to 1.3 MeV) and angular dependence (0°, 30°, 60°). The influence of beta irradiation on the indication of $H_p(10)$ is smaller than 2% of the dose for beta-radiation sources such as 147Pm, 85Kr, 90Sr in terms of $H_p(0.07)$.

Conclusions: Our results demonstrate that the hybrid pixel detector approach is a promising route to a dosemeter for pulsed radiation useful for real-time dosimetry. It enables active radiation protection of occupationally exposed workers.

EPD035 / #170

DOSIMETRY IN HIGH DOSE RATE PHOTON FIELDS USING THE DOSEPIX DETECTOR

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Portable X-ray generators are commonly used in veterinarian medicine, non-destructive testing, and forensic investigations. Some of these X-ray generators produce X-ray pulses with very low pulse durations and very high dose rates which might lead to pile up in active personal dosemeters. In a cooperation between the Erlangen Centre for Astroparticle Physics and the German National Metrology Institute (PTB), we present a measuring procedure to determine the personal dose equivalent in pulsed photon fields with very high dose rates.

Methods: The measurements are carried out using 3 pixelated silicon based particle detectors covered with different filters. The 256 pixels are realized with 2 different active pixel areas to extend the measurable photon flux. The analysis is carried out via a neural network trained on simulation data. The simulation procedure and the analytical methods are outlined. The measurements are performed with a battery-powered, pulsed X-ray generator with a fixed tube voltage of 150kV and a pulse duration of about 115ns. The mean energy of the applied X-ray spectrum is 55keV.

Results: We will show results on measurements with dose rates in range from $1.6 \cdot 10^3$Sv/h to $1.6 \cdot 10^5$Sv/h whereas the Hp(10)-response could be determined to be in a range of 0.68 to 1.47. The data is normalized to the mean of the measured response values.

Conclusions: The presented results demonstrate the functionality of the detector system and the analytical method.

EPD036 / #174

ULTRA-HIGH DOSE-RATE DOSIMETRY AT A SYNCHROTRON-BASED FACILITY WITH AN ACTIVE BEAM SCANNING DELIVERY SYSTEM FOR P, 4HE, 12C AND 16O

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Feasibility of ultra-high dose-rate (uHDR) delivery at high dose with low and high LET particle beams is under investigation to complement further radiobiological observation and modelling of dose-rate effects with photon and electron beams. A thorough assessment of dosimetric, temporal and spatial active-beam scanning field delivery parameters are needed for single spill extraction at FLASH dose-level/dose-rate. This work presents uHDR dosimetry standardization for p, 4He, 12C, 16O irradiations at a synchrotron-based facility with a raster-scanning system.

Methods: An irradiation setup was proposed directly outside the beam nozzle for standard dose rate (SDR) and uHDR delivery of a 8x8x20mm³ homogeneous spread-out Bragg Peak with a monoenergetic 16-spot plans. Dose-level and field homogeneity adjustment (against beam-width variation) are performed using a 2D ionization chambers array at SDR. Absolute dosimetry and field verifications are conducted in both SDR and uHDR with a pinpoint ionization chamber and EBT3 films. Tuning of the beam delivery time, and its recording, are made possible through feedback from the monitor chamber current to the extraction system.

Results: The presented workflow was successfully implemented to perform uHDR irradiation with different particle species at various dose-levels/dose-rates for biological experiment.

Conclusions: At our facility, main limitations for FLASH irradiations are the maximum number of particles injected into the synchrotron and the spill extraction time. These system features can be optimized to a certain extent and could be further improved from specific hardware updates driving particle beam FLASH closer to clinical application.

EPD037 / #210

A NEW MODEL OF GAS CHAMBER FOR UHDR RANGE

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: In the clinical practice, ionization chambers (IC) represent the standard for the commissioning of medical linacs. Nevertheless, their use in UHDR range is not currently possible, due to the amount of charge produced by each pulse. Being E_0 the electric field, V_0 the polarization and p the free electron fraction within the IC, their relevance in the three ranges is discussed in figure.

	Conventional dpp ≤ 0.5 cGy/p	IOeRT dpp ≤ 20 cGy/p	UHD
What is E inside IC?	$E = E_0 = V_0/d$	$E = E_0 = V_0/d$	$E \neq E_0 = V_0/d$
Is p relevant for saturation evaluation?	p can be NOT relevant considered	P must be considered	P must be considered
Does E change within pulse time and within IC volume?	$\frac{\delta E}{\delta x} = 0; \frac{\delta E}{\delta t} = 0$	$\frac{\delta E}{\delta x} = 0; \frac{\delta E}{\delta t} = 0$	$\frac{\delta E}{\delta x} \neq 0; \frac{\delta E}{\delta t} \neq 0$

When working in UHDR region, ICs are affected by two different phenomena that makes the standard theory not applicable. The electric field inside the chamber is variable during the pulse time and within IC volume. The general behaviour is difficult to be described, due to the two competing effects: ion collection decrease (recombination) and ion collection increase (secondary electrons generation).
Methods: 50 Gy/p is the maximum reasonable dose in a single pulse that can be delivered in the Flash perspective (ELIOT protocol for breast cancer and assuming a 100% Flash sparing effect). In order to realize an IC capable of measuring such dose, we aim to find those/that particular conditions/configuration which can remove the ion-ion recombination and avoid secondary uncontrolled electrons generation.
Results: Within this framework, we provide a detailed analytical model and, consequently, design and build a new model of gas chamber which can work up to 50 Gy/p, with a final accuracy around 3%.
Conclusions: A patent on the new gas chamber has been filed. Chamber theory and its design will be described and its prototype presented, together with the first measurements with ElectronFlash beams.

EPD038 / #285

MULTI-LEAF FARADAY CUP FOR QUALITY ASSURANCE IN RADIATION THERAPY WITH ELECTRON AND ION BEAMS AT CONVETIONAL AND ULTRA-HIGH DOSE RATE

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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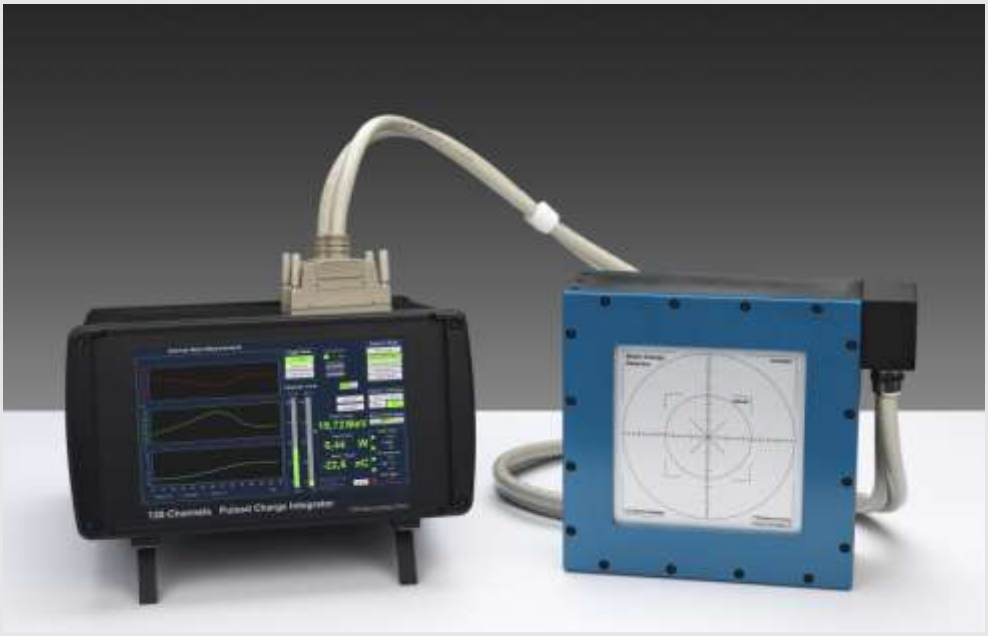
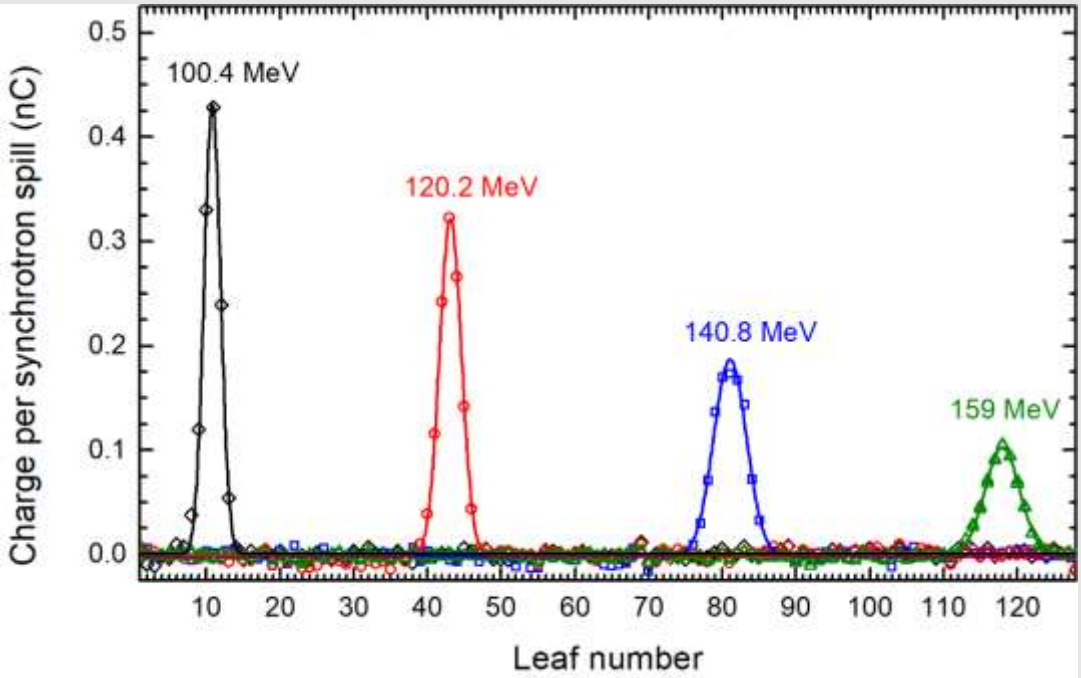
Background and Aims: For quality assurance in radiation therapy with high-energy electrons, protons or carbon ions, the beam energy has to be checked in clinical routine. This test is time-consuming and requires expensive equipment. If the dose rate is varied by orders of magnitude to compare ultra-high dose rate with conventional irradiation, one should be able to measure the energy quick and reliable and independently of the accelerator readouts or manufacturer's specifications. For this purpose, a portable Multi-Leaf Faraday Cup (MLFC) was developed (Fig.1), with a readout electronics whose is not influenced by the dose rate.



Methods: The MLFC was irradiated with protons with energies between 64 – 252 MeV from a synchrotron source. Aluminium disks were placed in front of the MLFC as range shifter. Charge and energy were measured per synchrotron spill (Fig.2). Furthermore, the MLFC was tested in electron beams of conventional and ultra-high dose per pulse.



Results: For monoenergetic electron or proton beams energy differences of 80 keV (0.8%) or 60 keV (0.1%), respectively, can be clearly distinguished.

Conclusions: Due to the measurement principle, which is independent of the dose rate, the MLFC is suitable for quality assurance of charged particle radiation with conventional as well as ultra-high dose rate, for short pulses as well as for continuous radiation. Energy and intensity can be measured quick and reliable. Acknowledgement: This project 18HLT04 UHDpulse has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.

EPD039 / #21

DOSE RATE MEASUREMENTS IN PRE-CLINICAL PROTON FLASH STUDIES WITH FAST INORGANIC SCINTILLATOR DETECTOR

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Time resolved dosimetry is key to ensure correct FLASH delivery. The high dose-rates and required time resolution pose a challenge for many dosimeter types. Scintillators are a good candidate for real-time FLASH dosimetry. In this study, the dose-rate response of a scintillator dosimeter was investigated and used for in vivo dosimetry in pre-clinical mice studies.

Methods: A fast detector system, which measures the instant dose rate with 50kHz rate was developed. The system had four fiber-coupled scintillating ZnSe:O crystals of sub-millimeter dimensions. The high time resolution allowed for measurement of the dose-rate for each beam spot during FLASH proton beam scanning delivery (Fig 1A). The system was first calibrated against an Advanced Markus Chamber at instantaneous dose-rates of 0-1000Gy/s. The calibrated system was then used to determine the field dose-rate in pre-clinical experiments, where three dosimeters were placed behind the leg of each irradiated mouse. The experiments took place over two rounds with the detector components being detached and reassembled after calibration and between rounds.

Results: The detector signal showed non-linear response, however without saturation. Preliminary calibration was performed with a third-degree polynomial dose-rate dependence (Fig 1B). The deviation between measured and log-file estimated field dose-rate was 3.1Gy/s overall and <1.6Gy/s for individual detectors in a round (Fig 2A,B).

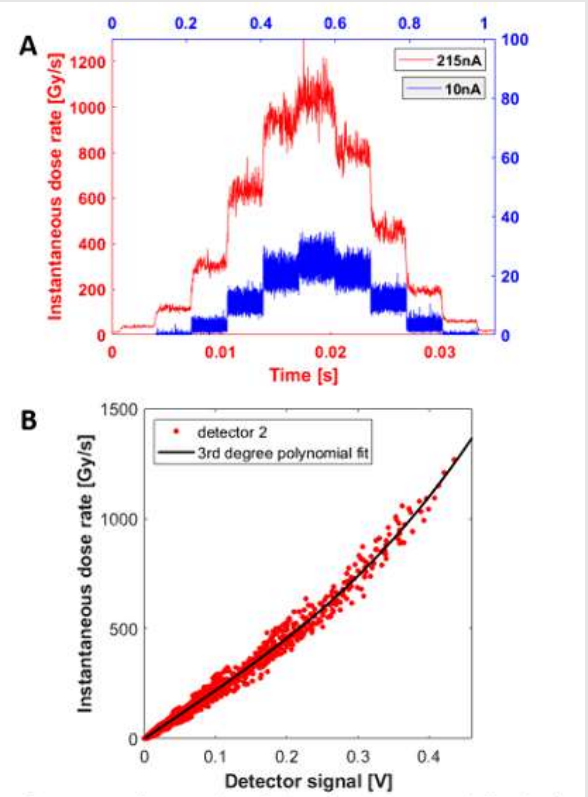

Figure 1: A) Example of the detector signal for high dose-rate delivery (215nA, ~90Gy/s field dose-rate, red) and low dose-rate delivery (5nA, ~2Gy/s field dose-rate, blue). Each plateau in the signal corresponds to a single beam spot. Note the difference in dose-rate values and timescale. **B)** Dose-rate response curve for one of the detectors. Each data point corresponds to a single spot. The response is fitted to a 3rd degree polynomial function.

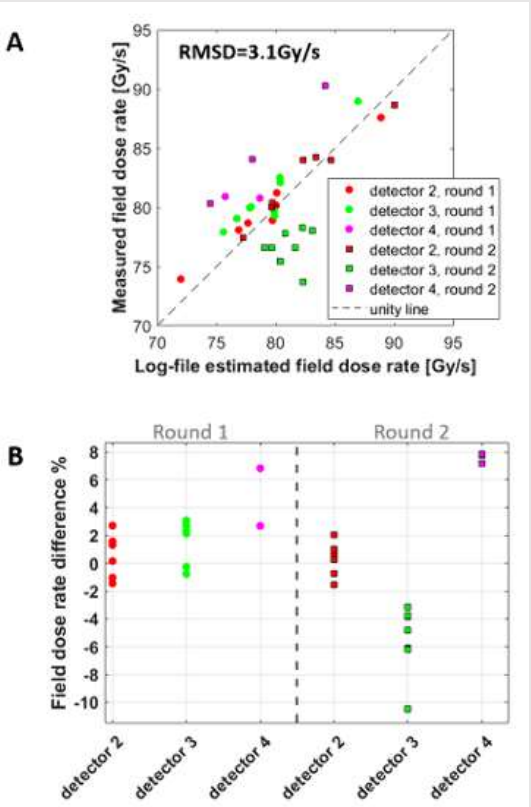

Figure 2: A) Field dose-rate for 36 pre-clinical mice irradiations, that took place in 2 rounds. The measured field dose-rate, found from the integrated dose divided by the total measured duration, is compared to the field dose-rate calculated from nominal dose delivery divided by the logged total duration. **B)** Percentage difference of measured and logged field dose-rates shown in A, for the two rounds of irradiations. The detector components were detached between rounds.

Conclusions: The large dynamic range of the dosimeters cover both conventional and FLASH dose-rates. The use in pre-clinical studies allows for in vivo dose-rate validation during FLASH treatments. A calibration is needed when the detector components are detached.

EPD040 / #217

ULTRA-HIGH DOSE RATE DOSE DELIVERY AND MONITORING FOR PROTON BEAMS

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: FLASH radiotherapy uses ultra-high dose rate aiming at reducing normal tissues damage as compared to conventional dose rate. Our aim is to provide proton irradiations with similar dose rates at the µs time scale as the electron beam irradiations that demonstrated normal tissue sparing and to develop accurate proton dose delivery control.

Methods: A pulsed beam (<=1 kHz frequency, >=5 µs pulselength) of 150 MeV protons from the UMCG PARTREC cyclotron is used for ultra-high dose rate irradiations. Dose delivery control using ionisation chambers and non-intercepting inductive beam monitors is investigated. For the latter a collaboration with Bergoz Instruments has been established; tests of their newly developed device are under way. Faraday cup and activation measurements, free from saturation effects, are used as benchmark.

Results: Proton beams with a current up to 2 µA have been produced, corresponding to a peak dose rate of about 10^5Gy/s for this routinely delivered 3 mm FWHM pencil beam. Further increase up to >=10 µA is under development. First measurements with a prototype dual gap ionization chamber have shown that also nitrogen-filled chamber exhibit significant saturation effects at this dose rate. Additional measurements with an updated design and other gases are in preparation.

Conclusions: The capability to deliver 10^5 Gy/s proton irradiations has been demonstrated. Ionisation chambers can be used for dose delivery control if recombination can be reduced, inductive beam intensity monitors may be an alternative. This work was supported by EU Horizon2020 grant 730983 (INSPIRE).

EPD041 / #270

FLASHDC PROJECT: DEVELOPMENT OF A BEAM MONITOR FOR FLASH RADIOTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: FLASH radiotherapy brings severe challenges to dosimetry, beam control, and verification. A FLASH beam monitor able to measure the rate of impinging particles per pulse is a crucial step to validate the FLASH effect. The simultaneous request of spatial modulation in dose delivery and the request of high-dose average and instantaneous rates typical of FLASH, make an accurate beam control non-trivial: dose-rate independence, wide dynamic range and high spatial and temporal resolution, are the needed requirements for such a monitor. Until now there are no technologies available that fully meet the needed requirements.

Methods: The FlashDC project aims to develop an innovative beam monitor for FLASH, based on the physical phenomenon of air fluorescence, never exploited for this kind of device. Using air as a medium in which fluorescence is developed allows to minimize the impact of the detector on the beam line and to have a device simple and cheap to produce. Fluorescence in air provides a signal unsaturated by the high number of particles per pulse, typical for FLASH, with a very wide dynamic range.

Results: A first prototype of the monitor has been developed, consisting in a parallelepiped of black PVC filled with air and read at the two edges by two photomultipliers able to provide temporal and spatial reconstruction capabilities fitting the needed resolutions for FLASH application.

Conclusions: A set of preliminary measurements with the prototype monitor using electrons beams and the obtained results will be shown. Finally, the performances expected with a final possible device will be presented.

EPD042 / #293

MEASUREMENTS OF SCATTERED RADIATION PRODUCED IN ELECTRON BEAMS USING MINIPIX TIMEPIX3 FLEX

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Improvements of a new method for cancer treatments involve the complete characterization of both primary and secondary contributions from the radiation in ultra-high dose rate pulses (UHDpulse) beam. This study proposes a comprehensive analysis of the backscatter radiation produced by an electron beam in FLASH radiotherapy with the ADVACAM's prototype, MiniPIX TimePIX3 Flex detector.

Methods: Composition, spatial, time and spectral data were acquired with the TimePIX3 ASIC chip detector at the Microtron electron Accelerator of the Nuclear Physics Institute CAS, Prague, Czech Republic. The stray radiation was measured behind PMMA plates of 1 cm thickness. TimePIX3 detectors with silicon sensors of 100 and 500 µm were periodically shifted at different angles and lateral positions toward the direct incidence of the beam.

Results: For different delivered dose rates, using the MiniPIX TimePIX3 detector placed at a distance of 10 cm from the direct beam, we were able to discriminate types of particles that form the scattered radiation during the irradiation process and to calculate the scattered dose rates (Figure 1).

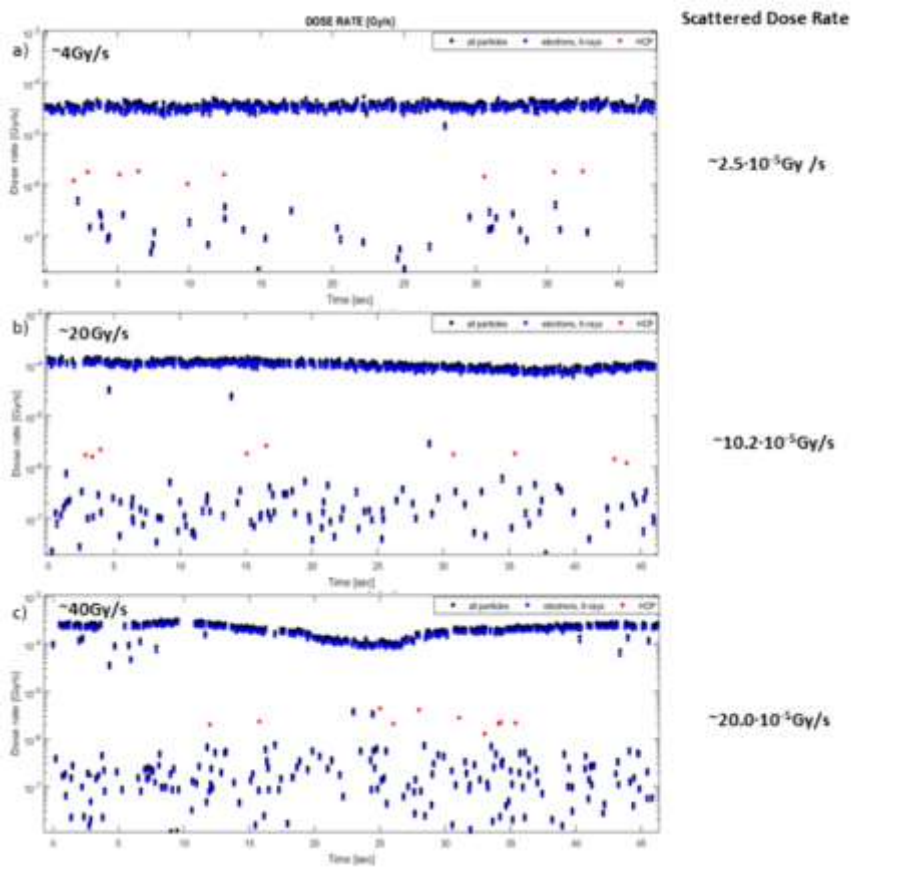

Figure 1. Dose rate measurements of scattered radiation at 10 cm distance from the primary beam at different delivered dose rates, a) 4Gy/s, b) 20Gy/s, and c) 40Gy/s measured with a MiniPIX TimePIX3 detector with 500 μm silicon sensor.

Conclusions: The ability of the detector to identify particles that come from the secondary radiation in the case of the UHDpulse emphasise the detector's efficiency in modern techniques used in radiotherapy.
Acknowledgements: 18HLT04 UHDpulse has received funding from the EMPIR program.

EPD043 / #133

ESTABLISHMENT OF A FLASH RADIOTHERAPY FACILITY AT NPL AND DOSIMETRY STUDY

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Recent FLASH radiotherapy (RT) studies have shown promising results, including improved RT outcomes, reduced treatment times and sparing normal healthy tissues. However, due to the high dose rates involved, there are several dosimetric challenges, such as lack of reference conditions and appropriate dosimetric detectors. This work aims to establish a FLASH electron facility at NPL and conduct a proof-of-principle dosimetry study.

Methods: The X-ray mode for 6MV of an Elekta Synergy Clinical Linac (MLCi2), installed at NPL, was modified by removing the flattening filter, tungsten target and internal monitor chamber. A monitor chamber was installed externally to bypass the linac interlocks and a pulse counter was used to interrupt the beam after the desired number of pulses were delivered. A first dosimetric assessment of the 6 MeV ultra-high dose rate (UHDR) electron beam was performed with EBT3 Gafchromic films, alanine and in-house built aluminium calorimeter at 55cm source-to-surface distance (SSD) and 6cm × 6cm field.

Results: During the first phase, a successful delivery of a FLASH electron beam operating in the pulse counting mode was achieved. Preliminary measurements were acquired to verify the dose rates achieved.

Conclusions: The study is currently ongoing and aims to fully investigate the dosimetric characteristics of this beam and perform absolute dosimetry employing the UK primary standard electron graphite calorimeter, alanine, film and ionisation chambers. The measurements will be complemented with Monte Carlo modelling to allow for the calculation of necessary correction factors. "This work resulted from the project 18HLT04 UHDpulse which received funding from the EMPIR programme."

EPD044 / #43

PROTON BEAM DOSIMETRY AT ULTRA HIGH DOSE RATES: EVALUATION OF THE USABILITY AND THE DOSE RATE DEPENDENCY OF VARIOUS RADIOCHROMIC FILMS.

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: The ARRONAX facility can deliver proton beams in low and ultra-high dose rates (UHDR) (7500 Gy/s). Our beamline, tuned for 68 MeV, is adapted to preclinical irradiations and specifically set up to easily shift between conventional and UHDR irradiation conditions. As a good control of the dosimetry is a pre-requisite of UHDR experimentations, we evaluated the usability and the dose rate dependency of various radiochromic films in different conditions.

Methods: We compared the response of three types of radiochromic films: EBT3 and EBT-XD (GAFchromic™), and OrthoChromic OC-1 (OrthoChrome Inc.), after proton irradiations at various mean dose rates (0.25, 40, 1500 and 7500 Gy/s) and for 10 different doses (2-130 Gy). We also evaluated the impact of the linear energy transfer (LET) in the response of each film, for 3 different LETs (1.4±0.1, 4.3±0.6 and 8.1±2.4 keV.µm^{-1}), and the impact of the pulse structure: (i) multiple pulses (instantaneous dose rate D_p=7500Gy/s; width=100µs) at various frequencies and (ii) a single pulse with various D_p.

Results: Significant differences were observed in the responses of EBT3 and EBT-XD films between irradiations in conventional (0.25 Gy/s) and UHDR (7500 Gy/s) conditions, for doses superior to 10 Gy. No significant difference was observed for all films for mean dose rates less than or equal to 1500 Gy/s. No impact was found associated to the pulse structure nor the LET.

Conclusions: EBT3 and EBT-XD films are not appropriate for proton beam dosimetry above 10 Gy at UHDR (≥7500Gy/s). OrthoChromic films could be used in these irradiation conditions.

EPD045 / #306

RADIOBIOLOGICAL MECHANISMS IN MICROBEAM RADIATION THERAPY (MRT)

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Microbeam Radiation Therapy (MRT) is an innovative preclinical concept in radiotherapy that collimates X-ray radiation in micrometer-wide, planar beams. Previous research has shown that MRT substantially spares normal tissue, while being equally effective in tumor ablation. In order to validate doses measured with radiochromic film dosimetry, biological dosimetry using the cytokineses blocked micronuclei (CBMN) assay was applied on a cellular level.

Methods: CBMN assay was performed using CHO cells after homogeneous irradiation to establish a dose response curve, and afterwards with either sham or microbeam. At least 1000 binucleated cells were analyzed with Metafer (Metasystems, Germany). Microbeam radiation was performed at the XenX irradiation device (XStrahl, UK), equipped with a special microbeam collimator. Planar microbeams with a peak-width of 50 µm and a center-to-center distance of 400 µm (PVDR of 42) were produced.

Results: The dose-response curve was fitted with the linear equation (y=0.44x + 0.13). Irradiations with a physically calculated peak dose of 2 Gy and a valley dose of 0.05 Gy resulted in 2.05 +/- 0.12 Gy and 0.02 +/- 0.05 Gy respectively using biological dosimetry. However, after irradiations with a calculated peak dose of 82 Gy and a valley dose of 2 Gy, the micronuclei which were counted in the valleys equaled to 2.29 +/- 0.02 Gy.

Conclusions: This is the first study determining precisely the absorbed doses in the peak and valley regions of MRT. Slightly higher measured doses than the physically planned doses in the valleys indicate effects on a cellular level, which could be due to bystander effects or enhanced cell migration.

EPD046 / #70

FIRST TEST OF FLASH WITH CONTINUOUS LINE PROTON SCANNING

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Originally FLASH effect was discovered at the conventional linacs but also is expected at the proton therapy because of the feature of the proton accelerator which can output higher dose rate among the commercial any accelerators. Sumitomo Heavy Industries, Ltd. (SHI) has been developing the proton therapy system using cyclotrons. Besides, the ripple filters have been developed to form SOBP as the approach of fast irradiation.

Methods: To obtain the FLASH effect, over 40 Gy/s dose rate and over 8 Gy dose are required within single irradiation. OARs and skin require these dose amount and dose rate as the FLASH effect spears the normal tissue. In this study, SHI defined the dose-average dose rate was used as the dose rate. This means the irradiation must complete in 0.2 s when 8 Gy is delivered with 40 Gy/s. 230 MeV mono-layer beam was selected, which was available to output highest beam current over 150 nA at the nozzle and the 20 mm SOBP ripple filters were equiped in the nozzle. Scanned beam was employed and scan pattern covered 4 cm x 4 cm at isocenter to make uniform dose distribution. The delivered dose was measured by Advanced Markus Chamber: Type 34045 from PTW in solid phantom. This test was conducted in non-clinical mode.

Results: SHI's system achived delivering 11 Gy to 4 cm x 4 cm x 2 cm target volume within 0.17 s.

Conclusions: SHI's proton cyclotorn system achived 55 Gy/s into 32 cm^3 target volume.

EPD047 / #167

DOSIMETRY OF EXPERIMENTAL CARBON-ION MINI-BEAMS TOWARD 'CARBON-KNIFE' AND 'CARBON-FLASH'

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Carbon-Knife with carbon-ion mini-beams is expected to be an efficacious treatment for cancerous and/or non-cancerous diseases with mm sizes, because of its advantages of Bragg peak and consequent dose concentration with sharper penumbra. For application of such fine beams, dosimetry is quite essential but often difficult even using well calibrated dosimeters, because of the smaller beam size compared with the dosimeter sensitive area. We proposed dose distribution reconstruction method and estimated dose rate distributions for carbon-ion mini-beams. Furthermore, we explored the potential application of such high dose rate beams to carbon-flash.

Methods: Dose-Area-Product (DAP) rate distributions were measured with a diode dosimeter (sensitive area of 1 mm^2) for carbon-ion mini-beams with the beam size of 1 mm at surface and near Bragg peak depth. Lateral dose rate distributions at respective depths were reconstructed from the measured DAP rate distributions using the proposed iterative reconstruction method. For the application to biological experiments using the carbon-flash beams, different dose rate beams were also examined.

Results: In the reconstructed dose rate distributions, high dose rate of ~90 Gy/s at the beam center and sharp penumbra of $P_{80\text{-}20}$~0.2 mm were obtained at the Bragg peak and surface depths within the 1 mm beam size, respectively. Wider-sized carbon flash beams without the collimator were obtained for biology experiments.

Conclusions: The proposed method could estimate dose rate distributions of carbon-ion mini flash beams with 0.1 mm spatial resolution. The details of different dose-rate carbon-ion beams will also be presented.

EPD048 / #139

MAGNETICALLY FOCUSSED MINIBEAMS FOR A COMBINATION OF PMBRT AND FLASH

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Proton minibeam radiation therapy (pMBRT) [1] is a novel therapeutic strategy, combining the normal tissue sparing of sub-millimetric, spatially fractionated beams with the improved ballistics of protons. Current implementations of pMBRT at clinical energies are suboptimal due to their use of mechanical collimators which substantially reduce the dose rate. To improve these shortcomings, we recently proposed a new nozzle design suitable for the generation of magnetically focussed and scanned minibeams in a clinical context [2]. This technique can increase the irradiation flexibility and allows to maximise the dose rate which makes it a promising approach in particular regarding a combination of pMBRT and FLASH.

Methods: Monte Carlo simulations (TOPAS [3]) were performed to compare irradiation plans delivered with magnetically focussed proton minibeams and mechanically collimated minibeams. Dose distributions in a water phantom were compared as well as irradiation efficiency and neutron yield. Clinically relevant energies of 100-150 MeV were considered.

Results: Compared to collimated beams, magnetically focussed minibeams showed improved dose distributions (20-60 times higher degree of spatial fractionation, benefitting normal tissue sparing), as well as an increased irradiation efficiency (up to two orders of magnitude) and a significantly reduced neutron yield.

Conclusions: Minibeam generation through magnetic focussing, realised with our new nozzle design, was shown to provide substantial advantages over mechanical collimation. In particular, the higher irradiation efficiency allows to drastically increase the dose rate and thus pave the way towards a combination of pMBRT and FLASH. [1] doi:10.1118/1.4791648 [2] doi:10.1038/s41598-020-58052-0. [3] doi:10.1118/1.4758060

EPD049 / #240

EXPERIMENTAL DOSIMETRIC ESTIMATION OF VOLUME RESCANNING FOR SPOT SCANNING PROTON THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Breath-induced intrafractional motion of tissues leads to a significant distortion of dose distributions when irradiated with a scanning proton beam. One of the techniques of motion compensation is rescanning. This one is based on multiple repeated irradiations of the entire volume or individual iso-energy layers with a dose that is a multiple of the prescribed dose. This leads to an increase in the homogeneity of the dose field due to the averaging. This work demonstrates an experimental estimation of the volume rescanning technique in spot scanning proton therapy (SSPT) using a dynamic phantom.

Methods: Estimation is based on the analysis of average dose, dose homogeneity and dose gradient. Simulation of intrafractional translational motion is performed using the non-anthropomorphic water dynamic phantom. Dosimetry is carried out using EBT-3 films installed in the moving target.

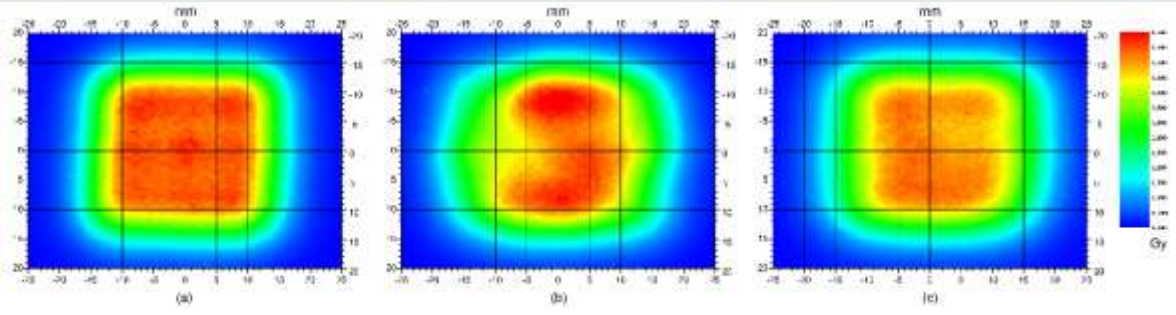

Fig. 1: Lateral dose distribution: without motion and rescanning (a), with motion with a period of 4,3 s, amplitude of 10 mm and without rescanning (b), and with motion and 10-iterative rescanning (c).

Results: Dose distributions were obtained at amplitudes of motion of 2, 5, 10 mm for prescribed dose of 6 Gy at 1, 2, 4, 6, 8, 10 rescanning iterations. For each case values of the average dose, dose homogeneity and dose gradient were calculated and compared with corresponding values in the case of no movement.

Conclusions: Volume rescanning improves the homogeneity of dose distribution, removes hot and cold spots. However, the dose gradients deteriorate in proportion to the amplitude of motion, and the irradiation time increases.

EPD050 / #272

EXPERIMENTAL VERIFICATION OF THE EFFICACY OF PBCT FROM PHYSICAL AND BIOLOGICAL ASPECTS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Recently, proton boron capture therapy (pBCT) has attracted attention as a method to enhance the treatment efficacy of proton therapy. However, the physical origin and biological effect of pBCT is yet debatable due to the lack of experimental data. It is thought that the p+11B→3α nuclear capture reaction plays a key role, although α particles are only produced in low quantities and thus cannot fully account for the observed efficacy of pBCT. In this paper, we first conducted experiments to search for possible channels contributing to α production not limited to p+11B→3α, and subsequently examined its biological effects on various cancer cells.

Methods: In the physical experiment, α particle production rates between proton and boron were measured for protons above 10 MeV, where no experimental data exists. In addition, the biological efficacy of pBCT was investigated by measuring the cell viability of MIA-PaCa-2 and DU145 cells during proton SOBP irradiation.

Results: The measured cross section of α-production was less than 10 mb for 10-70 MeV protons, which implies that there are no other channels exceeding the 3α reaction. In the biological experiments, we performed experiments with BPA-accumulated MIA-PaCa2 cells and observed that the biological effects were not as effective as previously reported. Further experiments using DU145 cells are now ongoing.

Conclusions: To verify the effectiveness of pBCT, we examined the cross section of α particle production at proton energies of 20-70 MeV. We further conducted systematic comparison of MIA-PaCa2 and DU145 cells with and without BPA-accumulation. These results are systematically discussed to examine yet unresolved mechanisms of pBCT.

EPD051 / #113

DEVELOPMENT OF A NOVEL IMAGING TECHNIQUE WITH VERY HIGH ENERGY ELECTRONS IN THE CONTEXT OF RADIOTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: We present a novel imaging technique using multiple Coulomb scattering of electrons with energies from O(10) to O(100) MeV. Future very high energy electron (VHEE) beams radiation therapies are expected to have bunched pencil beams with the possibility of control of the electron beams directions.

Methods: The electron beam is a bunched beam consisting of pulses of up to 1MHz. The direction of each bunch can be controlled, and at the minimum beam size of about 100μm in diameter, the beam is equal or smaller than the spatial resolution of the reconstructed image. When a bunched electron beam passes through a target, the electrons are deflected by multiple Coulomb scattering, and the spread of the electron beams depends on the material budget of the traversed material. In our experimental setup, the beam spread is measured by a AGIPD sensor, which is a silicon pixel sensor placed behind the target. The material budget distribution of the target is reconstructed from the beam spread.

Results: Monte Carlo simulations are performed to verify the selection of the sample, detector placement positions and the beam intensity. The experimental setup and the signal processing of the AGIPD sensor are precisely reproduced in the the Allpix^2 simulation framework. The feasibility and the expected performance of the imaging technique will be presented based on the result of the simulation study.

Conclusions: We introduce a novel imaging technique with the VHEE beams and show the feasibility and the expected performance of the technique based on Monte-Carlo simulation studies.

EPD052 / #84

A REVIEW OF RECENT STUDIES INVOLVING THE DOSIMETRY AND FOCUSSING OF VERY HIGH ENERGY ELECTRONS FROM LINEAR ACCELERATORS AND LASER-PLASMA WAKEFIELD ACCELERATORS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Very high energy electron (VHEE) beams are the basis of a potentially valuable radiotherapy modality because of their increased penetration depth relative to low energy electrons, and reduced sensitivity to tissue inhomogeneities relative to photons. Low energy electrons (4-22 MeV) are not suitable for treating tumours deeper than a few centimetres. Focussed electrons exceeding 50 MeV can penetrate deeper, achieve better dose conformation than their photon counterparts, and reduce healthy tissue toxicity. VHEEs can be produced at a relatively low cost and on the millimetre-scale using laser-plasma wakefield accelerators. Their high energies and ultra-short bunch durations could enable FLASH radiotherapy if the charge can be significantly increased.

Methods: Here at Strathclyde we have compared various dosimetry methods to determine those best suited to high dose-rate regimes. Additionally, we have experimentally compared depth-dose distributions of beams of several energies and f-numbers focussed in a water phantom with the theoretical prediction.

Results: Gafchromic film has been shown to be reliable for VHEE dosimetry, and for radiochromic film and alanine no energy dependence up to 50 MeV was observed. Focussed VHEE beams display an on-axis dose enhancement at a depth of 5-6 cm. This method reduces healthy tissue toxicity and increases delivery precision.

Conclusions: Our work thus far has been illuminating in the areas of dosimetry and focussing VHEEs to sufficiently concentrate dose for investigations of the FLASH regime in the treatment of deep-seated tumours. Future studies aim to develop further the understanding of the appropriate physics, chemistry and biology to facilitate translation to the clinic.

EPD053 / #196

RECENT STUDIES TOWARD AN EFFECTIVE USE OF LASER-DRIVEN VERY HIGH ENERGY ELECTRONS FOR RADIOTHERAPY: FEASIBILITY ASSESSMENT OF ADVANCED IRRADIATION SCHEMES AND PERSPECTIVES FOR FLASH

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: The use of Very High Energy Electrons (VHEE) for radiotherapy is deserving a growing attention, due to the potential to provide doses/dose rates of interest for the FLASH radiotherapy. In this scenario, laser-driven electron acceleration is regarded as one of the most promising routes for the development of compact and reliable devices with the required parameters for a medical use. Laser-driven electron beams, due to their ultrashort duration, also feature a peculiar time structure, with ultrahigh instantaneous dose rate, whose role and potential in radiobiology is still to be addressed. We report on recent experiments aimed at assessing dose deposition for deep seated tumors with laser-driven VHEEs.

Methods: We employed VHEE pencil beams, driven by a 100TW laser, to demonstrate the feasiblity of advanced irradiation schemes typical of current radiotherapy modalities. Absolute dosimetry was carried out, using both experimental data and Monte Carlo simulations.

Results: The measurements showed control of localized dose deposition and modulation, suitable to target volumes at depths 5-10 cm with mm resolution. Monte Carlo simulations provided additional data for further experiments.

Conclusions: Laser-driven VHEE pencil beams have been demonstrated to exhibit the required properties to treat deep tumors. Based on these experimental findings and on numerical simulations, we discuss features and potentialities of laser-driven VHEE sources for radiobiology experiments aimed at deepening the understanding of the mechanisms underpinning the FLASH effect. The main requirements and the perspectives for a longer term translation of a laser-driven electron radiotherapy into the real clinical practice will be also outlined.

EPD054 / #304

CONDITIONS FOR RADICAL-RADICAL RECOMBINATIONS AT ULTRA-HIGH DOSE RATE FOR DIFFERENT LET AND PARTICLES

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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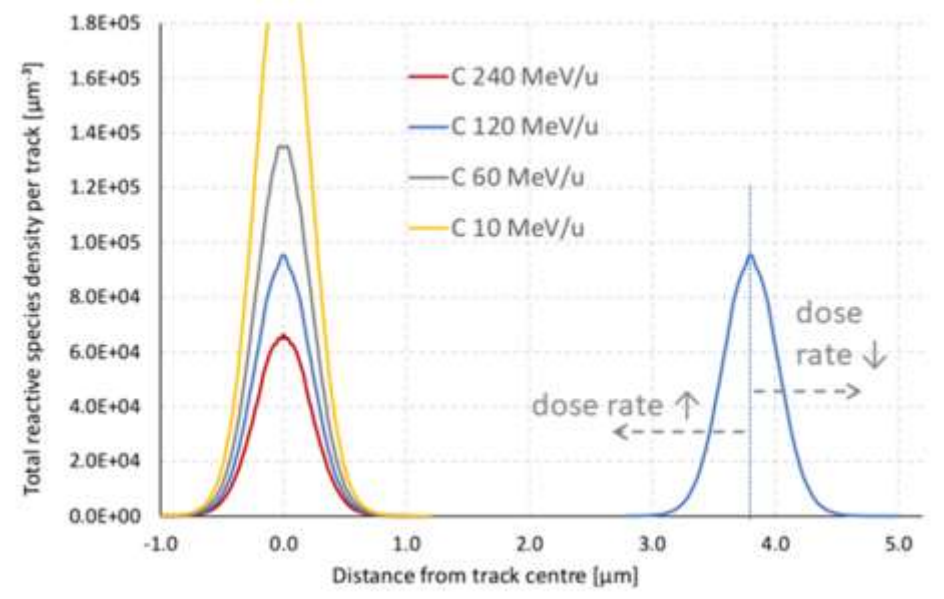
Background and Aims: For ion beam therapy, the LET distribution across the irradiated tissue volume ranges over several tens of keV/µm. Therefore, the possible LET dependence of a protective FLASH effect should be investigated. No published in vivo data exists to date on FLASH effects with high LET radiation.

Methods: We analysed several dependencies of the main mechanisms hinted to be responsible for a FLASH effect at different LET values in order to search for possible differential effects between tumor and healthy tissues. We center mainly on differential radical production and chemical track overlaps (enabling intertrack recombination) while considering also the effect of oxygenation. The chemical radiation tracks were simulated in water with the TRAX-CHEM MC code (Boscolo et al., Int. J. Mol. Sci. 2020) and combined with particle fluences to establish limit dose rates (dose-averaged dose rate for scanned beams or intra-pulse dose rate) where a recombination can be expected. Data for carbon ions are compared to those for corresponding isorange protons, and electron cases.

Results: Compared to protons, a carbon ion track generates a much larger total radical number, whereas the radical yields (per deposited energy) are suppressed due to (dose-independent) intra-track reactions. No track superpositions are observed within the timeframe of the chemical stage even for supposed dose-averaged dose rates >10^4 Gy/s.



Conclusions: The evaluated radiation chemical pathways do not predict a FLASH protection under realistic conditions of C ion irradiation. The possible experimental observation of a C FLASH effect could contribute to rule out some candidate mechanisms also at low LET.

EPD055 / #66

INTER-TRACK CHEMISTRY IN HIGH-DOSE RATE IRRADIATION ON WATER RADIOLYSIS SIMULATION: A GEANT4-DNA STUDY

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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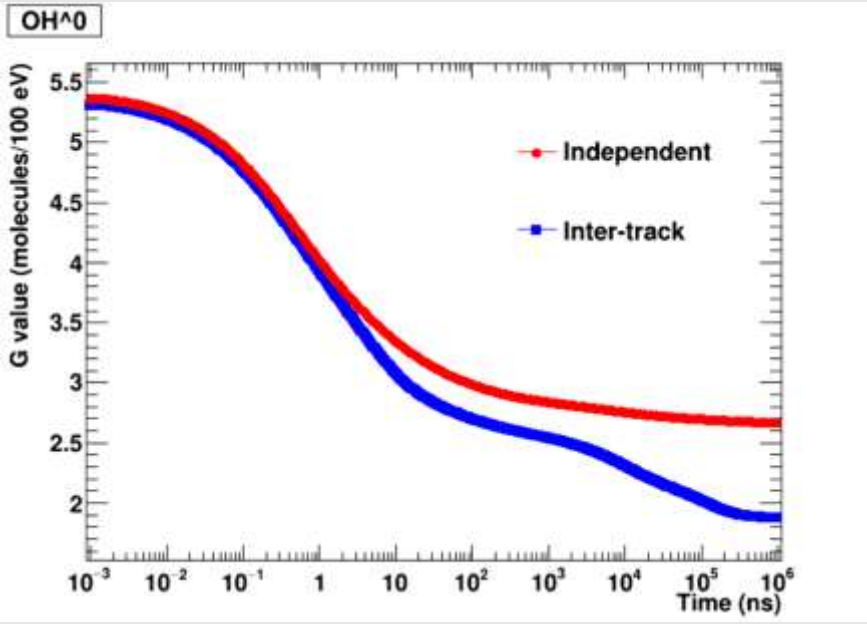
Background and Aims: Monte Carlo track structure simulation usually assumes the low dose situation that all the radiation tracks are independent of each other. However, at the high dose rate such as therapeutic beam, inter-track effects might be significant. This study aims to develop the inter-track chemistry model and to evaluate the influence of inter-track chemistry in water radiolysis simulation using Geant4-DNA.

Methods: "chem6" water radiolysis example available in the public version of Geant4-DNA enables to calculate radiochemical yields (G-values) with independent reaction time method. For inter-track chemistry, all the information of initial species (time and position) are stored and generated in proper chemistry time. In order to evaluate the influence of inter-track chemistry, 100 MeV proton beam is irradiated at an edge of 5x5x5 μm^3 water phantom, and the G-values are assessed with and without the inter-track chemistry.

Results: During the chemical stage from 1 ps to 1 ms, the number of •OH radical is indeed decreased with inter-track chemistry up to 30% because the generated •OH radicals are scavenged out with the radicals generated by the other tracks as shown in Figure 1. The influence of the inter-track chemistry is increased as a function of time because this effect is cumulative.



Conclusions: In this work, Geant4-DNA is extended to assess the inter-track effects for medical physics purpose. In further, the damage yields on DNA geometry according to the dose rate would be evaluated, and oxygen depletion model for the prediction of oxygen enhancement ratio could be suggested.

EPD056 / #290

CURRENT STATUS OF THE TRAX-CHEM EXTENSION TO THE HOMOGENEOUS CHEMICAL STAGE

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: TRAX is a Monte Carlo track structure code, developed to simulate radiation induced interactions on the molecular level. With its chemical implementation TRAX-CHEM (Boscolo et al., Chem. Phys. Lett. 2018), it provides a step-by-step description of all radiolytic events caused by charged particles in a water target, up to the end of the “heterogeneous” chemical stage (1μs). To better quantify the chemical evolution leading to the indirect radiation damage and the fate of radicals produced, a further extension is required. Interactions with other solutes and biomolecules, during the “homogeneous” biochemical stage (up to 1s), should be simulated.

Methods: From a discrete characterisation centered around single tracks, the problem shifts towards a continuous description based on species concentration distributions. Here radicals of neighbouring tracks, originated from the initial fluence delivered, diffuse and react with each other and with the biological environment. In this homogeneous solution, various molecules like DNA nucleotides and lipids are sensitive to damage. Moreover, new radicals are generated and other species intervene as reaction partners (e.g. enzymatic antioxidants as scavengers). Depending on the specific environment simulated (tumour/normal cells), different buffered pH can be encountered.

Results: Computationally, a numerical resolution of the set of reaction equations will be realised. Along with that, the optimal transition point between the two stages must be established.

Conclusions: The pool of generated molecular products will contribute to understand the relevance of crucial mechanistic issues, e.g. LET, oxygenation and dose rate impact, towards the final outcome, realising how, when and to which extent different reactions compete.

EPD057 / #67

SIGNIFICANT CHANGES IN YIELDS OF 7-HYDROXY-COUMARIN-3-CARBOXYLIC ACID PRODUCED UNDER THE FLASH RADIOTHERAPY CONDITION

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: FLASH radio therapy has a great advantage compared to the conventional radiotherapies. The effectiveness of FLASH radiotherapy has been verified by biological experiments. However, the mechanism of FLASH is an open question. Therefore, we aim to elucidate the mechanism of FLASH by radiation chemistry experiments.

Methods: Coumarin-3-carboxylic acid (C3CA) solutions were prepared with concentrations from 20 to 0.2 mM. When C3CA reacts with hydroxyl radicals, 7-hydroxy-coumarin-3-carboxylic acid (7OH-C3CA), which is a fluorescent product, is formed. By investigating the dose rate dependence (0.05 to 150 Gy/s) of fluorescent intensity from 7OH-C3CA formed under proton beams using fluorescence spectrophotometer connected to HPLC, we addressed to clarify the mecanism of FLASH radiotherapy.

Results: The radiation chemical yield (G value) of 7OH-C3CA decreases monotonically with increasing dose rate. The G value is constant under the FLASH condition. This trend is seen at all C3CA concentrations. A plausible interpretation of the present finding is the oxygen depletion induced by reactions between oxygen molecules and water radiolysis products (e_{aq}^-, $H^\cdot$). It is considered that the rapid consumption of oxygen by the ultra high dose irradiation is the main reason for the sparing effect. To validate our interpretation, the G value of 7OH-C3CA under aerobic condition is compared to that under the hypoxic condition by bubbling of Ar gas. In the presentation, we discuss the mechanism of FLASH radiotherapy from the radiation chemistry based on the experimental results.

Conclusions: To understand the mechanism of FLASH radiotherapy, we should focus on roles played by oxygen contributing the segmentation of damaged DNA.

EPD058 / #275

A FLASH-RT-SPECIFIC GENE PROFILE DRIVING ANTI-TUMOR EFFICACY?

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: The majority of research to date on ultra-high-dose-rate (UHDR/FLASH) radiotherapy (RT) has focused on studying the “FLASH effect”. Here, we investigated the glioblastoma (GBM) tumor response to FLASH versus conventional modalities of RT with a focus on mechanism and cell signaling pathways.

Methods: U87 GBM cells (ATCC) were xenografted in Swiss Nude mice and irradiated using a single 20-Gy dose administered at UHDR (2 pulses, 100 Hz, 1.8 µs pulse width, 0.01 s delivery) or CONV (~ 0.1 Gy/s) dose rates with the Oriatron/eRT6 (PMB, CHUV). Tumors were sampled at 24 hours post-RT and samples were used for RNA profiling (GIF, UNIL).

Results: A FLASH-RT-specific enrichment profile was found. It overlapped with gene sets of GLI1 knockdown, proteasomal subunit knockdown, and NFE2L1/NRF1 targets in the RNA sequencing (RNA-Seq) data that was consistent between experiments done in duplicate. These expression data most likely indicate proteasome inhibition, which can activate p53-independent apoptosis. Furthermore, GLI1 downregulation might decrease hedgehog signaling inhibiting tumor growth and preventing the formation of radioresistant neuropheres. We are currently working to confirm these FLASH-specific changes at the protein level.

Conclusions: Here we discovered FLASH-RT-specific expression profile enrichments that were not detected in the CONV-RT or unirradiated control tumor samples 24 hours post-RT. GLI1 downregulation, proteasome inhibition, and NRF1 signaling likely contribute to tumor control after exposure to FLASH-RT.
Acknowledgement: The study is funded by SNF Synergia grant (FNS CRS II5_186369)

EPD059 / #168

SURVIVAL, CYTOKINES, AND INTESTINE RESPONSE AFTER 6 MV X-RAY FLASH OR CONVENTIONAL ABDOMINAL IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Mice were exposed to 6 MV X-ray ultra-high dose rate (FLASH) or conventional dose rate (CONV) abdominal irradiation to study the survival, cytokines and small intestine response.

Methods: BALB/c nude mice received 16 Gy and 10 Gy FLASH (>150 Gy/s) or CONV (0.2 Gy/s) abdominal irradiation. Mice were sacrificed within 24 hours post-irradiation (PI) or followed up to 6 weeks. Serum was collected to quantify cytokine response of tumor necrosis factor-alpha (TNF- α), interleukin (IL) -6, and IL-10. Histological analyses of hematoxylin and eosin staining were accessed for intestine damage. Dihydroethidium staining of small intestine frozen sections was used to detect reactive oxygen species (ROS).

Results: Histological analysis of intestine from mice sacrificed within 24 hours PI (16 Gy) showed FLASH irradiation induced less acute intestine damage than CONV irradiation. After 6 weeks follow-up, FLASH irradiated mice (16 Gy) showed faster body weight recovery and survived longer than CONV group. Cytokine response from mice sacrificed 6 weeks PI (10 Gy) showed FLASH irradiated mice had lower inflammatory cytokine (TNF-α and IL-6) concentrations and higher anti-inflammatory cytokine (IL-10) concentration, however, the cytokine response from mice sacrificed within 24 hours PI (16 Gy) has opposite trends. Moreover, higher ROS signal intensities of small intestine sacrificed 24 hours PI (16 Gy) was found in FLASH group than in CONV group.

Conclusions: FLASH irradiation produced more ROS and acute inflammation in the small intestine. However, the cytokine response and mice survival probability at the late stage indicate FLASH irradiation protects mice from radiation toxicity without compromising survival.

EPD060 / #85

IMPACT OF DOSE RATE DELIVERED WITH ELECTRON, PROTON AND PHOTON BEAMS ON THE DEVELOPMENT OF ZEBRAFISH EMBRYOS

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: To investigate occurrence of the FLASH effect using various quality of beam, wt zebrafish (AB) embryos were irradiated with electron, proton and photon beams at various dose and dose rates.

Methods: Zebrafish embryos (n>20; 4-4.40hpf) were irradiated at 8-12Gy with eRT6/Oriatron, 5.5MeV electrons at 0.1 (conventional), 1400 and >10^6Gy/s (FLASH, 1 pulse); transmission proton irradiations at 0.1, 1 (conventional) and 1400Gy/s (FLASH), 232MeV with Gantry 1 (continuous cyclotron beam) and Xrad 225CX/225KeV photons-Cu Filter 3mm-13mA-2.27Gy/min (conventional). Dosimetry was performed as described in (Jorge, 2019; Christensen, 2021 and Nesteruk, 2021). Survival and development were monitored as well as cell death and proliferation.

Results: The development of embryos was not impaired by 8Gy delivered in 1 pulse with electron, whereas higher dose (10-12Gy) and lower dose rate (0.1Gy/s) decreased the size of embryos but were not lethal. LD90 was reached at 12Gy conventional photon beam and the development of the remaining embryos was impaired at any of the doses tested. Interestingly, the development of embryos was not impaired by proton beam at 8 and 10Gy independantly of the dose rate, whereas higher doses decreased the size of embryos in a dose rate-independent manner and were not lethal. Investigation of cell death and proliferation is ongoing.

Conclusions: These studies show that the biological response of zebrafish embryos (a stem-cell like model) to protons at all dose rates is similar to ultra-high dose rate electron irradiations.
Acknowledgement: This study has been funded by an industrial grant from Varian Medical Systems Inc. (Palo Alto, CA, USA)

EPD061 / #19

FLASH IRRADIATION WITH PROTONS OF HUMAN COLON ORGANOIDS – A NEW APPROACH TO STUDY NORMAL TISSUE SPARING

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Previous in vivo studies on mice have shown that FLASH irradiation of the abdomen reduces tissue toxicity and increases survival of the animal compared to conventional irradiation (CONV). The intestinal tissue has a high turnover rate and is continuously renewed by proliferating LGR5+ stem cells that produce differentiated cells, which undergo apoptosis or are shed into to the intestinal lumen after some days. Human colon organoids exhibit crypt structures composed of stem cell niches and a proliferative compartment that produce differentiated cells recapitulating the in vivo situation to great extent.

Methods: To assess whether ultra-high dose rates are a suitable form for abdominal irradiation we compared the expression levels of enterocyte differentiation markers (EDM) in colon organoids after FLASH, CONV and sham irradiation. Organoids were irradiated with 68 MeV-protons at Helmholtz-Zentrum Berlin with single doses of 13.5 Gy (14.8 Gy (cobalt gray equivalent(CGE)). The dose rate averaged 77.5 Gy/s (83.3 CGE/s) and 0.2 Gy/s (0.22 CGE/s) for FLASH and CONV, respectively.

Results: Compared to sham-irradiated group both forms of irradiation affected organoid growth and cell survival. Compared to FLASH, expression analysis revealed that CONV causes a very strong upregulation of EDM (KRT20, AQP8 and CAR4) and a down regulation of the LGR5 stem cell marker.

Conclusions: Organoids are a suitable model to study FLASH. The data so far indicate that FLASH affects healthy tissue to less extent while CONV compromises the stem cell niche and hinders tissue regeneration. Further exploitation of these findings is of high importance to improve irradiation for abdominal tumors.

EPD062 / #214

MODULATING THE FLASH EFFECT ON A CELLULAR LEVEL FOR VARIABLE OXYGEN LEVELS

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: Several studies in the past suggest that the FLASH effect is due to oxygen depletion: Radiolysis of the cytoplasm would cause radicals which then react with dissolved O2, creating a hypoxic and thus radio-protective environment. Although biological data show a clear oxygen dependence of the FLASH effect, it is still unclear what the biological mechanism is. In a previous study, we were able to show that less O2 was depleted at higher dose-rates, which contradicts the oxygen depletion hypothesis. Therefore, other O2 related mechanisms need to be investigated.

Methods: H460 and PANC1 cells were irradiated with 225kV photons at different dose-rates (2 Gy/min – 40 Gy/s) at low and medium O2 levels. The O2 levels were selected between 0.1%-4% O2 using a hypoxic chamber and were monitored with an oxygen sensor in the cell culture flask before, during and after irradiation to allow for stable O2 conditions.

Results: Preliminary data indicate a clear dependence of the cell survival on both dose-rate and oxygen level. We were able to get robust data for very low O2 regimes of 0.1%-2% O2 which showed a strong increase of cell survival towards lower O2 values and this effect being overly dominant in FLASH dose-rates. Further analysis of the impact of oxygen level modulation is ongoing.

Conclusions: Although the FLASH effect depends on oxygen, the mechanism behind is most likely not related to radiation-induced hypoxia. Instead, we will pursue the mechanism in further studies to untangle the strongly linked effects of dose-rate and oxygen exposure.

EPD063 / #242

FLASH DOSE-RATE HELIUM ION BEAMS: FIRST IN VITRO INVESTIGATIONS

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: To investigate the impact of LET and O_2 concentration on biological response to ultra-high dose-rate (uHDR, FLASH) helium ion beams compared to standard dose-rate (SDR) irradiation.

Methods: Beam delivery settings for raster-scanned helium ions at both uHDR and SDR were tuned to achieve >100 Gy/s and 0.15 Gy/s, respectively. For both SDR and uHDR, plan optimization and calibration for 10x10mm^2 fields was performed to assess in vitro response at lower LET (4.5 keV/µm) and higher LET (16 keV/µm) conditions. Clonogenic assay and early and late DNA damage response (γH2AX) of human lung epithelial cancer and normal tissue cells were used as biological indicators for the cellular response to uHDR and SDR irradiation for specified oxygen concentrations levels (1%, 21%).

Results: Average dose-rates for both lower and higher LET were 193 Gy/s and 0.15 Gy/s for uHDR and SDR, respectively. γH2AX signal, a surrogate for DNA damage response was lower, whereas consecutively cell survival was higher, for cells irradiated with uHDR as compared to SDR at 1% O_2 for dose values >= 8 Gy and both LET levels. This difference in cellular response was not seen at 21% O_2 where cell survival and DNA damage response were unchanged at studied dose-rates.

Conclusions: The first uHDR delivery of raster-scanned particle beams was achieved using helium ions, reaching FLASH-level dose-rates of >100 Gy/s. Baseline oxygen levels play a pivotal role, irrespective of investigated LET, for observation of an uHDR sparing effect for helium ions.

EPD064 / #149

EFFECT OF FLASH IRRADIATION ON RADIATION-INDUCED CELL FATE OF THE GLIOBLASTOMA CELL LINES.

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MECHANISMS

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Background and Aims: FLSH irradiation (FLASH-RT; >40 Gy/s) is in the spotlight as an irradiation technique that can show the same or higher cancer treatment effect while significantly reducing damage to normal tissues compared to the conventional irradiation (CONV-RT; 3~10 cGy/s). In this study, we investigated the effect of FASH-RT on the radio-response of glioblastoma (GBM) cell lines compared to CONV-RT.

Methods: GBM Cells (U251 and LN428) were irradiated with 10 MeV electron beam at a dose rate of 132.2Gy/s (FLASH) or 0.1Gy/s (CONV), by a modified clinic linear accelerator. The irradiated dose was confirmed with EBT-XD film. Clonogenic survival assays, cell cycle and western blot analysis, and RNA seq were performed to evaluate the biological effects of CONV-RT and FLASH-RT in GBM cell lines.

Results: Cell cycle analysis and Western blot analysis showed that subG1 fraction, and the expression of cleaved parp and caspase3, respectively, were increased in FLASH-RT cells compared to the CONV-RT cells. Clonogenic survival activity was much lower in FLASH-RT cells than CONV-RT cells. RNA seq analysis showed the significant changes in the transcriptional regulation related genes between FLASH- and CONV-RT GBM cells.

Conclusions: Our data suggest that FLASH-RT is more effective than CONV-RT in terms of cell death, but possible molecular mechanisms should be investigated in the future. Acknowledgement This study was supported by a grant of the Korea Institute of Radiological and Medical Sciences (KIRAMS), funded by Ministry of Science and ICT (MSIT), Republic of Korea (No. 50571-2021).

EPD065 / #185

A FIRST LOOK AT MOTION EFFECTS ON FLASH DELIVERY FOR CLINICAL TRIALS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Proton beam FLASH delivery drastically changes the conditions under which pencil beam scanning interplay effects occur. FLASH deliveries are on a timescale of tenths of seconds as opposed to tens of seconds for conventional delivery. The impact of target motion on FLASH delivery is investigated under a variety of clinical conditions. FLASH planning is possible using a non-clinical research treatment planning system. This system supports the planning and dose rate calculation for FLASH proton transmission plans. Using this system, FLASH plans are recalculated with modified spot lists to simulate the influence of various motions on structures of interest.

Methods: We analyze the change in dose distributions for a target in a phantom irradiated by a FLASH transmission field caused by simulated patient motion. Spot positions in the TPS are adjusted based on the amplitude and period of motion parallel and orthogonal to the primary scanning direction and the known spot timings of the delivery system.

Results: An analysis of the dose, dose rate, target coverage, and gamma pass rate are presented under FLASH conditions. For motions orthogonal to the primary scanning direction substantial impact to the gamma pass rate is observed.

Conclusions: Although FLASH delivery is extremely fast, under certain conditions the impact of motion can be significant. Further evaluation of clinical parameters under FLASH delivery conditions is needed to develop a suitable clinical strategy.

EPD066 / #186

COMPARING PREDICTED AND RECONSTRUCTED DOSE RATES FOR FIRST CLINICAL PROTON FLASH TRIAL TREATMENT PLANS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Considering that dose rate will be part of the prescription for FLASH treatments, dose rate quality assurance (QA) will be required as well. Thus, a pencil beam scanning (PBS) dose rate calculation algorithm [1] has been implemented in a Varian Eclipse treatment planning system (TPS) research environment. Calculated TPS dose rates of first clinical proton FLASH trial (FAST-01) treatment plans are compared with actual delivered dose rates.

Methods: A set of 250 MeV FLASH transmission plans with field sizes of 7.5 cm x 7.5 cm and 7.5 cm x 10 cm and a target dose of 8 Gy in 5 cm depth were delivered with a Varian FLASH enabled ProBeam machine. Spot timings as well as monitor unit (MU) information extracted from ProBeam scanning nozzle logfiles were used in place of predicted values for TPS-based PBS dose rate recalculation of the delivered plans.

Results: The percentage volume receiving at least 40 Gy/s in the reference depth fluctuated (with few exceptions) by less than 10% of the predicted value. The results are based on a threshold dose of 0.01 Gy for the PBS dose rate calculation and refer to a 2 Gy isodose region of interest (25% of prescribed dose). Correct prediction of the dose rate distribution (as per today's ProBeam AC250 cyclotron current stability) was confirmed.

Conclusions: A PBS dose rate algorithm implemented in an Eclipse research environment enables dose rate prediction for nominal machine settings and dose rate reconstruction for delivered FLASH plans. [1] https://doi.org/10.1002/mp.14456

EPD067 / #140

PLAN QUALITY EVALUATION OF TRANSMISSION PROTON PENCIL BEAM SCANNING FLASH TREATMENT PLANNING FOR HYPO-FRACTIONATED LUNG CASES

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: This study aims to evaluate transmission proton pencil beam scanning (PBS) FLASH radiotherapy (RT) planning for lung cancer patients. The dosimetry characteristics of the FLASH plans were quantified in comparison to conventional intensity-modulated proton therapy (IMPT)-stereotactic body radiation therapy (SBRT) plans.

Methods: Proton transmission plans of 34Gy in 1 fraction for a cohort of 7 consecutive lung cancer patients were optimized with 5 fields using multiple-field-optimization (MFO) and an in-house developed tool. The 3D average dose rate (ADR) and dose-averaged dose rate (DADR) distributions were calculated. RTOG0915 dose metrics were used to compare the FLASH and clinical lung IMPT plans.

Results: The FLASH plans resulted in worse CTV Dmax compared to the IMPT plans, as 114.7±4.6% vs 107.7±2.1% ($p<0.01$). The lung $V_{7.0Gy}$ and $V_{7.4Gy}$ were 717.5±378.0cc and 667.8±359.2cc compared to 488.2±245.5cc and 464.5±231.2cc between FLASH and IMPT plans ($p<0.01$). The FLASH plans yielded significantly higher (both $p<0.05$) D_{5cc} (13.9±7.2Gy vs. 6.7±11.5Gy) and D_{max} (20.9±13.6Gy vs. 17.1±13.1Gy) for esophagus. Similar trends were observed in the other OARs but did not achieve statistical significance due to the variation of target location and small cohort size. The average ADR $V_{40Gy/s}$ of the OARs is 79.0±3.5%, lower than that using the DADR which is 97.0±0.9%.

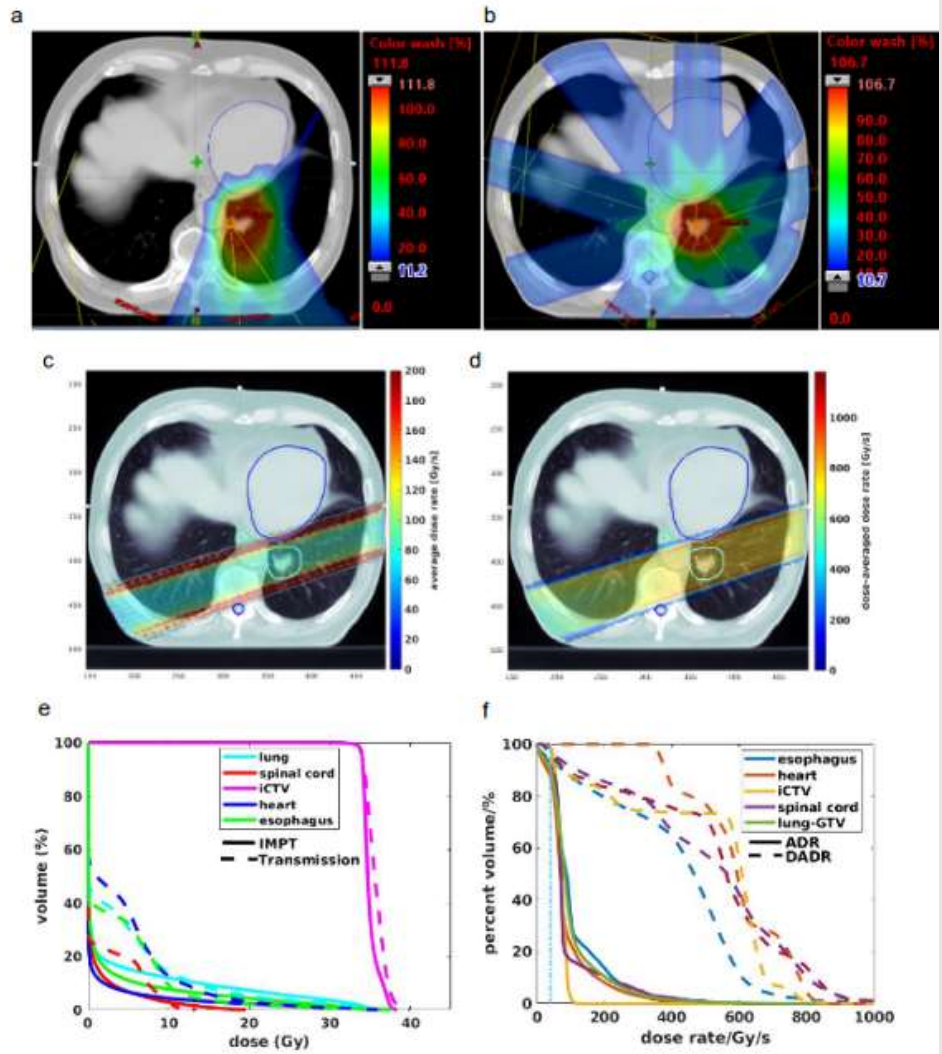

Fig. 1 (a) An IMPT plan dose color wash superimposed on a CT slice. (b) A transmission plan dose color wash superimposed on the same CT slice. (c) One field of ADR distribution superimposed on the CT slice. (d) The same field of DADR distribution superimposed on the CT slice. (e) The averaged IMPT and transmission plans' DVHs of the 7 patients. (f) An example of the dose rate volume histogram (DRVH) of one patient's transmission plans using ADR and DADR methods.

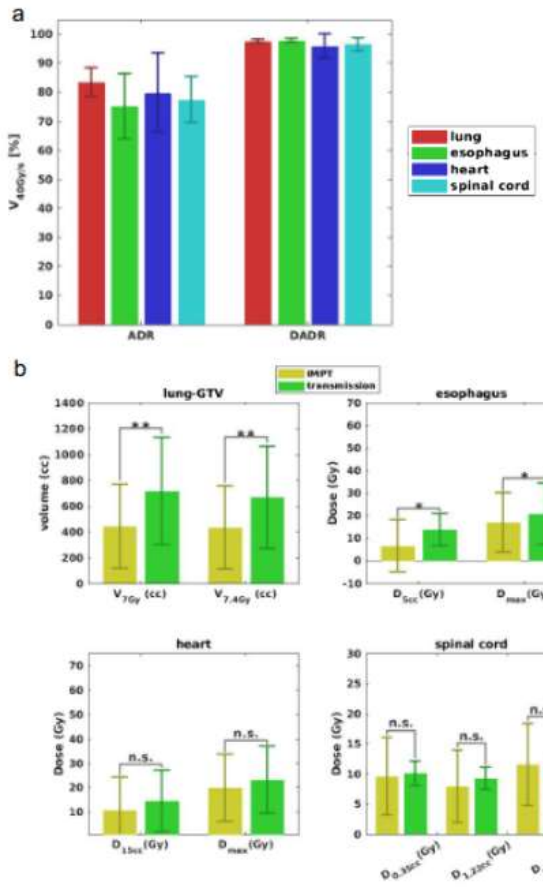

Fig. 2 (a) The distribution of the OAR V40Gy/s using ADR and DADR methods. (b) The distribution of RTOG0915 OAR dose constraints for IMPT and transmission plans. * indicates $p < 0.05$, ** indicates $p < 0.01$, and n.s. indicates non-significant.

Conclusions: Transmission plans result in inferior plan quality to conventional IMPT due to the nature of transmission beam and less optimization flexibility. A 400 minimum MU/spot can ensure 80-100% OAR FLASH dose rate coverage for both ADR and DADR. The potential biological benefit of transmission FLASH despite its inferior dosimetry requires investigation.

EPD068 / #209

COMBINING DOSE AND DOSE-RATE INFORMATION FOR BETTER FLASH TREATMENT PLANNING

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Over the last decade, numerous studies have shown the benefit of ultra-high dose rate (FLASH) irradiation in both animals and human patients. While FLASH clinical trials rely on the proper delivery of dose and dose-rate to the patient, combining and displaying the two information in a meaningful way to a clinician is a prerequisite for a successful treatment planning.

Methods: A set of proton transmission fields (lungs tumor targeted) have been created in ECLIPSE™. The plan was optimized to deliver 34 Gy to the PTV in a single fraction while maintaining 80 % of the lungs irradiated volume above 40 Gy/s for each field. The Pencil Beam Scanning (PBS) dose rate distribution [1] was computed for each field, based on ProBeam machine delivery parameters. The dose distribution for voxels with a dose-rate over 40 Gy/s was calculated and superimposed to the patient CT to evaluate the plan quality. Moreover, the Dose Volume Histograms (DVHs) for each voxel and for voxels with dose-rate over 40 Gy/s (Dose Rate DVH) were compared. [1] https://doi.org/10.1002/mp.14456

Results: The fraction of irradiated volume receiving at least 40 Gy/s and more than 2 Gy was 84 % for lungs (92 % for esophagus). For lungs, esophagus and heart, the difference between the DVHs and Dose Rate DVHs was smaller than 2% for doses above 2 Gy. The dose homogeneity in the PTV was within the RTOG recommendations.

Conclusions: The new set of tools proposed here will support the development of treatment planning for FLASH clinical trials.

EPD069 / #267

A FEASIBILITY STUDY OF DEEP SEATED TUMOR TREATMENTS COMBINING FLASH EFFECT AND VERY HIGH ENERGY ELECTRON BEAMS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Over the past decades, technological advances have improved the efficacy of radiation therapy (RT) cancer treatment. Nevertheless, the RT potential is still limited by normal tissue complications. On the other side the specific interactions of charged particles with matter can help in sparing the healthy tissues. Very High Energy Electron (VHEE) beams have been explored in the past as they have enough energy to reach deep seated tumours. However, the availability of VHEE and other charged particles in the clinic has been hampered by the size, complexity, and ultimately high cost of the beam production system. In this context, a compact VHEE accelerator represents a promising perspective, and it could also allow to deliver FLASH treatments. In this contribution we investigate the potential of electron beams in deep-seated tumors treatment, presenting the results in few selected cases (prostate, head and neck).

Methods: We have developed a VHEE Treatment Planning System combining an accurate Monte Carlo (MC) simulation with a simple modelling of the FLASH effect.

Results: The tumour coverage and the dose absorbed by the organs at risk have been compared, carrying out a quantitative analysis comparing the obtained Dose Volume Histograms, with a clinically applied IMRT plan and a proton plan.

Conclusions: The results demonstrate that FLASH therapy with VHEE beams of 70-130 MeV is competitive with standard RT and could allow a better sparing of the healthy tissues. The impact on deep-seated tumors will be discussed also in view of the results obtained with proton beams.

EPD070 / #34

DEVELOPMENT OF A DISCRETE ORDINATES BOLTZMANN SOLVER WITH BIOLOGICAL EFFECT FOR TREATMENT PLANNING OF FLASH PROTON THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Discrete ordinates methods offer an efficient alternative to Monte Carlo simulation but have not been widely used in particle therapy, and there is particularly a need to include modelling of the FLASH effect. This work therefore aims to develop a Boltzmann solver for proton therapy including FLASH.

Methods: The incident proton beam with continuous slowing down approximation was modelled as a fixed source, with discrete direction and energy ordinates being used to calculate scattered proton fluence due to nuclear elastic scattering. Five transport sweeps were used to determine proton fluence, which was then multiplied by mass stopping power to provide absorbed dose. An RBE for proton radiation of 1.1 was used throughout. The biological effect, b, of FLASH was modelled as a linear dose reduction at doses above 10Gy: $b=d-H(d-10)(d-10)\lambda$, where d was the absorbed dose, H was the Heaviside step function, and λ was the dose reduction factor, estimated as 0.2.

Results: Calculation of absorbed dose and biological effect takes several minutes using 16 CPU cores. Due to higher dose in the spread-out Bragg peak than in the surrounding volume, the sparing due to FLASH is higher in the target region, suggesting that diffuse tumours interspersed with normal tissues may benefit most.

Conclusions: The discrete ordinates method offers an efficient dose calculation for proton therapy, with straightforward modelling of the FLASH effect. There is potential for inclusion of further cellular and biological mechanisms, which is likely to be necessary for accurate modelling of local hypoxia in the clinical setting.

EPD071 / #310

PATTERNS OF FAILURE FOR HPV-NEGATIVE SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX: POTENTIAL UTILITY OF ELECTRON FLASH

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH IN THE CLINIC

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Background and Aims: Squamous cell carcinomas of the oropharynx that are not associated with the human papillomavirus (HPV) have a higher propensity for treatment failure and are commonly believed to be radio-resistant. Thus, the use of intensified treatments including FLASH radiotherapy should be considered as a means of improving the therapeutic ratio in this population. However, delineation of failure patterns, particularly with respect to spatial distribution, would be instructive to better understand whether electron FLASH could potentially be employed.

Methods: The medical records of 77 patients treated with radiation for HPV-negative squamous cell carcinoma of the oropharynx were reviewed. Fifty patients were treated by primary radiation; 27 were treated with post-operative radiation. Patients with evidence of distant metastasis at diagnosis were excluded. For patients who experienced local-regional failure, the original IMRT plans were retrieved and the epicenter of the recurrent tumor volume identified on axial imaging was fused using deformable image registration.

Results: A total of 40 patients experienced local-regional disease progression, and a total of 60 recurrent lesions were identified. Thirty patients had one isolated site of recurrence. The mean volume was 39 cc (range 3 to 109 cc). The mean distance from the epicenter of these lesions to the skin surface was 2.0 cm (range, 0 to 5 cm).

Conclusions: Spatial analysis demonstrate that the vast majority of treatment failures were located at a distance which may have been conducive to electron treatment. These data suggest that FLASH radiotherapy delivered as a boost to initial sites of disease may potentially improve control.

EPD072 / #25

A PRELIMINARY STUDY ON RADIATION PROTECTION REQUIREMENTS FOR A FLASH IOERT LINAC

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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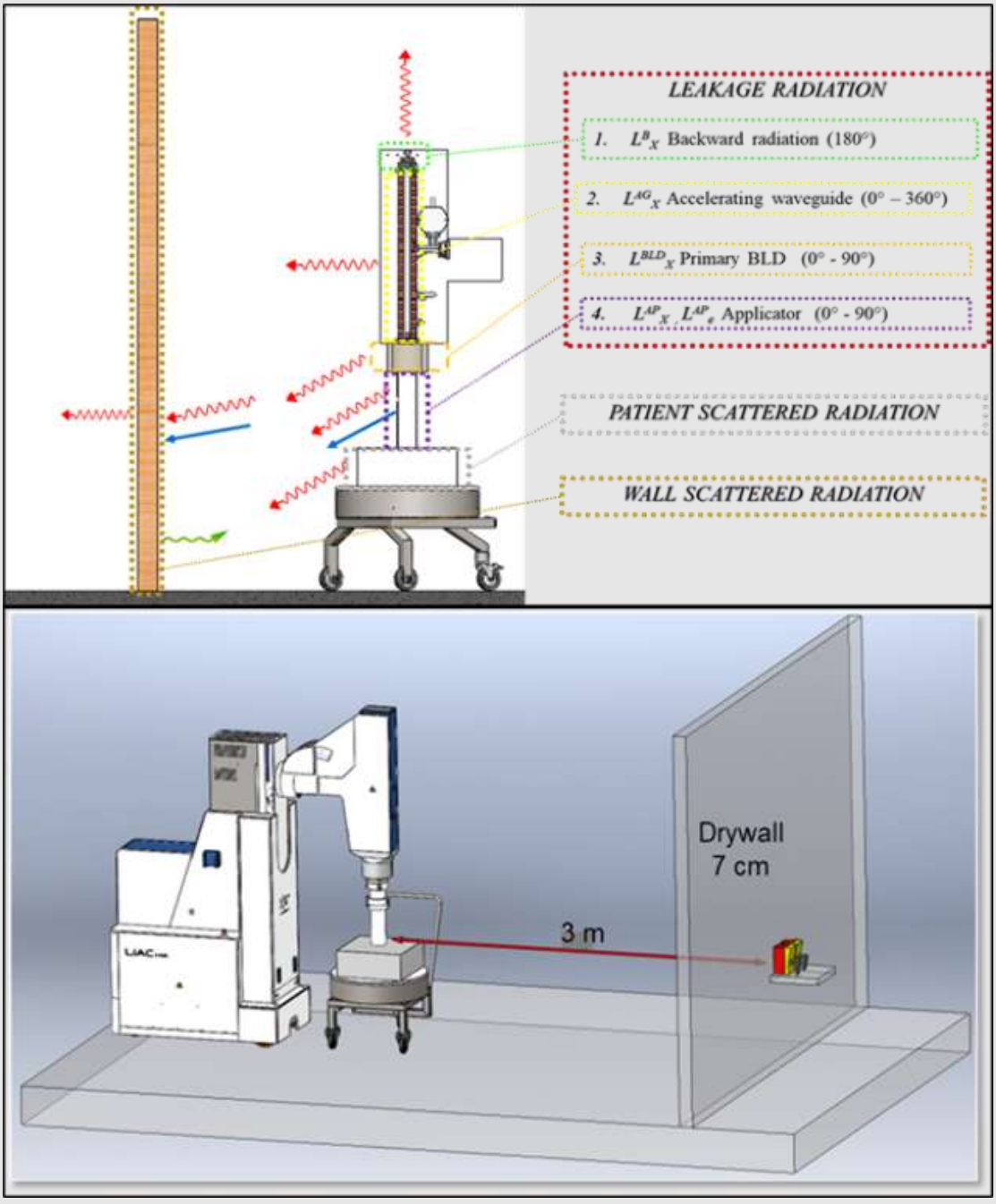
Background and Aims: Radiation protection is one of the challenges to be managed before bringing Flash into clinic. There are two crucial aspects: a technology capable of delivering the Flash doses minimizing the stray radiation (SR) produced and the approach to be adopted in barriers dimensioning. We discuss how the integral dose approach (NCRP151) leads to reasonable results, while an instantaneous dose rate (IDR) approach leads to barriers over dimensioning. The analysis is based on measurements and Monte Carlo (MC) simulation, (FLUKA).

Methods: The IOeRT linac chosen for this study is LIAC HWL, the best in the class respect to radiation protection performances. The figure shows the sources of SR (up) and the experimental setup implemented in FLUKA (down).



Results: The agreement between experimental measurement and MC results is good. MC simulation shows that the SR produced by patient cannot be less than 0.1 µSv/Gy. Assuming this value as the minimal one, in a typical OR (3 m distance, 7 cm of drywall) it will be possible to deliver 200 Gy/week (NCRP151 threshold of 20 µSv/week). The IDR approach (10 µSv/h) would never allow IOeRT, neither with LIAC HWL dose rate (DR=30 Gy/min) nor with a Flash linac. The value 0.1 µSv/Gy, when multiplied by DR=1000 Gy/s, yields to an IDR of 0.36 Sv/h. Around 3.5 TVL are needed, more than 130 cm of concrete!

Conclusions: A systematic comparison between experimental and MC data were performed for LIAC HWL. Such analysis shows that IDR approach for a Flash linac would lead to barriers over dimensioning.

EPD073 / #236

ON THE OXYGEN DEPLETION AND HYDROGEN PEROXIDE FORMATION IN THE PROTON RADIOLYSIS OF WATER AT ULTRA-HIGH (FLASH) DOSE RATES: INFLUENCE OF DISSOLVED OXYGEN CONCENTRATION.

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: The administration of curative doses of radiation for cancer treatment is severely limited by normal tissue toxicities. FLASH radiotherapy (FLASH-RT) is a new irradiation method that uses ultra-high dose rates (>40 Gy/s) to deliver large doses of radiation to tumors almost instantly (<100 milliseconds). Healthy tissue is dramatically spared using this method without compromising tumor control, resulting in a markedly increased therapeutic index compared to conventional radiation delivery that is administered at much lower dose rates (~0.03 Gy/s) and over minutes. Clearly, the FLASH effect contradicts classical radiobiology principles. To date, there exists a lack of understanding of the underlying mechanisms behind this effect.

Methods: Given that living cells and tissues consist mainly of water, we investigated the impact of high-dose-rate effects on the radiolysis of water by energetic protons from a radiation chemistry perspective. Monte Carlo track chemistry simulations of multiple, simultaneously interacting proton tracks were used along with a “instantaneous pulse” irradiation model to quantify the effect of different oxygenation levels (from 10 to 1250 μM) on the transient yields and concentrations of O_2 consumption and H_2O_2 formation induced in the ps-ms time scale.

Results: Our calculations show a pronounced oxygen depletion, simultaneously with a substantial increase in the H_2O_2 concentration, as a function of dose rate. In irradiated (~10^{10} Gy/s) O_2-saturated water, the oxygen consumption reaches a maximum of ~500 μM around 60 ns.

Conclusions: This result supports the mechanism of oxygen depletion hypothesis to explain the normal tissue-sparing effect of FLASH.

EPD074 / #263

RADIATION PROTECTION AND SAFETY IMPLCATIONS FROM BREMSSTRAHLUNG CONTAMINATION IN LINEAR ACCELERATORS CONVERTED TO FLASH-RT

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Recent interest in FLASH-RT has led many investigators to convert clinical linear accelerators to deliver FLASH-RT electrons. However, when operated at high energies and at FLASH-RT dose rates, contamination bremsstrahlung photons from the scattering foil are an order of magnitude higher than the photon beams for which shielding was designed. In this study, we investigate the shielding and radiation protection impact of converting a Varian 21EX linac to deliver 16 MeV electrons at 200x clinical dose rates.

Methods: We performed a radiation survey for photon and neutron equivalent dose in areas occupied during FLASH-RT delivery. An egsNRC Monte Carlo simulation of the transmission of all electron energies was performed in concrete to obtain TVLs to evaluate shielding requirements.

Results: Our FLASH-RT electrons deliver 780 µSv/hr in the uncontrolled area, above the US federal limit (20 µSv in a single hour). However, exceeding this limit requires a ~9200 Gy experimental dose, which is unlikely to be achieved during biological experiments. Likewise, dose to the staff entering the vault due to neutron-activated linac components is initially 25 µSv/hr, but dissipates quickly. Finally, TVL values were calculated by Monte Carlo.

Conclusions: Bremsstrahlung contamination photons of higher energy FLASH-RT electron beams exceed the dose rates of photon beams for which radiation protection programs and shielded vaults were designed. Other investigators would be prudent to confirm the adequacy of their radiation safety program, particularly for vaults designed for low-energy photon beams. Values for TVLs of electron bremsstrahlung contamination photons are provided to investigators to evaluate their shielding requirements.

EPD075 / #39

LOGISTICS OF A FLASH-RT PROGRAM IN CLINICAL SETTING

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: A FLASH-RT program was established at Dartmouth-Hitchcock Medical Center in minimally-modified clinical setting by joint efforts of biomedical engineering, radiation oncology, radiation biology and medical physics teams. Various projects on dosimetry, chemical sensing, translational studies have been conducted. The aim is to share logistical considerations and experience on running a FLASH-RT program to support institution-wide academic activities with an ultimate goal of treating human patients with FLASH-RT.

Methods: A linac was converted in the clinical setting by qualified engineers to deliver an ultra-high dose rate (UHDR) electron beam. Routine safety and dosimetry checks were done by physicists for every reversible conversion. Long-term record-keeping and retrospective surveys were carried out to demonstrate the feasibility, safety, stability and accuracy of this dual-purpose (FLASH and conventional RT) approach. The FLASH-capable linac has been utilized as shared resource to support institution-wide academic activities as well as normal clinical treatments.

Results: With its safety (no accident or FLASH-related malfunction), flexibility (> 60 conversions in a year), reliability (~3000 hours in flash mode and ~10^5 Gy accumulative dose delivered at isocenter) and accuracy (~5% conversion-to-conversion variations) demonstrated by commissioning and long-term user experience, the FLASH-RT platform has been actively utilized for researches in five major categories 1) FLASH beam dosimetry; 2) real-time beam delivery monitoring and control; 3) oximetry and chemical sensing; 4) preclinical/translational small/large animal treatment with tumor control and normal tissue complication endpoints and 5) treatment plan and delivery optimization.

Conclusions: A FLASH-RT program in clinical setting is established at Dartmouth with joint efforts, promoting collaborative projects to advance FLASH-RT to clinical treatment.

EPD076 / #53

SIMULATION AND EXPERIMENTAL VALIDATION OF A PROTOTYPE ELECTRON BEAM LINEAR ACCELERATOR FOR PRECLINICAL STUDIES

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: In this work, measurements and Monte Carlo simulations have been carried out to model a prototype electron beam linear accelerator (ElectronFLASH LINAC, SIT), with the aim of interpreting radiobiological experiments.

Methods: The ElectronFLASH LINAC is able to produce 5 to 7 MeV electron beams at dose-rates ranging from Gy/min to thousands of Gy/s, and is used to study the radiobiological effects of ultra-high dose-rates. Dose distributions have been simulated using the TOPAS3.3/Geant4.10.5 Monte Carlo platform, and measured in air and water phantoms using a 2D scintillating screen detector, radiochromic films, ionisation chambers and alanine dosimetry which were benchmarked with each other. Parameter optimisation (mean energy and spread, beam size, divergence and emittance) was performed using the non-linear least squares method to define the source description file. A relationship between the absolute dose, the number of primary electrons of the simulation and the LINAC parameters (pulse width, and number) was defined. The simulations of realistic experimental conditions for cell irradiations and voxelized mice CT images were performed.

Results: Measured and calculated dose profiles for several beam configurations (conventional or FLASH dose-rate) were compared in order to validate the beam emittance model. The agreement for all conditions was better than 1 mm. A good agreement between the experimental dose distributions and results obtained with the simulations was also found (<2% dose differences).

Conclusions: The results of this work, achieved with a prototype electron LINAC, and more generally applicable to many accelerators, will support the analysis of radiobiological experiments for preclinical research with FLASH electron beams.

EPD077 / #177

DEVELOPMENT OF A PULSED HIGH-ENERGY PHOTON REFERENCE FIELD FOR TESTING DOSEMETERS USED FOR RADIATION PROTECTION MEASUREMENTS BEHIND SHIELDINGS FROM HIGH ENERGY ACCELERATORS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: The performance of radiation protection dosemeters can be compromised by pulsed high-energy radiation fields. Well-characterized reference radiation fields are therefore necessary to ensure reliable measurement with such devices. The aim of this research is to establish a fully-characterized pulsed photon reference field resembling increased ambient dose levels such as those occurring behind (insufficient) shielding of medical and research accelerator facilities. This reference field could then be used for type testing dosemeters typically used for ambient or personal dosimetry.

Methods: A commercial medical linear accelerator or dedicated research accelerator at PTB was chosen as the radiation source. The shielding consisted either of an existing wall or a thinner, artificially constructed radiation protection wall comprising concrete compositions typically used for radiation shielding.

Results: Measurements of radiation levels behind the shielding (with respect to the beam direction) were conducted using a secondary standard ionization chamber to allow for traceability to national standards. Energy spectra behind the wall was determined by measurements and unfolding techniques with a passive few-channel spectrometer for pulsed photon fields. Monte Carlo simulations of the energy spectra behind the wall were also performed at multiple distances (along beam axis), which showed good agreement with measurements. The PTB Bonner sphere spectrometer NEMUS was used to characterize the neutron component and dose contribution to the radiation field.

Conclusions: Preliminary comparisons of secondary standard measurements with commercial dosemeters suggest significant under response, which highlights the need for obtaining such reference radiation fields. The project is funded by the BfS (project no. 3619S2236).

EPD078 / #278

ON THE RADIOLYTIC OXYGEN DEPLETION IN THE PROTON RADIOLYSIS OF WATER AT ULTRA-HIGH (FLASH) DOSE RATES: INFLUENCE OF COMPETING SCAVENGERS

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: FLASH radiotherapy, the almost instantaneous delivery of large doses of therapeutic radiation at ultra-high dose rates, is a new irradiation method that has the potential to dramatically reduce the toxicity of normal tissue while maintaining full anti-tumor activity. The underlying mechanism(s) behind this effect remains unknown. One widely considered hypothesis is the radiolytic oxygen depletion (i.e., hypoxia) in the time range from pico- to milli-seconds, followed by radioresistance of the irradiated tissue. This hypothesis, however, has been challenged because of the high concentrations of competing scavengers of radiation-produced hydrated electrons that exist in irradiated cells.

Methods: Monte Carlo track chemistry simulations of multiple, simultaneously interacting proton tracks in oxygen-saturated water were used along with an “instantaneous pulse” irradiation model to quantify the effect of the presence of a hydrated electron (e^-_{aq}) scavenger (S) of various “scavenging powers” (rate constant ´ concentration), acting in competition with oxygen, on the transient yields and concentrations of O_2 consumption.

Results: In the absence of S, our calculations show a pronounced oxygen depletion near 0.2 ms at very high dose rates (~10^8–10^{10} Gy/s). However, the magnitude of this depletion decreases rapidly when the scavenging power for the (e^-_{aq} + S) reaction increases from 0.1 to 1000-fold that for the (e^-_{aq} + O_2) reaction (~3 ×10^7 s^{-1}).

Conclusions: Competing scavengers can strongly down-modulate or even cancel out the extent of radiolytic oxygen depletion in irradiated cells and must be considered when seeking to explain the normal tissue-sparing effect of FLASH.

EPD079 / #47

COMPACT LINAC-BASED X-RAY FLASH RADIOTHERAPY SYSTEM

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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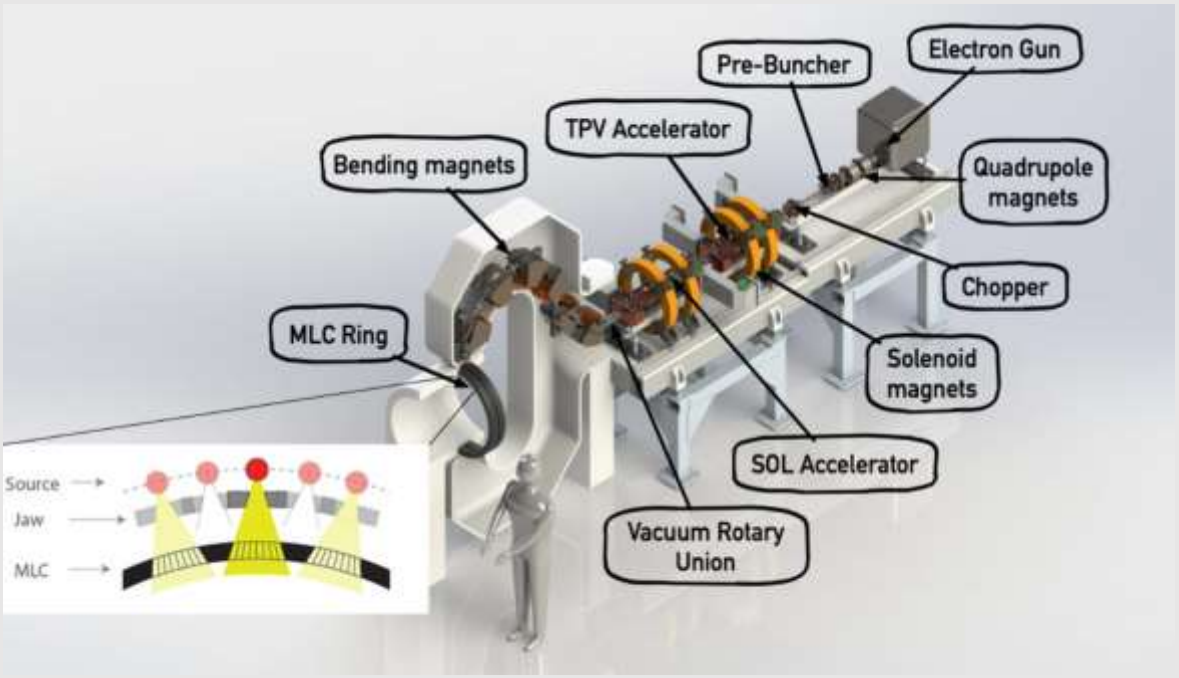
Background and Aims: Emerging evidence indicates that the therapeutic window of radiotherapy can be significantly increased using ultra-high dose rate dose delivery (FLASH), by which the normal tissue injury is reduced without compromising tumor cell killing. The dose rate required for FLASH is 40 Gy/s or higher, 2-3 orders of magnitude greater than conventional radiotherapy. Among the major technical challenges in achieving the FLASH dose rate with X-rays is the linear accelerator that is capable of producing such a high dose rate.

Methods: We will discuss the design of a high dose rate X-ray 12 MeV linac with 300 Gy/s output at 100 cm cm for future clinical application. We will also present the status of our ongoing project to build a preclinical system as a demonstration, which will produce 300 Gy/s at 20 cm for small animal studies

Results: The linac is novel as to our knowledge there has never been a linac built for delivering therapeutic X-rays with such a high dose rate. While it builds on mature accelerator technologies that have been demonstrated already to produce high-power electron beams, such a high-power electron beam has never before been used to produce a high-quality therapeutic X-ray beam. We will overcome challenges in the cooling of the X-ray target as well as the ability of the accelerator to reliably deliver such a high-power electron beam to a precise, stable focus

Conclusions: This paper will present the details of such linac design.


Pre-Buncher
Electron Gun
TPV Accelerator
Bending magnets
Quadrupole magnets
Chopper
MLC Ring
Solenoid magnets
SOL Accelerator
Vacuum Rotary Union
Source
Jaw
MLC

EPD080 / #52

EXPERIMENTAL FLASH SET-UP USING A LOW ENERGY PROTON BEAM FOR IN-VITRO IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 02 - FLASH MODALITIES

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Background and Aims: Recent investigations in vivo showed that short pulses of photons and electrons with high dose rate (> 40 Gy/s), known as FLASH dose rate, are less harmful for healthy tissues and as efficient as conventional dose-rate irradiation to inhibit tumor growth. In the case of protons however, FLASH effects have not been studied much in part due to the limited availability of facilities that can achieve such high dose rates.

Methods: In order to investigate the biological mechanism behind FLASH effect with proton beam accelerated from a continuous particle accelerator, we developed an electromagnetic deflection system, allowing us to control the exposure time of cells to the high current beam on the ALTAÏS particle accelerator at LARN laboratory. We also developed a real-time beam profile read-out using a scintillator and a CCD camera to allow us to observe the topography of the beam and ensure its homogeneity. Finally, the dose-rate is given by a faraday cup by reading the current of the beam. The irradiation set up for CONV-PT is already available at LARN and will be used to compare the results of FLASH with CONV-PT.

Results: The complete system has been validated using unlaminated ETB3 and HD-V2 Gafchromic film to ensure the dose deposition and its homogeneity in the sample holder.

Conclusions: A simple and complete pulsing device is proposed to allow in vitro proton irradiation compatible with a continuous-beam particle accelerator. This system could allow other facilities to start doing in vitro flash research.

EPD081 / #143

S-BAND LOW ENERGY LINEAR ACCELERATOR FOR FLASH IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: The S-band LINAC ElectronFlash4000 (EF4000, SIT - Sordina IORT Technologies S.p.A.), recently installed at the Institut Curie (Orsay-France), is entirely dedicated to FLASH irradiations for preclinical studies and basic research. It has been designed to deliver high dose-per-pulse (up to 30 Gy) and high dose rate in the pulse (>10^6 Gy/s). In this work, we report on the LINAC RF and beam dynamic design to fit those requirements. In addition, the beam output of the machine is measured and compared to Monte Carlo (MC) simulations with FLUKA code.

Methods: The EF4000 S-band (2.998 GHz) electron linear accelerator was optimized at the energy of 5 and 7 MeV. Several RF and beam dynamics simulations with CST code were carried out for the optimization of the main RF parameters. After the installation at Institut Curie, dosimetry measurements were done in order to characterize the machine performances. The results obtained by using Gafchromic EBT-3 and EBT-XD films were compared with the Percentage Depth Dose and transverse profiles from MC simulation.

Results: The S-Band EF400 was designed and manufactured ensuring peak current up to 100 mA, pulse width variable between 0.5 and 4 μs and pulses repetition frequency up to 250 Hz. A good agreement between experimental and simulation dosimetry results is also achieved.

Conclusions: The LINAC was successfully commissioned for radiobiological studies and is currently in full operation. It is able to reach dose per pulse and dose rate suitable for the FLASH irradiations with the output beam parameters stable and reproducible day to day.

EPD082 / #231

THE ARRONAX PLATFORM FOR PROTON FLASH IRRADIATION: FROM BEAM PRODUCTION TO THE TARGET

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: ARRONAX facility hosts an accelerator that can produce a wide quality of beams: protons, deutrons and alpha up to 70 MeV. The beam ranges from low (<1 pA) to high (up to 350 µA) intensities and using a homemade chopper device, irradiation durations and frequency rates can be redefined. With this system, the cyclotron can deliver a large range of mean dose rates from low (<1 mGy/s) to high (>1 MGy/s) values. Several developments have been conducted to allow preclinical research with Very High Dose Rate (VHDR) proton beam.

Methods: The pulsing system is installed in the injection section and devised to modify the bunch train length, from a few µs to a few seconds with a maximum period of 150 kHz. A specific tuning of the cyclotron parameters has been set up to deliver a stable (geometric and intensity), versatile (fast-changing of the beam intensity), and reproducible beam for VHDR irradiations. A cooling system at the exit window allows to extract the beam with an intensity of several tens of µA. A set of degraders, collimators, and several detectors are installed and characterized to monitor the beam and irradiate the target with a homogeneous spot (15mm) in VHDR conditions (10kGy/sec).

Results: Several experiments with zebrafish embryos have been successfully realized with the VHDR beam. The various settings from the production to the target irradiation will be presented.

Conclusions: A new preclinical research platform for VHDR proton experiments is developed and opened to collaboration.

EPD083 / #28

A PORTABLE BEAM CURRENT MONITOR FOR ULTRA-HIGH DOSE RATE ELECTRON BEAMS

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: A beam current monitoring system (BCM) has been built based on an integrating current transformer design implemented for the NRC research LINAC. The BCM can, non-destructively, measure the absolute charge of individual electron pulses with instantaneous currents as high as 200 mA, comparable to FLASH deliveries.

Methods: A toroidal core of supermumetal is fixed with its axis coincident with the beam axis, near the exit window of the accelerator flight tube (Figure 1). The pulsed electron beam induces a response that is processed by a differential amplifier to remove cable-generated electrical noise. The output, which is directly proportional to the electron beam current and can be read on a pulse-by-pulse basis, is fed into a 12-bit ADC. A single turn calibration loop enables the BCM to be calibrated using a precision current pulser.

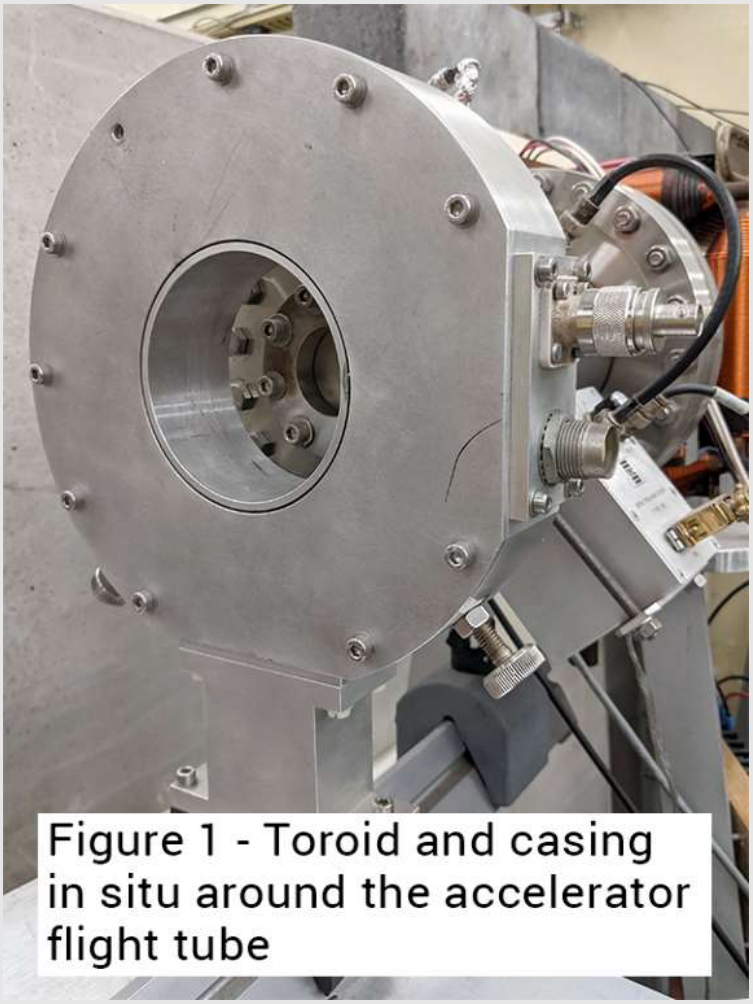

Figure 1 - Toroid and casing in situ around the accelerator flight tube

Results: Figure 2 shows the output of the BCM for a nominal 1 μs test pulse, with rise and fall times of <5 ns. The rise and fall times of the output pulse are <8 ns, fast enough to resolve FLASH electron pulses. Precision was found to be better than ±0.1 %. The fractional droop at the end of the pulse was measured to be about 0.5 %/μs; however, this is accounted for during the calibration.

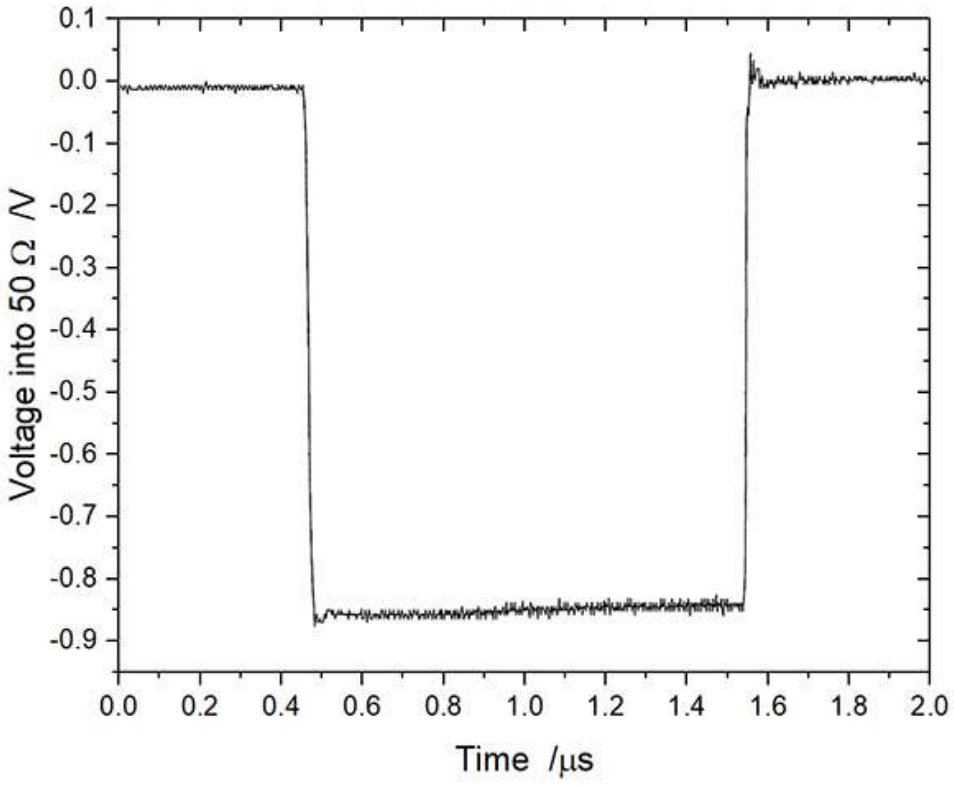

Figure 2 - The output signal of the BCM for a test input pulse

Conclusions: The performance of a BCM capable of measuring individual electron pulses is characterized. The output response is relatively free from RF interference, it has a fast rise time (~10 ns) and is stable enough to be calibrated for absolute charge measurements.

EPD084 / #145

COMMISSIONING OF THE FLASH MOBETRON SYSTEM AT MD ANDERSON CANCER CENTER

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: The field of FLASH radiation therapy (RT) has been hindered due to limited availability of units capable of producing FLASH irradiation. The early work was conducted either on prototypes or on modified clinical linear accelerators. However, the field is now seeing an increase in commercial options. One of the first commercial units introduced to the market was the Mobetron unit from IntraOp medical. This unit is capable of producing dose rates up to 1000 Gy/s with both 6 and 9 MeV electrons.

Methods: The FLASH Mobetron was acquired by our institution in the spring of 2021. The unit is currently undergoing commissioning for both pre-clinical and future clinical use. The commissioning process is based on the AAPM Task Group report 72. A multi-detector approach is used, and we employ both ion chambers, Gafchromic film, and TLDs in the commissioning process.

Results: Early data show high reproducibility of the FLASH beams. Maximum output variation through a single day was <3%. The day-to-day variation was within 1.5%. The linearity of pulse width and number of pulses was within 2%. Excellent correlation between Gafchromic film and TLDs was seen.

Conclusions: The FLASH Mobetron represents one of the first commercial FLASH units that will be available for clinical translation. However, careful commissioning of these units is critical to allow for safe performance of early clinical trials using FLASH RT. In this study, we have verified a commissioning protocol that will lay the foundation for future commissioning processes of electron FLASH units.

EPD085 / #11

PLATFORM FOR DELIVERY OF PROTON FLASH RADIATION RESEARCH IN A MOUSE MODEL

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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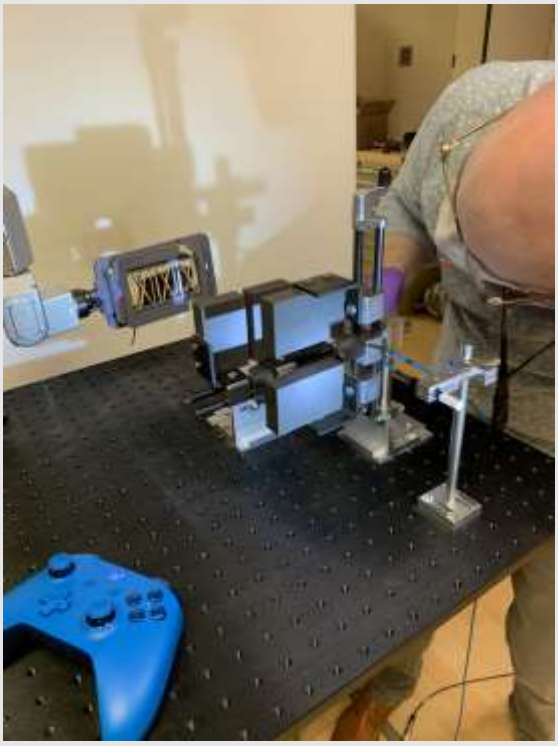
Background and Aims: An integrated platform has been created at the University of Washington Medical Cyclotron Facility to conduct proton FLASH research on a mouse model.

Methods: A cyclotron beamline has been modified to produce a 6cm diameter scattered beam at dose rates between 0.1 to 100 Gy/s. Dose is monitored using a microDiamond detector connected to a Keithley 6517B electrometer. The diamond detector is calibrated against an Advanced Markus chamber. The electrometer is integrated with the cyclotron control system to deliver the desired dose. A GUI allows researchers to set the dose, deliver beam, and record dose, dose rate, and delivery time without accelerator operator assistance. A wirelessly controlled, six-axis robotic arm acts as the mouse support and positioning assembly with a 3D printed mouse bed attached as the end effector. The beam is collimated with variable graphite jaw collimators and field shape is verified with a light field.



Results: Six irradiation sessions have been conducted irradiating 30 mice per session with both FLASH (60Gy/s) and conventional dose rate (0.5 Gy/s) protons. The time to position a mouse at isocenter and adjust and verify the radiation field shape is on the order of 30 seconds. Conventional rate dose is reproducible to within 0.01 Gy. FLASH dose can vary as much as 2Gy between runs.

Conclusions: Mouse positioning and field adjustment is fast and user-friendly. Work is currently underway to improve light field and collimator accuracy. A new electrometer from Pyramid Technical Consultants is being investigated to improve FLASH dose reproducibility.

EPD086 / #201

MAXIMIZATION OF THE DOSE HOMOGENEITY IN THE PLATEAU FOR A LOW-ENERGY PRECLINICAL PROTON BEAM LINE

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: The ARRONAX cyclotron offers the possibility to investigate the FLASH effect using 68 MeV proton beams at ultra-high dose rates (up to 7500 Gy/s), and to easily modify the structure of the beam. This energy is compatible with the irradiation of small biological samples in the plateau (cells or zebrafish embryos). Nevertheless, larger target volumes (mice) require a larger dose homogeneity in the plateau. In this study, we evaluated the feasibility of maximizing the dose homogeneity in the plateau by adjusting the collimator material.

Methods: GATE Monte Carlo toolkit v9.0 was used to model our proton beamline. Two collimator materials were evaluated by comparing profile and depth dose distributions computed via the simulation of the irradiation of a water tank: brass (standard material in clinical routine) and aluminum (widely used in nuclear physics).

Results: The scattering of protons had two impacts: it contributed to increase the homogeneous length of the plateau and it degraded the lateral homogeneity near the collimator exit. With an aluminum collimator, which increased the dose contribution of scattered protons, the homogeneous plateau was 1.7 times longer than with a brass collimator (16 mm against 9.3 mm).

Conclusions: The use of aluminum for our collimator as an alternative to brass enabled us to increase the dose homogeneity in the plateau but it requires to increase the distance between the collimator and the biological sample. Our proton beamline is now ready for future preclinical experiments on FLASH effect using mice.

EPD087 / #247

DEVELOPMENT OF FLASH CONTROL SYSTEM FOR IMPLEMENTATION OF ULTRA-HIGH DOSE RATE ELECTRON BEAMS USING A C-BAND LINEAR ACCELERATOR

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: A 6-MeV electron linear accelerator (LINAC) based on C-band microwaves for medical applications was constructed in 2015 at the Dongnam Institute of Radiological & Medical Sciences (DIRAMS). A FLASH control system of the 6-MeV LINAC was developed to generate ultra-high dose rate electron beams.

Methods: The software for the FLASH control system was coded in LabVIEW to implement a function of a pulse-mode operation with a modulator PLC, a pulse generator, and a single-board computer (SBC, LattePanda Alpha). When the FLASH control system transmits the number of pulses and the repetition rate to the SBC via TCP/IP, the SBC generates signals with a TTL logic and sends into the external trigger of the pulse generator (DG535) which distributes the synchronized timing pulses to the modulator PLC to control the magnetron and the electron-gun of the LINAC.

Results: The DIRAMS LINAC can be operated in continuous mode and pulsed mode with an RF efficiency of 70% by the help of an auto frequency control. In the pulsed mode, the FLASH control software can choose the number of pulses and a pulse repetition rate up to 200 Hz for ultra-high dose rate electron beams.

Conclusions: The FLASH control system was developed by combining the several sub-systems of the SBC, the modulator PLC, the pulse generator, etc. Using the FLASH system the dose per pulse was achieved as 4.22 +/- 0.12 Gy/pulse in a dose rate of 422 Gy/s at 20 cm of SSD for 10 pulses with a pulse repetition rate of 100 Hz.

EPD088 / #309

FIRST FEASIBILITY TESTS OF A SYNCHROTRON BASED FLASH EXTRACTION CONCEPT

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: The dose rate in conventional radiation oncology as well as in light ion beam therapy is in the order of Gy/min. The promising concept of FLASH radiotherapy with its beneficial biological response requires significantly higher dose rates in the order of 40 Gy/s or more. The feasibility to achieve those dose rates in cyclotron based facilities has been demonstrated in several studies, but primarily at highest energies which compromises the dose sparing of healthy tissue, the key benefit of proton therapy. In this study, the feasibility of extracting FLASH relevant high dose rates from a synchrotron has been investigated using fast betatron, RF driven and constant optics slow extraction (COSE) methods.

Methods: A PMMA phantom was exposed with a 179 MeV proton beam in clinical (Gy/min) mode with fast extraction. Dose was determined at 2 and 4 cm depth using Gafchromic EBT3 films and an Advanced Markus chamber (PTW, Germany), respectively.

Results: of a feasibility test using proton beams show dose rates around 200 Gy/s in the central 5 mm of an approx. 10mm FHWM beam. The total applied dose was measured to up to 8.8 Gy per spill burst.

Conclusions: The feasibility of FLASH dose rates at a synchrotron based facility was demonstrated for a single proton energy, but it is conceptually valid for any energy or particle species. This may potentially allow for exploitation of the FLASH effect and dose sparing simultaneously using an existing synchrotron facility.

EPD089 / #179

CHARACTERIZING MEASUREMENTS IN PULSED X-RAY FIELDS FOR RADIATION PROTECTION DOSIMETRY WITH TIMEPIX3

E-POSTER DISCUSSION: E-POSTER STATION 03 - FLASH MODALITIES

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Background and Aims: The short timed and highly intense temporal distribution of pulsed radiation is a big challenge for detector development. This has a significant impact on the development of active dosemeters as well as on the possibilities to characterize pulsed radiation fields.

Methods: The Timepix3 pixel detector was chosen as a promising candidate to help solve these difficulties. The detector profit from the fact, that it consists of many small active detectors which enables it to handle high flux rates. Additionally, the Timepix3 provides spatial information by the 55 µm pixel pitch, temporal resolution of 1,56 ns and energy information of every single photon. The Measurements were carried out in the reference field for radiation protection dose quantities for pulsed x-ray radiation (GESA) at PTB, Braunschweig. Pulse durations down to 200 µs can be applied. The dose in every pulse is measured by a monitoring ionisation chamber and the time resolved intensity was measured by a PIN-silicon diode for reference.

Results: The Timepix3 pixel detector was evaluated up to a pulse doserate of 1 Sv/h at the x-ray radiation field of PTB. Time resolved energy histograms were investigated with integration time of only 20 µs. Also, the angle of the incident radiation was determined with a especially designed absorber setup and calculated with a fast particle filter algorithm.

Conclusions: The investigations performed in this dedicated reference radiation field show the high potential of this detector for radiation protection measurements of pulsed radiation as it occurs at flash therapy centers.

EPD090 / #154

EFFECT OF FLASH IRRADIATION ON RADIATION-INDUCED CELL FATE OF THE NORMAL LIVER AND LIVER CANCER CELL LINES.

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: FLASH radiotherapy using electrons and photons (FLASH-RT; >40 Gy/s) showed the similar effect on tumor tissues as conventional radiotherapy (CONV-RT; 3~10 cGy/s) reducing normal tissue damages. In this study, we compared the biological effects of CONV-RT and FLASH-RT on normal liver and liver cancer cells.

Methods: Human hepatic stellate (LX2) and hepatoma (Hep3B) cell lines were irradiated with 10 MeV electron beam at a dose rate of 132.2Gy/s (FLASH) or 0.1Gy/s (CONV), by a modified clinic linear accelerator. The irradiated dose was confirmed with EBT-XD film. Clonogenic survival assays, cell cycle and western blot analysis, and RNA seq were performed to evaluate the biological effects of CONV-RT and FLASH-RT in liver cell lines.

Results: In cell cycle and Western blot analysis, FLSH-RT increased subG1 fraction, cleaved parp and caspase-3 expression compared to CONV-RT. In the clonogenic survival assay, FLASH-RT significantly increased the radiation sensitivity compared to CONV-RT. However, there was no significant difference in the effects of FLASH-RT and CONV-RT in LX2 cells. RNA seq analysis showed the critical changes in the intracellular signal transduction and angiogenesis between FLASH-RT and CONV-RT in Hep3B cells, whereas there was no significant difference in LX2 cells.

Conclusions: In Hep3B cells, Flash-RT had a significantly higher apoptosis inducing effect than CONV-RT, but there was no significant difference in normal LX2 cells. Acknowledgement This study was supported by a grant of the Korea Institute of Radiological and Medical Sciences (KIRAMS), funded by Ministry of Science and ICT (MSIT), Republic of Korea (No. 50571-2021).

EPD091 / #44

HOW TO IMPROVE HEALTHY TISSUE PROTECTION FROM RADIATION INJURY?

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Radiotherapy is customary implemented in cancer treatments with curative intent. It is very often accompanied with the development of moderate to high levels of treatment-related toxicity that interfere with the completion of the initial treatment plan. To enhance curing chances, the aim is to expand the therapeutic window by lowering of normal tissue radiation injury using combined treatment in order to improve post-treatment outcomes. FLASH radiotherapy, characterised by the delivery of a large radiation dose within 0.1 sec, has been presented as a novel form of radiotherapy that enables reduction of normal tissue toxicity while keeping similar efficacy on tumours. In contrast, the DNA repair inhibitor, AsiDNA, has been developed as a tumour radiosensitizer, but recently revealed additional properties in normal tissue protection.

Methods: In vitro normal and tumour cell models were exposed to irradiation along with AsiDNA in various growth conditions (e.g. pO_2) to address tumour and healthy tissues sensitivity and cell cycle perturbations.

Results: Hypoxia together with proliferation state appeared to differentially alter the cell sensitivity to FLASH irradiation. AsiDNA can modify this response by altering the cell cycle.

Conclusions: The identification of a novel role of AsiDNA on normal cells through G1/S-phase arrest directs to a possible protection of normal dividing tissue from genotoxic treatments, whilst reduced chromosome damage by FLASH relative to conventional RT has been observed specifically in normal cells. Our purpose is to investigate the combination of both modalities with a view to enhancing the therapeutic window of radiotherapy.

EPD092 / #220

DOSE-RATE MODULATE THE EVOLUTION OF TUMORAL CELLS IN CULTURE AFTER SINGLE DOSE IRRADIATION WITH LOW ENERGY PROTONS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Recent studies underline the great benefits of FLASH technique observed across various animal models, and also report the treatment of subcutaneous T-cell lymphoma in a human patient resulting in complete response and minimal toxicities. However, the details of the mechanism by means of the dose-rate modulate the cells responses remains still unrevealed. We present here preliminary results regarding the effect of dose-rate on some basic cellular processes, when the cells in culture are irradiated by a 1.9 MeV proton beam with doses commonly used in radiotherapy.

Methods: B16 melanoma cells were irradiated with protons using a setup developed at a 3 MV TANDETRON accelerator. The doses were 1 and 3 Gy and the dose-rate ranged from 0.02 to 250 Gy/s. The biological parameters followed in the experiments were: mitochondrial ROS production (MITOSOX assay), cell cycle phases distribution (PI flowcytometry assay) and the cellular senescence (CellEvent™ Senescence Green Assay Kit).

Results: As expected, all investigated parameters are depending on dose, but also a significant influence of dose-rate was observed. Particularly the mitochondrial ROS production monotonically increased with dose rate and the distribution of cells along the cell cycle phases after 24 h revealed a pre-apoptotic population increasing with dose and dose-rate.

Conclusions: These preliminary in vitro studies support the idea that proton irradiation at higher dose-rate can induce stronger cellular effects in tumoral cells.

EPD093 / #54

PHOSPHORESCENCE-BASED OXIMETRY FOR RADIOTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Molecular oxygen plays a key role in radiotherapy by enhancing damage created by ionizing radiation. In particular, oxygen dynamics has been suggested to underpin the FLASH effect, while little experimental data have been presented to support these theories, in part due to the limited ability to quantify oxygenation of tissue subjected to radiation. In this presentation we discuss the phosphorescence quenching method for biological oximetry in relation to its applications in radiation oncology research.

Methods: Oxygen measurements by phosphorescence quenching are based on phosphorescence decay times (lifetimes) of bio-compatible molecular probes, Oxyphors, that can be dissolved in the blood plasma or interstitial fluid. The measurements by phosphorescence quenching are absolute and independent of the probe's distribution in the environment and/or tissue optical properties.

Results: The phosphorescence quenching method can be implemented in different ways, ranging from "point" fiber-optic oximetry to wide-field imaging to depth-resolved two-photon phosphorescence lifetime microscopy. Using high-performance phosphorescent probes and a fast time-domain phosphorometer we demonstrate tracking of oxygen dynamics upon delivery of FLASH radiotherapy with temporal resolution reaching up to 3-4 kHz.

Conclusions: Oxygen-dependent quenching of phosphorescence is a non-invasive all-optical method for dynamic measurements and imaging of oxygen in vitro and in vivo that should aid studies in radiation biology and may help unravel the origin of the FLASH effect.

EPD094 / #60

FLASH SPARES NORMAL SALIVARY GLAND AND IMPROVES RADIATION-INDUCED SALIVARY DYSFUNCTION IN MICE

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Ultra-high dose rate irradiation (FLASH) is a novel therapeutic modality that has been reported to spare tissues compared to conventional dose rate. We aimed to investigate the effect of FLASH on salivary gland dysfunction caused by radiotherapy.

Methods: We administered single dose head and neck irradiation to mice with a 6 MeV electron beam at dose rate of 105.6-126 Gy/s (FLASH) or 0.03Gy/s (CONV), using a modified linear accelerator. The irradiated dose was confirmed with EBT3 film, and 9-76 Gy and 10-30 Gy were irradiated for FLASH and CONV, respectively. Parotid and submandibular glands were obtained from mice at 3 and 30 days after irradiation. Immunohistological examination and apoptotic assays were conducted to assess the radiation response.

Results: At three days post-irradiation, both 10 Gy and 30 Gy irradiated groups showed a greater number of salivary cells and increased expression of AQP5 in FLASH compared to conventional irradiated mice. As a late toxicity (30 days of irradiation), fibrosis did not show any significant difference, although FLASH group received much higher radiation dose. There was no difference in apoptosis between groups on post 3 days, but FLASH showed significantly less degree of apoptosis on 30 days after irradiation.

Conclusions: This study demonstrates that FLASH irradiation attenuates radiation-induced salivary gland damage, and can serve as a novel treatment modality for head and neck cancer.

EPD095 / #276

NOVEL TREATMENT APPROACH FOR GLIOBLASTOMA CHEMO-PROTON THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Glioblastoma (GBM) is one of the most common and aggressive forms of primary brain tumor. Despite advances in multimodality therapy for GBM, the overall prognosis remains poor. Particle radiotherapy, such as proton therapy (PBT) can be directed precisely to the tumor, sparing the nearby normal tissue and reducing the possible detrimental effect. Combining chemotherapy (i.e. temozolomide, TMZ) with proton therapy could be the key to a greatly improved glioblastoma prognosis.

Methods: In the first part of our studies, GBM cell lines and TMZ were used to study the effects of fractionated PBT at different points in the Bragg peak. The next part was aimed at developing radio-sensitizing agents, which enhance the effects of proton therapy in GBM treatment.

Results: We have shown that protons and X-rays influence GBM cellular proliferation and RNA integrity to different degrees and probably by a different mechanism. Furthermore, we have proposed a new approach and protocols, where a system containing nanocarriers functionalized with TMZ in combination with protons significantly overcomes GBM resistance. We demonstrated the power of this innovation by many physical, chemical, and biochemical key features in GBM models, finally filing a PCT patent application.

Conclusions: Understanding the effects of fractionated PBT and discovering the underlying mechanisms together with proposed a new approach and protocols are critical for the optimization of proton radiotherapy treatment scheme, especially in glioblastoma therapy. Acknowledgements: This study was partially funded by the Horizon 2020 project INSPIRE, No. 730983, and MRPO.05.01.00-12-013/15.

EPD096 / #13

FISHING FOR THE FLASH EFFECT: DEFINING THE CRITICAL PARAMETERS TO OBSERVE THE FLASH EFFECT WITH PROTONS IN A ZEBRAFISH EMBRYO MODEL

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Implementation of FLASH radiotherapy in clinical practice is held back by technical limitations and the lack of conclusive explanations of the underlying biological mechanisms. Here, we use a zebrafish embryo model to define the proton beam parameters and biological conditions critical for observation of the FLASH effect.

Methods: Irradiations were performed on a 70 MeV cyclotron. Experimental conditions are summarized below. Table 1

Embryos' age at irradiation, hpf	Dose, Gy	Number of pulses	Average conventional dose rate, Gy/s	Average FLASH dose rate, kGy/s
4	6, 8	1	0.25	7.5
10	5, 10, 15	4, 8, 12	0.07	1.3-1.6
28	30, 40	1	0.25	7.5

Embryos (15x3/condition) were observed till 120 hours post-fertilization (hpf). The following outcome measures were assessed: survival, body curvature, body length.

Results: There was no statistically significant difference for any of the endpoints between FLASH and conventional irradiation, except for 10 Gy-irradiated 10 hpf embryos, for which conventional treatment resulted in significantly less developmental abnormalities. We hypothesize that due to the combination of ~35-times higher average dose rate used in electron compared to proton experiments and the much better oxygenation of zebrafish tissues compared to mouse tissues no FLASH effect is observed in this system.

Conclusions: If the FLASH effect is observed in zebrafish embryos under hypoxic conditions with the same beam settings this will confirm the importance of tissue oxygenation in the FLASH effect. Moreover, in this case a zebrafish embryo tumor xenograft model may be used to compare the tumor control between FLASH and conventional proton therapy.

EPD097 / #160

INCREASE IN THE SIZE OF THE SURVIVAL CURVE SHOULDER WITH INCREASING DOSE-RATES: FLASH EFFECT ON CELL SURVIVAL

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: The imbalance between generation and elimination of reactive oxygen species is the primary cause of endothelial dysfunction leading to vascular damage. Since the FLASH effect of ultra-high dose-rates is hypothesized to prevent ROS-mediated cellular damage, we investigated the impact on endothelial cell survival caused by dose-rates from FLASH to conventional levels.

Methods: Cell survival curves were generated after irradiating the Mouse Tumor-derived Endothelial cell line (2H11) with increasing dose-rates. Four dose rates (1619 Gy/s, 152 Gy/s, 20 Gy/s, and 2 Gy/s) with high-flux photons were delivered at the European Synchrotron (ESRF) ID17-Biomedical beamline, and low-flux photons were delivered with the lowest dose-rate (0.017 Gy/s) using a Cobalt-60 source. The Linear-quadratic (LQ) and Multitarget models were used to fit the data.

Results: The LQ model best-predicted cell survival after Cobalt-60 irradiation, while the Multitarget model better predicted cell survival after dose-rates delivered by the ESRF. This difference seems to reflect the influence of the flux of photons. The extrapolation number “n”, which correlates with the shoulder's width, was directly proportional to the dose-rate, where n=3.4 for 1619 Gy/s and n=2.3 for 0.017 Gy/s. Since the shoulder is inversely proportional to the size of the radiation-induced bystander effect (RIBE), this also supports preliminary data that RIBE is reduced in FLASH exposures.

Conclusions: Our work demonstrates that the sparing effects of FLASH dose-rates increased the width of the survival curve shoulder. Moreover, our results indicate that in the case of a high flux of photons, the Multitarget model better describes the effects of FLASH dose-rates.

EPD098 / #147

OPTIMIZATION OF PROMPT GAMMA IMAGING AND POSITRON EMISSION TOMOGRAPHY (PG-PET) SYSTEM FOR IN-VIVO DOSE VERIFICATION IN CARBON-ION THERAPY: A MONTE CARLO STUDY

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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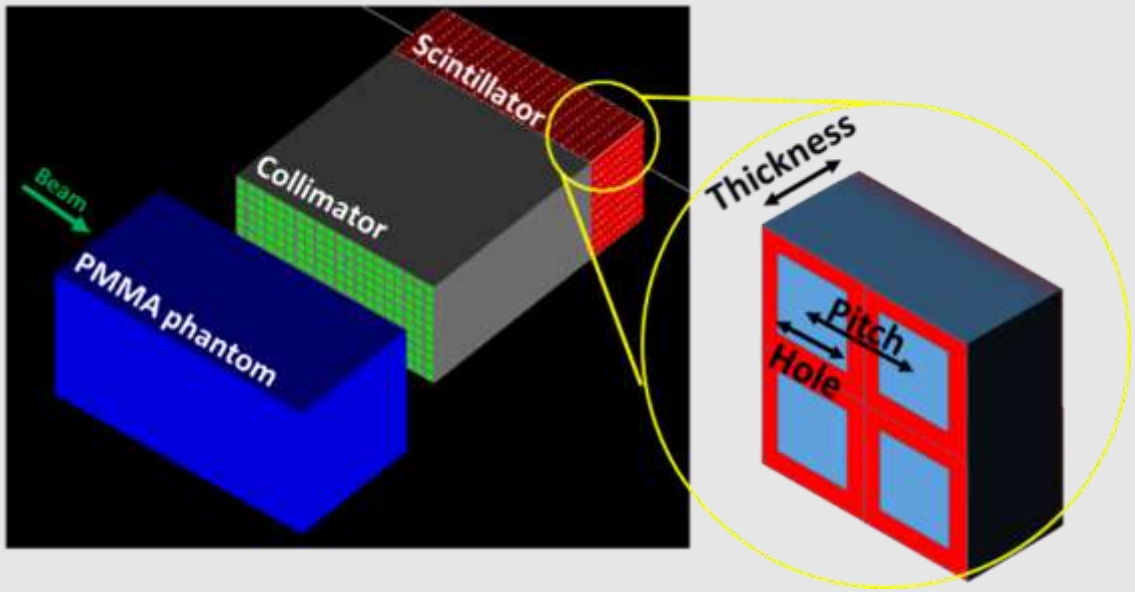
Background and Aims: In particle therapy, prompt gamma (PG) imaging and positron emission tomography (PET) are representative methods to evaluate the dose distribution in real-time and after the treatment, respectively. The aim of this study is to design the optimal geometry of a hybrid PG-PET module that measures the prompt gammas and positron emitters to increase the accuracy in determining the dose distribution in carbon-ion therapy.

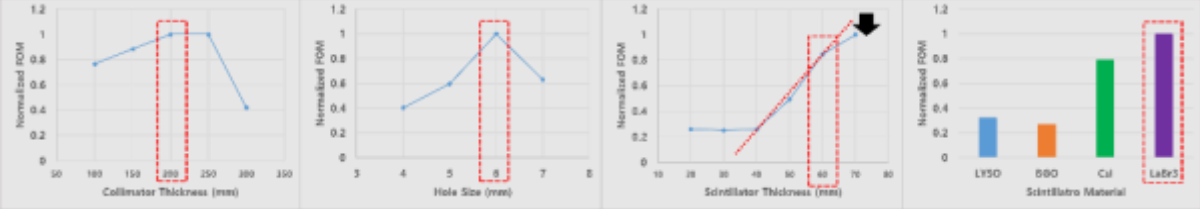
Methods: The Geant4 version 10.05 was employed to optimize the geometry to increase the detection efficiency of the hybrid PG-PET module. The module consisted of a 2-D scintillator array and a parallel-hole collimator as shown in Fig 1.



The optimization of the module geometry was carried out in terms of various parameters, such as scintillator material, scintillator thickness, collimator thickness, and collimator hole size. In the optimization, 260-MeV/u carbon beam was delivered to a PMMA phantom. For quantitative evaluation of the module geometries, a figure of merit (FOM) of the detection efficiency was defined as below:

$$FOM = \frac{Detected\ \ Signal}{Background\ \ Noise} \times (Peak\ \ Amplitude)$$

Results: Figure 2 represents the results of the optimization for geometry of the PG-PET module. The optimal scintillator was decided as $LaBr_3$ with 60 mm thickness. The optimal pitch size of the scintillator was 4 mm for measuring both the PGs and positron emitters. For the collimator, the optimal thickness was defined as 200 mm while hole size was optimized as 6 mm.



Conclusions: With the optimal geometry for the PG-PET detection system suggested in this study, experimental validation for the PG-PET module will be performed in our further study.

EPD099 / #151

ULTRA-HIGH DOSE RATE FLASH EFFECT ON HEAD AND NECK CANCER CELLS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: Although FLASH effect on normal tissue sparing has been reported, the effect on cancer cells has not been consistent. This study was conducted to show the effect and involved pathways of FLASH on head and neck (H&N) cancer cells.

Methods: H&N cancer cells (HSG and FaDu) were irradiated with 10 MeV electron beam at a dose rate of 132.2Gy/s (FLASH) or 0.1Gy/s (CONV), by a modified clinic linear accelerator. The irradiated dose was confirmed with EBT-XD film, and 3, 7, and 11 Gy were irradiated. We evaluated the cell cycle and the surviving fraction of cells with clonogenic assays. Furthermore, QuantSeq 3'mRNA sequencing was performed in each group at 11 Gy, and differentially expressed genes (DEGs) were identified. Database for Annotation, Visualization, and Integrated Discovery (DAVID) online tools were used to perform gene ontology (GO) enrichment analysis.

Results: The proportion of sub G0/G1 was higher in the FLASH group, and the surviving fraction was significantly decreased in FLASH through every dose range. A total of 1207 and 877 DEGs were identified, comprising 905 and 473 upregulated and 302 and 404 downregulated in FaDu and HSG cells, respectively. The GO enrichment analysis demonstrated that DEGs were mainly associated with as below; transcription, double-strand break repair via homologous recombination, and fatty acid metabolic process in FaDu cells; toll-like receptor 4 signaling, transcription, and oligosaccharide metabolic process in HSG cells.

Conclusions: This study demonstrates FLASH strengthens the therapeutic effect for H&N cancers, and DEGs were identified. Further research is needed on the biological mechanisms involved.

EPD100 / #212

APPLICATION TO IN VITRO AND IN VIVO EXPERIMENTS OF THE FLASH ELECTRON BEEM IRRADIATOR DEVELOPED BY DIRAMS

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: The Dongnam Institute of Radiological and Medical Sciences has been developed 6-MeV linear accelerator implementing the first FLASH electron beam radiotherapy (FLASH-RT) in Korea. In vitro and in vivo experiments were performed to investigate which beam conditions can cause different biological responses from electron radiotherapy at conventional dose rate (CONV-RT).

Methods: In vitro experiment using CCD18LU, HUVEC, BEAS-2B and A549 and in vivo experiment using male C57BL/6N mice was performed. Different dose rates from 58.0Gy/sec to 177Gy/sec were used in FLASH-RT.

Results: CCD18U, HUVEC and A549 cells were irradiated with FLASH-RT and CONV-RT of 1.21-20.8Gy. The dose rates of FLASH-RT were mean 158Gy/sec (range:121-177Gy/sec) and the dose rate of CONV-RT was 0.067Gy/sec. The viabilities of the 3 cell lines irradiated by FLASH-RT were not significantly different from those irradiated by CONV-RT in each doses. We irradiated CCD18LU and A549 cells with FLASH-RT of three different dose-rate ranges; mean 145Gy/sec (range:129-156), mean 95.0Gy/sec (range:94.4-95.7) and mean 61.8Gy/sec (range:58.0-64.9). The cell viabilities were not significantly different among those groups. Also, there were no differences of viabilities between FLASH-RT and CONV-RT in hypoxic conditions. The whole throax of C57BL/6N mice were irradiated with 17Gy/1fx of FLASH-RT and CONV-RT. Hair discoloration was obsereved in the mice receiving CONV-RT 4 weeks after irradiation, which is not observed in mice receiving FLASH-RT.

Conclusions: In vitro and in vivo experiments were feasible using ultra-high-dose-rate radiotherapy upto 177Gy/sec. Although there were no impacts of different dose rates on cell viabilities, skin reactions including allochromasia might be different according to dose rates.

EPD101 / #219

DNA DOUBLE STRAND BREAK REPAIR UNDER HYPOXIA FOLLOWING IRRADIATION WITH LASER DRIVEN PROTONS.

E-POSTER DISCUSSION: E-POSTER STATION 04 - FLASH MECHANISMS

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Background and Aims: The short burst nature of laser accelerated protons enables the irradiation of cells at dose rates >10^9 Gy/s. This has provoked interest in the use of laser-based technologies for ultra-high dose rate (UHDR) radiobiology. We irradiated stem-like glioblastoma cells (GSCs) and human skin fibroblast cells with laser-accelerated protons at a dose rate of 10^9 Gy/s, using the Vucan laser system at the Rutherford Appleton Laboratory, UK.

Methods: 15MeV protons were accelerated at intensities of ~10^{20} W/cm^2 from thin target foils. Dose measurements were provided by EBT3 Gafchromic films, calibrated with conventional proton beams. DNA double strand break (DSB) repair kinetics were studied using the p53 binding protein-1 (53BP1) foci formation assay under oxic and hypoxic conditions. Comparative irradiations were performed using a 225 kVp X-Ray source at Queen's University Belfast, UK.

Results: We observed similar 53BP1 foci repair kinetics in the fibroblasts and GSCs irradiated with 225kVp X-rays and UHDR protons under oxic conditions and increased residual 53BP1 foci in hypoxic GSCs compared to X-ray controls.

Conclusions: This data shows an enhanced induction of residual 53BP1 foci in hypoxic GSC samples irradiated with UHDR protons. This induction of greater residual damage in hypoxic samples is of potential interest for hypoxia targeted treatment strategies in the future as hypoxic regions are a common feature of tumours and are associated with resistance to radiotherapy. We would like to acknowledge funding from EPSRC projects EP/K022415/1 and EP/P010059/1.

EPD102 / #238

FEASIBILITY STUDY OF USING INNOVATIVE TECHNOLOGY BASED ON SILICON CARBIDE DETECTORS FOR FLASH IRRADIATIONS

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Accurate dosimetry and reliable beam monitoring are crucial for the assessment of the FLASH effect, as the uncertainties can have a relevant impact on the biological results. Dose measurements are challenging, as currently used detectors fails at ultra-high dose rates (UHDR). Therefore, the development of novel approaches is required. This work aims at studying the feasibility of an innovative solid-state technology based on ultra-thin SiC membranes (1-10 μm thickness) for irradiations with UHDR beams.

Methods: Monte Carlo simulations have been carried out to retrieve the energy deposition in the sensitive volume for different dose-rates per pulse for electron beams up to 7 MeV, and used as an input for investigating possible recombination effects through dedicated tools. A set of preliminary measurements have been also carried out with the aim of testing the response at different beam rates.

Results: Simulation results obtained with a typical beam time structure of an electron LINAC for FLASH irradiation (i.e. a pulse duration of a few μs), for 10^7 Gy/s as instantaneous dose rate result in a produced charge in the detector of less than 3 pC, showing a linear response even at dose rates several order of magnitudes larger.

Conclusions: Ultra-thin SiC membranes represent a promising alternative to currently used detectors for beam monitoring at FLASH regimes, being characterized by very good linearity and high radiation hardness, with a potential for being used also as detectors for relative dosimetry thanks to their high spatial resolution (down to 10 um).

EPD103 / #36

DESIGN OF A REAL TIME BEAM MONITOR FOR CONVENTIONAL AND ULTRA-HIGH DOSE RATE RADIOTHERAPY

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: This work focuses on the development of a real time beam monitor for Ultra-High Dose Rate (UHDR) machines dedicated to preclinical studies of the FLASH effect. It is developed for applications with the new electron accelerator located at the Institute Curie in Orsay (FR) for monitoring 5 and 7 MeV electrons with instantaneous dose rate up to 10 $Gy \cdot \mu s^{-1}$.

Methods: The beam monitor system consists of a Beam Current Transformer (BCT) associated to a small gap Ionization Chamber (IC) placed at the beam exit. The components of the BCT such as the ferrite core material, coil windings, shielding and front-end electronics have been optimized to achieve low noise (< 0.3 μA_{RMS}) and very low droop rate (< 0.02 %/µs).

Results: The BCT can measure beam currents up to 60 mA and pulse widths ranging from about 100 ns to several µs with excellent proportionality. The maximum irradiation field is limited to 95 cm^2 corresponding to an inner diameter of 11 cm. A selector on the electronic front-end can be switched for either used in conventional (few $Gy \cdot min^{-1}$) or UHDR irradiation mode. A prototype of the small gap IC currently measures the dose at the beam axis with an active area of 1 cm^2 but will be optimized to obtain the beam irradiation profiles in real time.

Conclusions: Preliminary results of the BCT will be shown as well as future prospects to provide a reliable beam monitor that can be used as a dose monitoring system after proper calibration.

EPD104 / #144

REAL-TIME DOSE ESTIMATION USING A BEAM CURRENT TRANSFORMER FOR FLASH PRECLINICAL STUDIES

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: Currently, the linear accelerators (LINACs) for treatment use a monitoring chamber to monitor the dose. This type of chamber consists of thin plates, so the energy loss of the radiation beams can be minimized. Under ultra-high dose-rate conditions, however, the output of the monitor chamber can also depend on the ion recombination and polarity effects, requiring additional calibration. In order to solve this problem, in this study, the beam current transformer (BCT) was used for ultra-high dose rate electron beam monitoring.

Methods: At the source to surface distance of 30 cm, the doses according to the number of electron beam pulses generated from the C-band research LINAC in Dongnam Institute of Radiological & Medical Sciences (DIRAMS) were measured using Gafchromic MD-V3 Films, and the beam currents were measured using the BCT at the same time.

Results: The beam currents and the doses increased linearly according to the number of electron beam pulses. Also, the outputs of the BCT increased linearly with the doses of the films. The coefficient of determination (R-square) between the measured data and the linear fitting equation was 0.9955.

Conclusions: Throughout this research, it was found that the irradiated doses can be estimated non-invasively using the BCT. It is anticipated that the BCT can be effectively used for monitoring of ultra-high dose rate radiation beams in various FLASH-RT studies. (The work was supported by the Dongnam Institute of Radiological and Medical Sciences (DIRAMS) grant funded by the Korea government Ministry of Science and ICT (Nos. 50496-2021 and 50493-2021))

EPD105 / #157

FLASH ELECTRON BEAM MONITORING USING A CLINICAL IONIZATION CHAMBER FOR CELL IRRADIATION

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: For cell irradiations using FLASH beams, it is necessary to monitor the radiation output in real time. A small clinical ionization chamber was mounted on a phantom for cell irradiation and dose monitoring was performed.

Methods: In this study, two types of dose monitoring methods were used. First, a parallel plate type (PTW-Advanced Markus chamber) or a cylindrical chamber (PTW-Semiflex) was mounted on the back side of the phantom, and the second, the cylindrical chamber was mounted on the side of the phantom. A radiochromic film (ASHLAND-MDV3) was inserted into the phantom, and the collected charge according to the number of electron beam pulses was measured with an electrometer (PTW-UNIDOSwebline) at the same time.

Results: The outputs of both ionization chambers increased almost linearly in proportion to the doses obtained by the film. However, the charge of the Advanced Markus chamber located on the back of the phantom was relatively smaller than that of the Semiflex chamber on the side.

Conclusions: When the chamber is located on the backside, the central axis transmitted beam can be monitored, but since it monitors X-rays generated in water, the signal is small. A large signal can be obtained when the chamber is located on the side, but it can be affected by changes in energy and beam profile when the small irradiation field is used. (The study was supported by the DIRAMS grant funded by the MSIT(50496-2021)).

EPD106 / #46

SILICA-BASED OPTICAL FIBRE WITH 10 MICROMETER CORE DIAMETER FOR PROTON FLASH MONITORING

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: In FLASH therapy with protons, especially when the Bragg peak is overlapped with the tumour, the monitoring of the beam during treatment is crucial for patient safety due to the steep dose fall-off. Optical fibres may be a good solution as they can provide beam information in real time and due to their small size even in vivo. Here, we demonstrate the application of telecom-grade optical fibres with a core diameter of 10 micrometers for proton beam monitoring at FLASH dose rates through the phenomenon of radiation-induced luminescence (RIL).

Methods: A 2.5 cm long 10-micrometre core diameter germanium-doped silica single-mode fibre from Corning (GeO_2 concentration of 5.8 wt. %) was spliced to a transport fibre and installed at the TRIUMF proton therapy centre. The RIL output was guided to a multi-pixel photon-counter (MPPC) from Hamamatsu, where the light was converted into a current and recorded.

Results: The left panel in figure 1 shows a typical trace of the Ge-doped fibre. The right panel shows the results from different dose rates. Within the uncertainties, the behavior between dose rate and light output is linear.

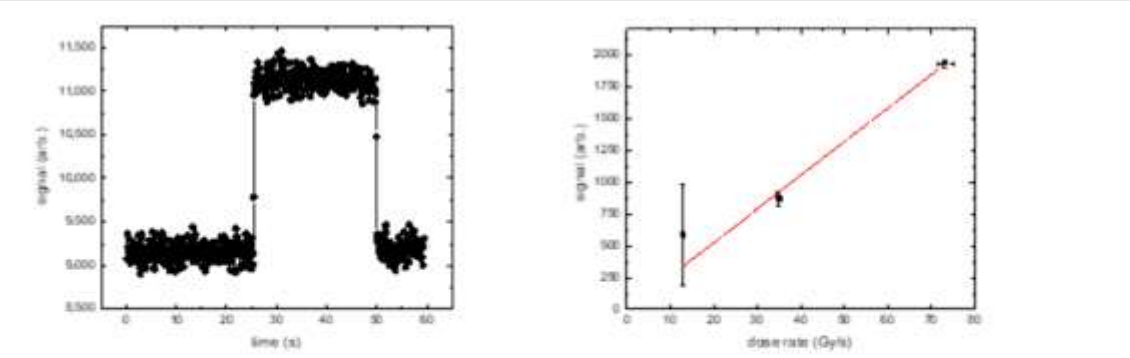

Figure 1: Left: Example of the Ge-doped fibre response as measured with the MPPC for a proton beam energy of 19.0 MeV and a dose rate of 73 Gy/s. Right: Ge-doped fibre response as a function of dose rate at a proton beam energy of 19.0 MeV. The red line is a linear fit through the origin with a slope of 26.3 ± 0.3 signal/(Gy/s).

Conclusions: We have demonstrated the RIL response from a 10-micrometer diameter Ge-doped silica fibre at FLASH dose rates in a proton beam. Since the RIL is most likely caused by a defect, the Germanium Lone Pair Centre (GLPC), at higher doses (> kGy) the RIL will most likely decrease. Further measurements with additional doses, dose rates, and energies will be conducted.

EPD107 / #141

EVALUATION OF DOSE CALIBRATION TECHNIQUES IN ELECTRON FLASH4000

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: With the hope of a rapid clinical translation of FLASH-RT, many efforts have been made to apply dosimetric standards for ultra-high dose rate irradiation. Accepted protocols recommend calibrating radiotherapy accelerators to deliver a specific dose per Monitor chamber reading Unit (MU) using ionization chambers for reference dose. However, neither monitor chambers or ionization chambers shall be used in ultra-high dose-per-pulse beams. Therefore, on ElectronFlash4000 linear accelerator, we performed the calibration of a prototype monitoring system using Gafchromic films and evaluated the associated uncertainties.

Methods: The FLASH beam monitoring is based on a measure of the beam current by a toroid at the end of the accelerating structure. By comparing the toroid temporal profiles with a secondary detector and their total output (i.e. integration over the gun pulse duration) with Gafchromic films, we have evaluated the stability and linearity of the toroid outputs for different pulse lengths, repetition frequencies and pulse doses in FLASH regime. In turn, the monitoring system has permitted to validate an optimized protocol for EBT-3 and EBT-XD Gafchromic film reference dosimetry.

Results: The noise and the droop rate of the monitoring system has been found to be the main factors of lack of stability and linearity, respectively.

Conclusions: In absence of standard system for dose measurement and monitoring in FLASH electron beams, the cross-check of a relative detector with excellent temporal resolution and good reproducibility with a reference detector with independent dose-rate response has allowed to achieve the equivalent of a clinical beam calibration, ensuring the daily use of ElectronFlash4000.

EPD108 / #239

REAL-TIME PROTON SOUND DETECTOR FOR SUB-MILLISECOND LATENCY BRAGG PEAK LOCALISATION FOR FLASH HADRON THERAPY

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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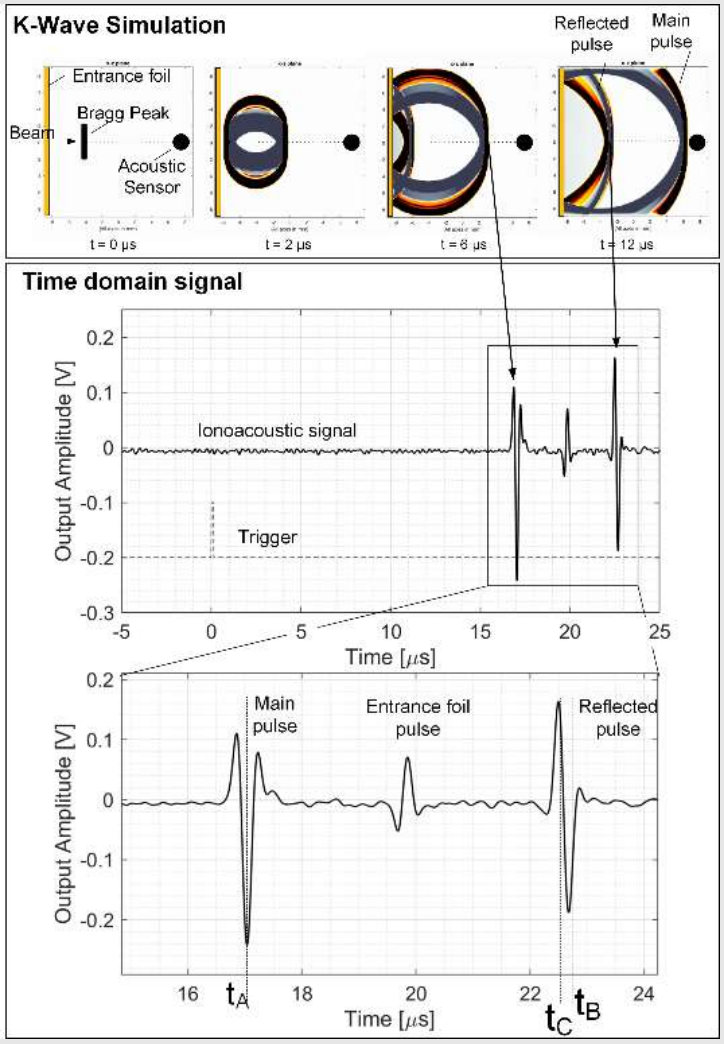
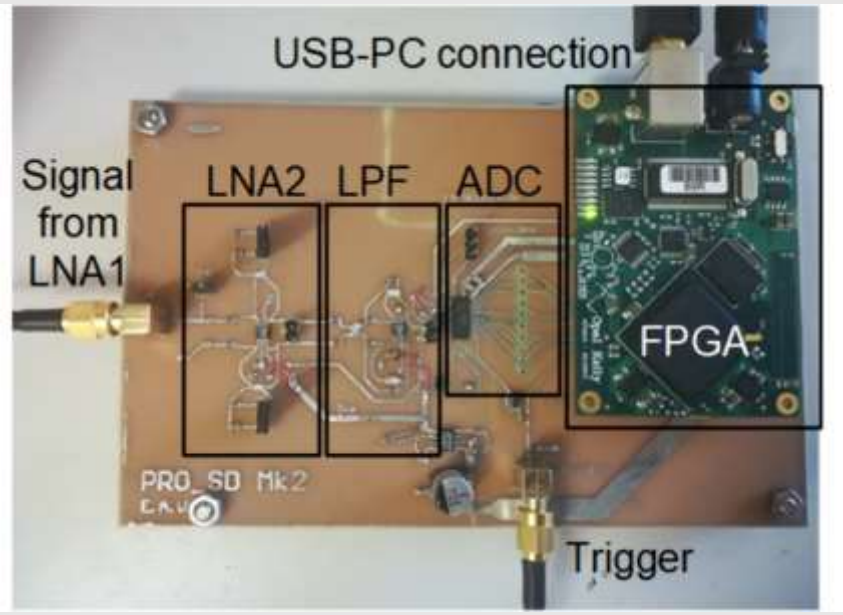
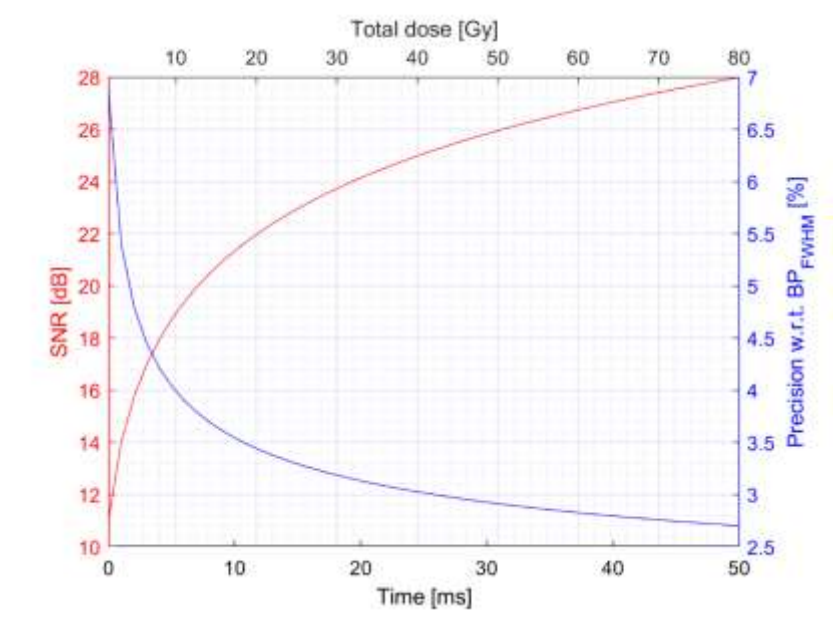
Background and Aims: Proton Sound Detectors (ProSDs) use the proton-induced thermo-acoustic signal generated by pulsed particle beams in energy absorbers to localize the Bragg peak in real-time with sub-mm precision by measuring the acoustic wave time of flight, with interesting envisioned applications in hadron therapy. Compared to nuclear imaging techniques, ProSDs have the ability to locate BP in the absorber with <1 ms latency, which is particularly interesting for real-time FLASH monitoring, but require dedicated high-performance electronics. For this reason, this document presents a real-time HW/SW monitoring system (called Real Time Proton Sound Detector, RT-ProSD) based on a ionoacoustic front-end and a real-time digital signal processing system implemented on FPGA and c++ GUI.



Methods: The ionoacoustic signal is acquired by a piezoelectric sensor and processed in analog domain by a dedicated front-end. The RT-ProSD exploits a FPGA-based dedicated digital design for event-driven (triggered by each beam shot) signal acquisition and a custom c++ GUI for signal processing and visualization.



Results: The RT-ProSD has been validated with a sub-clinical, high dose rate (1.6 Gy/shot at Bragg peak), 20 MeV proton beam. The RT-ProSD can acquire 1000 beam shots/sec, localizing the BP for each shot with 6.8% precision (22 μm) w.r.t. BP full-width at half maximum and achieving a final precision after 50 shots (50 ms or 80 Gy) of 2.7% (8.5 μm).



Conclusions: The low latency of the ProSDs makes them very promising for real-time monitoring of FLASH treatments but the development of dedicated detectors is essential to move this technique closer to clinical applications.

EPD109 / #237

ION COLLECTION EFFICIENCY IN A PLANE-PARALLEL TRANSMISSION CHAMBER OPERATED AT HIGH POLARIZING VOLTAGES IN A PULSED ELECTRON BEAM

E-POSTER DISCUSSION: E-POSTER STATION 01 - FLASH MODALITIES

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Background and Aims: One of the main challenges of a clinical implementation of ultra-high dose rate irradiation is to accurately monitor the radiation output. At high dose rates, ionization chambers suffer from a reduced ion collection efficiency due to ion recombination. To enable real-time monitoring of the electron beam from a clinical linear accelerator operated at ultra-high dose rates, this project aims to investigate the ion collection efficiency in a plane-parallel transmission chamber at high polarizing voltages.

Methods: A transmission chamber was positioned in a custom-made holder in an electron applicator at an Elekta Precise linear accelerator. The response of the chamber when exposed to ultra-high dose rate radiation was measured at applied negative polarizing voltages ranging from 80 to 1920 V. Dose-per-pulse values were measured with GafChromic EBT3 film positioned at 2 cm depth in a solid water phantom at a source-to-surface distance of 70 cm, and subsequently used to calculate the relative ion collection efficiency at each voltage level.

Results: The response of the transmission chamber increased with increased applied polarizing voltage. Above -1760 V, an avalanche effect in the response was observed. At the standard polarizing voltage (-320 V), the ion collection efficiency was 20.7%, which was increased to 43.2% at -1760 V.

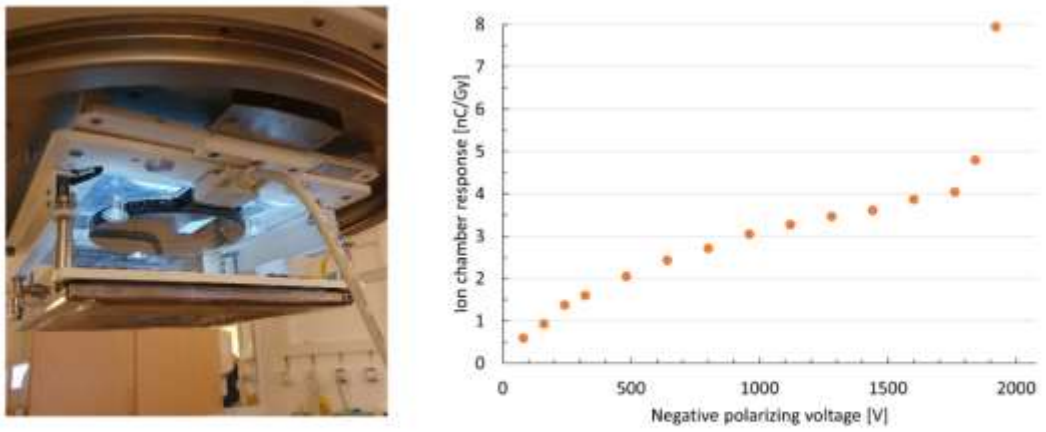

Figure 1. A transmission chamber positioned in a custom-made holder in an electron applicator (left) and the transmission chamber response at ultra-high dose rates as a function of the applied negative polarizing voltage (right).

Conclusions: The applied voltage over the transmission chamber can be substantially increased from the standard value before reaching the proportional region of a charge-voltage curve, increasing the ion collection efficiency. This setup allows for improved accuracy of real-time dose monitoring compared to existing linac monitor chamber solutions.

E-Poster Viewing Abstracts

EPV001 / #17

THEORETICAL ANALYSIS OF FLASH EFFECT ON TUMOUR CONTROL AND NORMAL TISSUE COMPLICATION PROBABILITY

E-POSTER VIEWING

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Background and Aims: The FLASH effect is referred to the sparing effect on normal tissues while mantaining antitumor efficacy in treatments with ultra-high dose rates. However, there is a lack of radiobiological models to predict the treatment efficacy and the oxygen effect in FLASH. This study aims at modelling TCP and NTCP for different initial oxygen tensions, estimating the theoretical therapeutic window, and assessing the FLASH effect.

Methods: A model for beta as a function of the initial oxygen tension was used on TCP and NTCP models for prostate tumour cells and normal bladder cells (an organ at risk). The classical TCP model and the Lyman NTCP model were used. Different initial oxygen levels were studied, ranging from 0 to 20%. The displacement of the 50% Effect Dose (ED50%) at the TCP and NTCP curves was calculated as a function of the initial oxygen tension for conventional-dose rate (CDR) and for FLASH.

Results: Changes in ED50% were found for both dose rates (as seen in Figure), whereas FLASH presented higher absolute values than CDR. The maximum difference between CDR and FLASH occurs at 1.6% of oxygen: 12.7% and 6.9% for TCP and NTCP respectively, maximizing the FLASH effect at this point.

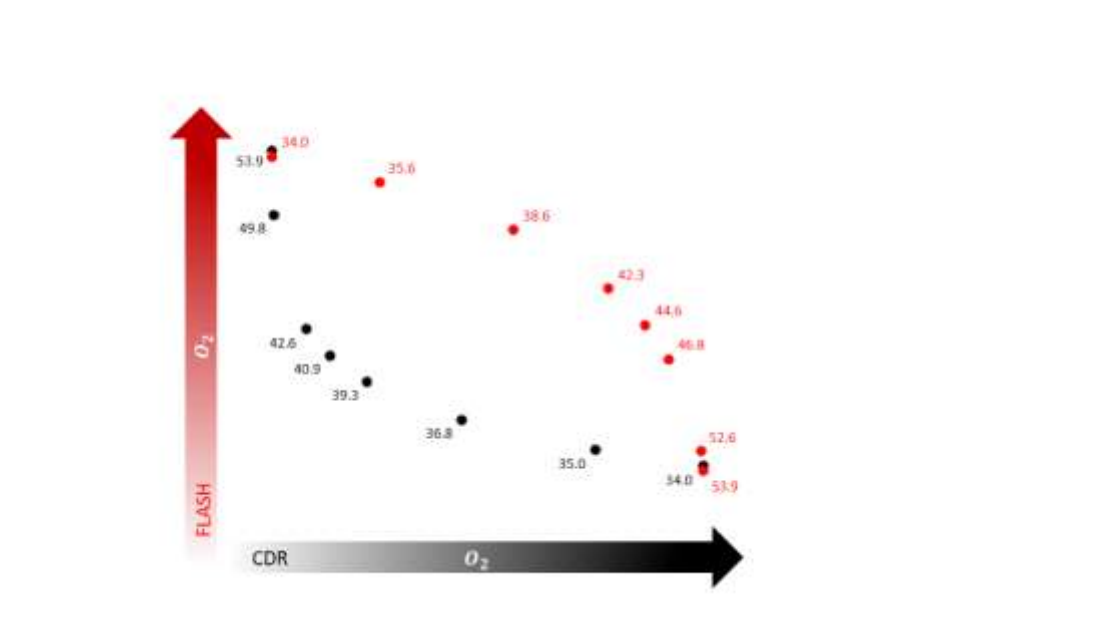

Figure: Effective dose (ED50%) for CDR and FLASH as a function of oxygen.

Conclusions: Different oxygen levels promote influence the TCP and NTCP curves, leading to a maximized therapeutic window for FLASH. The study of radiobiological models can aid the development of clinical protocols for FLASH.

EPV002 / #20

TIME-RESOLVED MEASUREMENTS OF PULSED BEAMS USING PLASTIC SCINTILLATORS AND SIPMS

E-POSTER VIEWING

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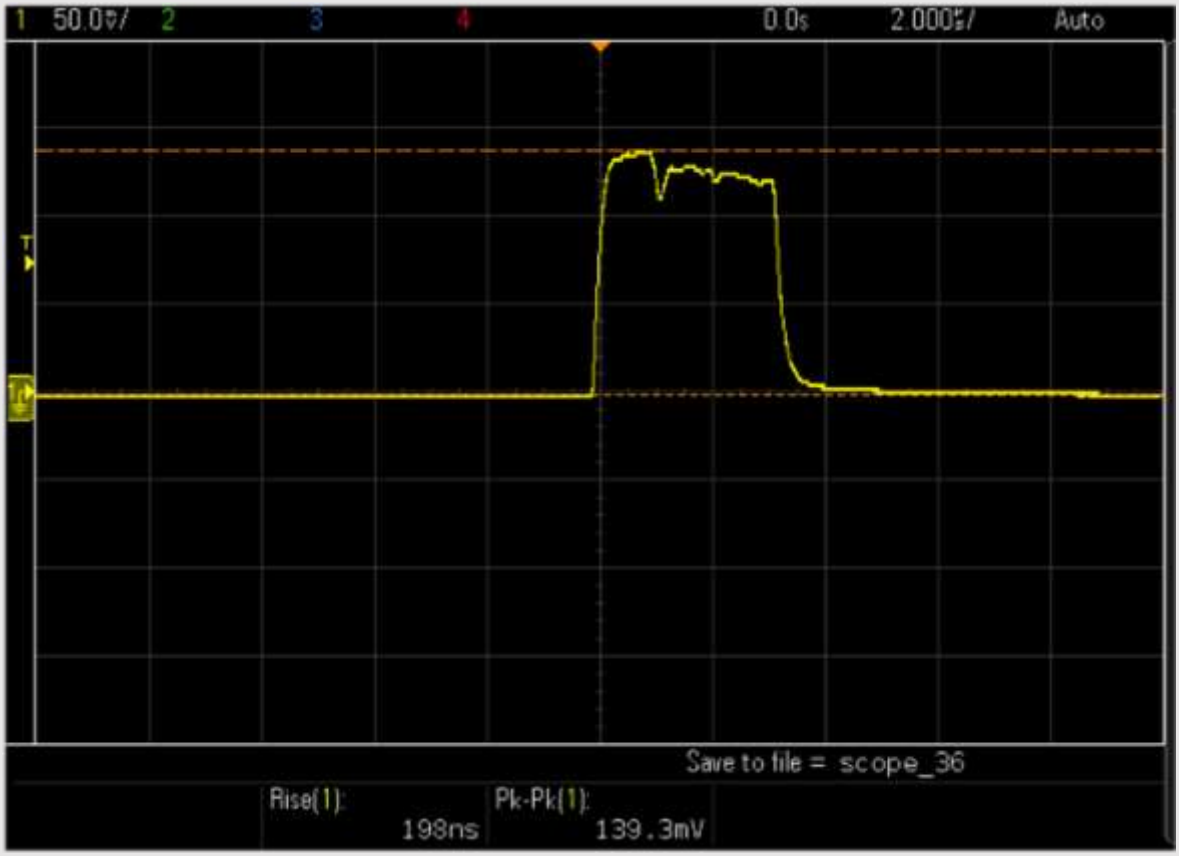
Background and Aims: Many current dosimeters are unable to resolve pulsed radiation beams and actively measure dose rate at the time scale and intensity required for accurate dosimetry in FLASH therapy measurements. This project aims to develop and characterize a plastic-scintillator-based detector to measure dose rate at the nanosecond-level.

Methods: A proof-of-concept detector was developed using a plastic scintillator affixed, using an optical coupling epoxy, to a plastic optical fiber (POF) terminating at an assembly, including a variable optical attenuator, which serves as an optical feedthrough into a light-tight housing containing a silicon photomultiplier (SiPM). Preliminary characterization and analysis were performed using an oscilloscope. The SiPM's performance was evaluated in a controlled environment using a waveform-generator-driven LED. Scintillator pulse characterization measurements were performed using a Varian TrueBeam and include dose-rate linearity, evaluation of rise/fall times, and general pulse shape observations.

Results: The SiPM quoted photon detection efficiency (PDE) was reproduced within 0.5%, the rise time was less than 10ns and only limited by the waveform generator output, and saturation was observed with increasing pulse width above 100ns. Characterization measurements of the scintillator/SiPM combination using the TrueBeam 6MV beam yielded ideal dose rate linearity within measurement resolution and observation of increased rise time with depth in water-mimicking plastic.



Conclusions: The detector demonstrated the ability to resolve pulsed beams at the nanosecond level, providing a path for further development of the dosimeter. Future work includes automation of pulse data collection along with expansion to a 2D array to fuse spatial and temporal information.

EPV003 / #31

3D RANGE-MODULATORS: DOSE SIMULATIONS UNDER THE ASPECT OF POTENTIAL FLASH IRRADIATION WITH PROTONS.

E-POSTER VIEWING

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Background and Aims: Radiotherapy with dose-rates above 40 Gy/s ("FLASH") could reduce side-effects in healthy tissue. Cyclotrons, however, must be operated at the highest energy to provide the necessary dose-rate. A 3D-range-modulator (RM), optimized for single energy and individual tumour shape, may present optimal solution for FLASH. The high particle range must be adjusted to the tumour depth using absorber. This work uses Monte Carlo (MC) simulations to investigate the effect of absorber in combination with 250 MeV protons on the dose distribution behind 3D-RM compared to reference simulation with 151 MeV without absorber.

Methods: The dose distribution of 3D-RM, previously optimized for 151 MeV protons and complex tumour shape, was simulated in water phantom (MC FLUKA). Two modifications were then performed: the energy was increased to 250 MeV and approximately 19 cm thick PMMA absorber was positioned immediately behind the RM and in front of the water phantom. In the subsequent simulation the dose from each scan-spot was scored individually, then assigned weighting factor and optimized for homogeneous dose in the target volume to account for the different energy and scattering. The final simulation was performed with the optimized scan-spots.

Results: There is good agreement between both dose distributions, 151 MeV without absorber and 250 MeV with absorber.

Conclusions: The 3D-RM is a promising method to achieve very fast treatment with high-degree of dose conformity and homogeneity in proton therapy with one energy. A 3D-RM in combination with high proton energy and the appropriate absorber could enable FLASH irradiation in the future.

EPV004 / #48

HIGH SPEED DETECTOR FOR FLASH PROTON THERAPY QA

E-POSTER VIEWING

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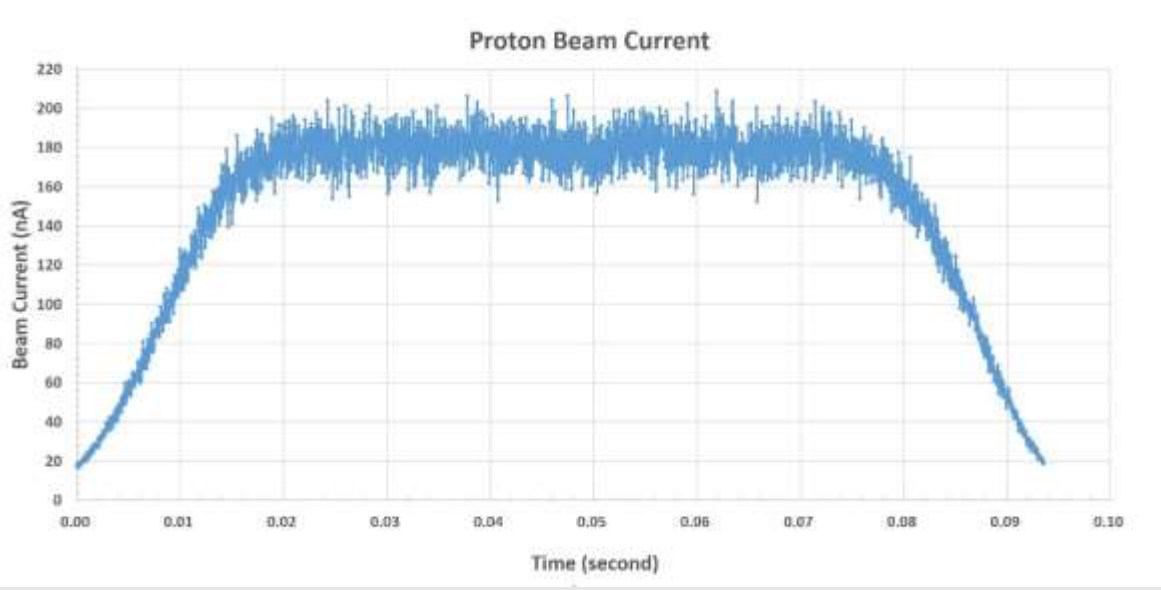
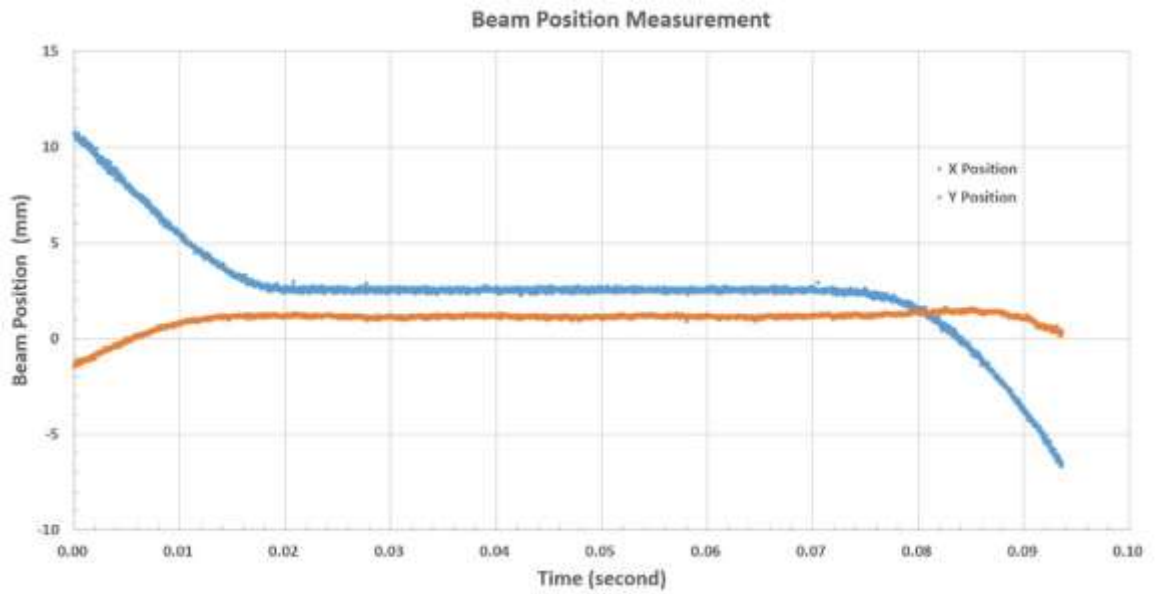
Background and Aims: Flash proton therapy has the potential to revolutionize radiation therapy, which treats the target tumor with an ultra-high dose rate (> 40,000 cGy/second) and a very short exposure time (< 1 second). This new treatment technology also brings new requirements to equipment used in the machine QA control.

Methods: We present a novel ionization detector, $CROSS_{flash}$, with an ultra-high measuring rate up to 40,000 Hz. With a such system, one measures the time evolution of all beam parameters, including beam positons and 2D dosage distributions, required by Flash proton therapy QA down to 25 μsec precision. $CROSS_{flash}$ was tested by 230 MeV proton beam with 180 nA in Particle physics and beam delivery core laboratory of Chang Gung Memorial Hospital, Linkou, Taiwan. It equips two copper beam stoppers controlled by electromagnets. The high current proton beam can be delivered with a very short period down to 0.1 second to simulate the condition of flash proton therapy.

Results: The first figure shows the proton beam current measurement in a 0.094 second delivery by $Cross_{flash}$. With the 40,000 Hz measuring rate, it shows clearly that the time evolution of opening and closing of beam stoppers. The proton beam was delivered at 180 nA for only 0.056 second.



The second figure shows the measurement of X-Y beam positons. The movement of beam position in X due to the magnet field of electromagnets can emulate the pencil beam scanning of flash proton therapy.



Conclusions: The performance of $Cross_{flash}$ in the condition of flash proton therapy is successfully verified.

EPV005 / #68

DEVELOPMENT OF A EUROPEAN METROLOGY NETWORK FOR RELIABLE RADIATION PROTECTION: PULSED HIGH ENERGY PHOTON REFERENCE FIELD AS A METROLOGICAL GAP IN RADIATION PROTECTION

E-POSTER VIEWING

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Background and Aims: The European regulation on ionizing radiation is laid down in COUNCIL DIRECTIVE 2013/59/EURATOM, which underpins the basic safety standards for protection against the dangers of ionizing radiation.

Methods: Legal metrology in radiation protection (RP) is a task at national, European and international level. A joint and sustainable European metrology network (EMN) should therefore be established as a central point. The construction of such an EMN was already planned by the consortium of the EMPIR project 19NET03 supportBSS[1]. The EMN aims to establish a long-term communication between the metrology and RP stakeholder communities and to identify metrological gaps.

Results: One gap was identified at the radiation protection approval of modern accelerator facilities for medical treatment and research. To verify the compliance with the legal limits, legally relevant dosimetric measurements around these facilities are needed. These measurements were usually carried out using area dosimeters. Currently, the suitability of these dosemeters in such high energy and pulsed radiation fields cannot be confirmed due to the lack of corresponding reference fields.

Conclusions: In order to close this gap, a project on the national level has been started at the PTB in Germany to establish such a reference field, which is funded by the BfS[2]. [1)]The project 19NET03 supportBSS has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme. 19NET03 supportBSS denotes the EMPIR project reference. [2)]The reference field is supported by the Bundesamt für Strahlenschutz (BfS) with project no. 3619S2236.

EPV006 / #79

SCINTILLATOR DETECTOR SYSTEMS FOR FLASH RADIOTHERAPY

E-POSTER VIEWING

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Background and Aims: To evaluate and develop scintillator detector systems optimized for FLASH radiation therapy (RT) dosimetry.

Methods: A systematic dose and dose-rate response test of the commercially available Exradin W2 scintillator detector system was performed using a 10-MV Varian TrueBeam FFF beam. The linearity of the detector response was tested by delivering between 200 and 800 cGy using dose rates from 100 to 3750 cGy/min.

Results: At 800 and 2,400 MU/min, the measured dose was within 0.15% of the delivered dose, and the slope of the linear fit of the data was 0.999 and 1.000, respectively. The standard error across the dose rates used was 0.04%, 0.04%, and 0.06% for measurements at 100 cm, 90 cm, and 80 cm SSD, respectively. The Exradin W2 scintillator detector produced consistent readings up to 3,750 cGy/min without exhibiting any saturation effects. These results are very encouraging for scintillators in general and could make them potentially good candidates for FLASH dosimetry.

Conclusions: The Exradin W2 detector displayed very beneficial properties when evaluated at dose rates up to 3,750 cGy/min (0.625 Gy/s). The continuation of this project is to evaluate this detector system at FLASH dose rates (>40 Gy/s) using the FLASH Mobetron (IntraOp Medical, Sunnyvale, CA). We will optimize the scintillating detector system to allow for high stability, reproducibility, dose linearity, and dose-rate independence in FLASH beams with minimal radiation damage induction.

EPV007 / #97

THE BIOMED RESOURCE AT TH WILDAU TO SUPPORT HP²EFLASH-RT@PITZ

E-POSTER VIEWING

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Background and Aims: The R&D platform “High Power High Performance electron FLASH Radiation Therapy at the Photo Injector Test facility at DESY in Zeuthen” (HP²eFLASH-RT@PITZ) under preparation closely works together with the Technical University of Applied Sciences Wildau (TH Wildau) as partner in close vicinity for the biological resources.

Methods: On the development path from fundamental physics to treatment of tumor patients biomedical studies will cover the in silico, in vitro and in vivo evaluation of radiation effects. In a hierarchical setup materials (e.g. polymers), phantoms, biological samples (e.g. DNA and biochemical reactions), cellular systems (e.g. cell cultures and organoids), simple organisms (e.g. fruit fly) as well as animal models (e.g. mice w/wo tumors) have to be investigated. All stages are accompanied by extensive modelling and simulation experiments.

Results: This will open ground for the fundamental understandig of the FLASH effect, help to appraise its suitability for therapy as well as it will support the 3R strategy, i.e. replace, reduce and refine animal experiments. After upgrade of the electron beam from 22 MeV to 250 MeV at PITZ the irradiation of more voluminous samples becomes possible and the experimental parameters have to be adjusted.

Conclusions: Potentially animal tumor patients can be integrated in the studies before first clinical studies with humans can be planned.

EPV008 / #98

A RADIATION BIOLOGICAL ANALYSIS OF THE POSSIBLE MECHANISM FOR THE OXYGEN EFFECT IN FLASH

E-POSTER VIEWING

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Background and Aims: There are at least two very plausible radiobiological mechanisms for the oxygen effect in FLASH: 1) Directly, by depletion of oxygen at critical molecular sites directly changing the amount of radiation damage; 2) Indirectly by modifying physiologically mediated changes in response to radiation damage via alterations in repair and/or cell signaling. The overwhelming amount of radiation-induced damage that ultimately leads to cell death occurs in DNA. Oxygen directly radiosensitizes by reaction with transient intermediates in the DNA. Hypoxia also can modify damage from ionizing radiation inducing changes in signaling and in repair mechanisms that differ between tumors and normal tissues.

Methods: Radiobiological Principles

Results: Based on studies with cells there are lesions in DNA that have lifetimes as long as 10^{-5} or 10^{-6} seconds. The pertinent distance from which oxygen can diffuse to the sensitive site is 100-1000 nm assuming the diffusion rate of oxygen is 2.1×10^{-5} cm^2/sec within the environment around the DNA. Therefore a technique is needed that can follow the oxygen level with spatial resolution of the nucleus and a time scale of 10^{-5} seconds or faster. No currently available method can do this directly. This might be done if detailed spatial distribution of oxygen inside the cell is known and the rate of oxygen depletion in a nucleus can be determined by a combination of direct measurements of oxygen, genomic alterations, and appropriate calculations.

Conclusions: Using established principles of radiation biology it should be feasible to rigorously determine if and how oxygen is involved in the mechanism of FLASH.

EPV009 / #128

PROTON DOSE MEASUREMENTS WITH PASSIVE DETECTORS AT HIGH FLUENCE

E-POSTER VIEWING

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Background and Aims: The precise determination of radiation dose deposited by ultra-intense ion bunches is of growing importance in pre-clinical and clinical research. Passive detector materials with wide dynamic range are less prone to saturation effects and therefore can be useful for dose monitoring as well as cross calibration of real-time devices.

Methods: We have irradiated two types of passive detectors with protons of 0.8 MeV, PADC (CR-39) and radiochromic films. The high sensitivity of PADC allows for single particle detection but track counting becomes difficult above 10^7 p/cm^2 due to overlapping pits. At higher fluences the optical density of the initially transparent material, measured with a flatbed scanner, correlates with the particle density.

Results: Our tests with PADC reaching a maximum fluence of the order 10^{11} p/cm^2 indicate that a correlation with the optical density can be inferred up to $5 \cdot 10^9$ p/cm^2 at least, a range which may be increased by optimized etching procedures. For radiochromic films of type EBT3-U the protons of 0.8 MeV deposit all their energy inside the sensitive layer. Here again, the grey values of uniform beam spots correlate with the fluence up to about 10^{11} p/cm^2. Previous tests with a different type of material, HD-V2, showed that this range can be extended by an order of magnitude.

Conclusions: Our results may be especially relevant for pre-clinical studies with cell cultures carried out with highly intense, laser-accelerated particle beams. Funded by Government of Spain, RTI2018-101578-B-C22, and by Generalitat Valenciana, AICO/2020/207, Fondo Social Europeo (Iniciativa de Empleo Juvenil), and IDIFEDER/2018/022.

EPV010 / #164

DEVELOPMENT OF THE LOW INTENSITY BEAM EXTRACTION MODE FOR PROTON IMAGING AT PROTOM SYNCHROTRON

E-POSTER VIEWING

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Background and Aims: Protom synchrotron is a medical accelerator specially designed for proton therapy. The synchrotron has an opportunity to accelerate protons up to 330 MeV. It makes proton imaging of the entire human body available without any restrictions. Using of proton imaging allows us to escape of proton range uncertainties in the patient body and makes the treatment process more accurate. Additionally, proton radiography can be used as a patient position verification tool instead of standard CBCT. Moreover, the proton imaging system has a lower equivalent dose received by the patient compare to similar X-ray imaging systems. However, proton imaging systems cannot work with beam intensity used in standard proton therapy. Therefore, there is a need to decrease the proton intensity for proton imaging implementation.

Fig. Protom Synchrotron

Methods: To implement low intensity beam extraction the following actions were performed: a decrease in the number of injected protons, modification of beam extraction mode for the accelerator, development of the extracted beam control and feedback system, development procedures for calibration and verification the extracted proton beams. Calibration procedures and measurements were performed with certified Protom Faraday Cup, PTW Bragg Peak Chamber and specially designed experimental photomultiplier detector.

Results: The study made it possible to achieve the values of the extracted beam intensity required for the implementation of proton radiography mode.

Conclusions: The development can be implemented in any proton therapy complexes based on the Protom synchrotron. This allow us to use initial synchrotron beam as a tool for patient verification and to eliminate proton range uncertainties.

EPV011 / #188

DELIVERY TO TARGET OF A MULTI-GY, MULTI-MEV TNSA PROTON BEAM WITH ULTRAHIGH DOSE-RATE

E-POSTER VIEWING

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Background and Aims: Laser-driven ion acceleration has been developed for more than two decades and is regarded as an affordable and effective technique for high gradient acceleration. The potential of a compact, laser-based ion accelerator for radiobiological and medical applications relies heavily on the control of the laser-target source and on the use of custom beam transport and delivery to the final target.

Methods: We have developed a beamline based on the so-called Target Normal Sheath Acceleration to deliver a proton beam radiobiological applications. We use the Target Normal Sheath Acceleration technique, driven by a 200 TW ultra intense laser to accelerate protons with a cut off energy of up to 10 MeV. We use permanent magnet quadrupoles to select protons at 6 MeV and transport them, in the form of a collimated beam, to the final target position in air. We measure the spectrum and the deliverable dose at the sample position for each shot.

Results: Our proton beamline is now established and parameters at sample position are being measured. We will show experimental results achieved very recently on the transport of the proton beam with a selected energy spectrum around 6 MeV. Our preliminary dosimetric measurements show a unique multi-Gy dose per pulse with a ultra high instantaneous dose rate.

Conclusions: The achieved specifications at the sample position are now established and offer unique exposure parameters for radiobiological studies. The combination of beam parameters will be discussed against the required specifications for the laboratory investigation of the Flash effect.

EPV012 / #191

THE EFFECT OF PROTON IRRADIATION ON RPL13 GENE EXPRESSION IN THE IN VIVO MODEL OF MOUSE MELANOMA

E-POSTER VIEWING

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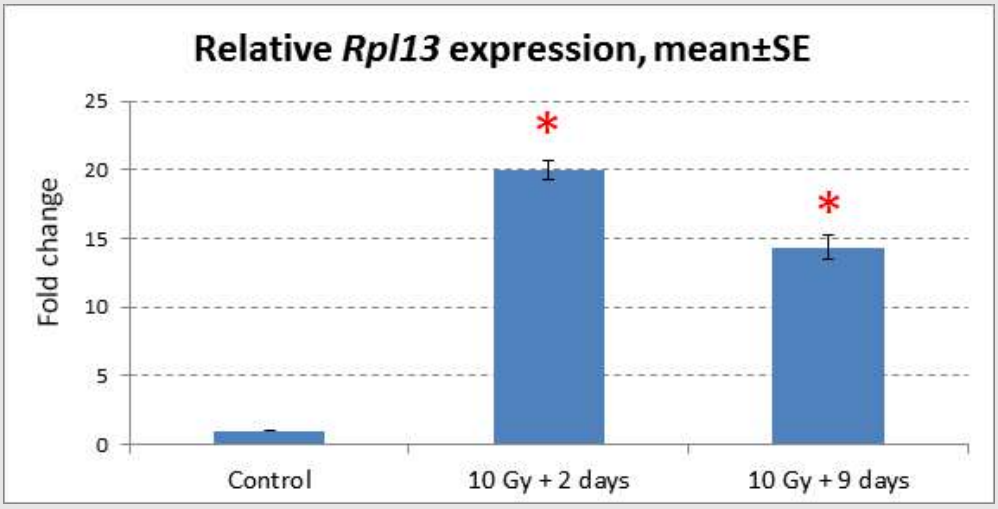
Background and Aims: Proton irradiation leads to activation of DNA repair genes in the cell. But it is not enough to achieve the necessary improvement in the efficiency of the repair processes, since the cell needs to translate mRNAs into the corresponding proteins. So, the activity of the translation apparatus can serve as a limiting factor for the ability of cells to repair DNA damage. The aim of this work is to evaluate the effect of proton irradiation on the expression of the Rpl13 gene encoding L13 protein of the large ribosome subunit.

Methods: B16 melanoma cells were irradiated with protons at a dose of 10 Gy 12 day after transplantation into the leg of mice. RNA was isolated from the peripheral fragments of tumors 2 and 9 days after radiation exposure. Real-Time PCR was used to analyze gene expression. Fold changes were determined using the ΔΔCt method against the Hprt and Ipo8, which stability was verified using BestKeeper and NormFinder algorithms.

Results: Proton irradiation leads to significant increase in Rpl13 gene expression: we indicate 20±0.73 fold change 2 days after irradiation and 14.3±0.88 fold change 9 days after irradiation. Differences are statistically significant (Mann-Whitney U Test: p=0.000011).



Conclusions: The revealed changes in Rpl13 expression may indicate a partial loss of ribosome function under the action of proton irradiation. Subsequently, the cell needs to restore the activity of the translation apparatus. In the future, we plan to include other components of the translation apparatus in the study, and compare the effects of proton versus gamma irradiation.

EPV013 / #206

THREE-DIMENSIONAL ELECTRONIC DETECTOR ARRAYS BASED ON AN ACTIVE-MATRIX READOUT CONFIGURATION FOR CONVENTIONAL AND FLASH DOSIMETRY

E-POSTER VIEWING

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Background and Aims: Advances in radiotherapy (RT) technology have transformed stereotactic treatments into routine modalities, while the advent of FLASH-RT may be a paradigm change altogether. In either case, experimental three-dimensional (3D) verification of an RT dose distribution is urgent. Electronic detector arrays for quality assurance (QA) remain two-dimensional (2D) and possibly unsuitable for an effective FLASH-RT verification. A spherical and cubic 3D electronic detector arrays were constructed as proof-of-principle to address this need. Based on an active-matrix (AM) readout configuration, data collection should be reliable for conventional and FLASH beams, according to simulations.

Methods: Two 3D electronic detector arrays of semi-spherical and cubic configurations were constructed, and their FLASH response simulated using pulses from an electronic emulator. These were 100-300 Hz pulses with pulse amplitudes of 3 µs and 1 µs for conventional and FLASH beams, respectively. The emulator could also generate 100 MHz pulses to simulate a cyclotron-based proton beam. A 1000-diode 3D detector array response was tested with the emulator.

Results: AM response for conventional and FLASH beams had a linearity deviation of < 1% for 1-35 Gy. For conventional, dose per pulse were 0.3-1.3 mGy for 19-305 Hz, and dose rates of 2-24 Gy/min. For FLASH, dose per pulse was 1 Gy for 100-300 Hz and dose rates of 100-300 Gy/s.

Conclusions: These results strongly suggest that the AM readout configuration in the 3D electronic detector arrays are quite capable to provide accurate detection of a FLASH as well as a conventional radiotherapy beam.

EPV014 / #223

FEASABILITY STUDY OF IONOACOUSTIC SIGNAL DETECTION UNDER FLASH CONDITIONS AT A CLINICAL SYNCHROCYLOTRON FACILITY

E-POSTER VIEWING

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Background and Aims: Ionoacoustics is a promising approach for online range verification using pulsed ion beams. The deposited kinetic energy converts to heat energy and results in a thermal expansion thereby initiating an acoustic wave. Its detection provides information about the Bragg peak location, which can be used for adaptive treatment strategies. A major challenge in ionoacoustics is the poor signal-to-noise ratio (SNR) at clinically relevant dose levels. Adapting the pulsing structure and maximising the instantaneous beam current provides ideal conditions for SNR maximisation.

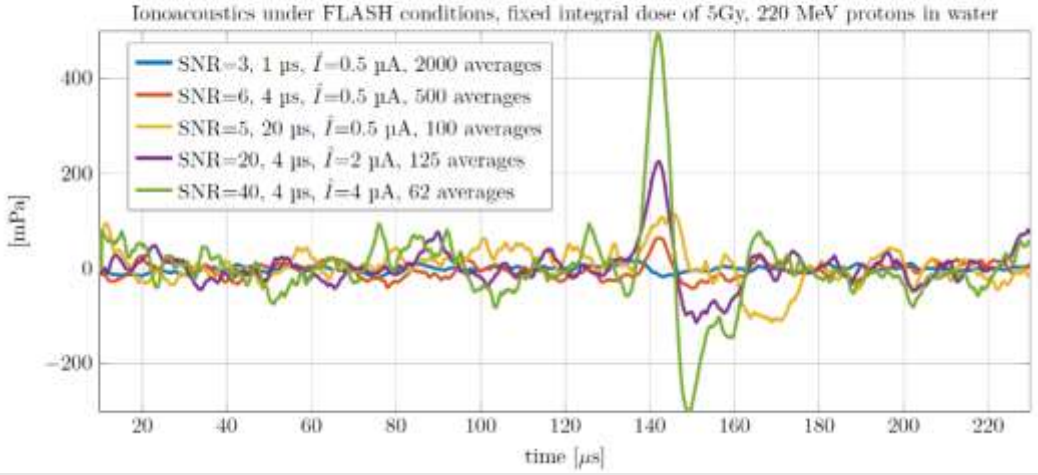
Methods: Ionoacoustic signals of 220MeV protons in water were simulated using an acoustic propagation simulation software (k-wave) and validated with experimental measurements. As high temporal gradients and pulse width influence the ionoacoustic amplitude, various beam currents and pulse widths were modelled in the remaining simulations assuming band-limited Gaussian noise for a synchrocyclotron facility under FLASH conditions.

Results:

FIG1 shows the expected signals and corresponding SNRs from different pulsing structures assuming a total dose deposition of 5Gy. For a constant instantaneous current, different pulse widths influence the signal amplitude. Suitable pulse widths for ionoacoustics lie between 2 and 10µs, which relates back to the spatial expansion of the Bragg peak. SNR improved drastically for an increased instantaneous beam current compared to previous experimental irradiation conditions.

SNR	PSNR	pulse width	# averages	dose rate	$\hat{I}$ inst. current	$\bar{I}$ DC current	tot. time
3	3	1 µs	2000	2.5 Gy s^{-1}	0.5 µA	0.5 nA	2000 ms
6	5	4 µs	500	10 Gy s^{-1}	0.5 µA	2 nA	500 ms
5	4	20 µs	100	50 Gy s^{-1}	0.5 µA	10 nA	100 ms
20	9	4 µs	125	40 Gy s^{-1}	2 µA	8 nA	125 ms
40	12	4 µs	62	80 Gy s^{-1}	4 µA	16 nA	62 ms

Table 1: SNR for different pulsing structures assuming a 1 kHz pulse repetition rate and a total integral dose of 5 Gy. Data refers to a C305X hydrophone sensor from Cetacean Research in water located 8 cm distal to Bragg peak. Color coding is identical to simulated pressure traces shown below. The second row highlighted in red indicates settings of a previous experiment. The lower half of the table relates to simulations under FLASH conditions. SNR calculation is based on the signal power over the entire signal length whereas PSNR is the ratio of maximum signal amplitude to standard deviation of noise.



Conclusions: FLASH RT conditions with an increased instantaneous beam current alongside a suitable pulse width are beneficial for ionoacoustic signal generation. These conditions allow increased signal detection, range verification and could enable dose reconstruction for clinically relevant settings. Funded by DFG.

EPV015 / #286

FIRST PHYSICS DESIGN OF BEAMLINE FOR ELECTRON FLASH RADIATION THERAPY AT PITZ

E-POSTER VIEWING

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Background and Aims: The Photo Injector Test facility at DESY in Zeuthen (PITZ) is preparing an R&D platform for electron FLASH radiation therapy, very high-energy electron (VHEE) radiation therapy and radiation biology based on its unique beam parameters: ps scale electron bunches with up to 5nC bunch charge at MHz repetition rate in bunch trains of up to 1 ms in length. The existing PITZ beam is routinely accelerated to ~22 MeV/c, with a possible upgrade to 250 MeV/c for VHEE radiation therapy in future.

Methods: The ~22 MeV/c beam will be used for beam transport and focusing preparation, dosimetry studies, and thin sample biology effects studies in the next few years.

Results: A beamline to extract and match the PITZ beam to the radiation biology experimental station is under physics design and preliminary installation, and first results will be presented.

Conclusions: We believe PITZ will be a great testbed for radiation biology studies with its wide beam parameter spaces.

EPV016 / #288

APPLICATION OF A 2D SCINTILLATION DETECTOR FOR PROTON PENCIL BEAM DOSIMETRY AT PROTOM SYNCHROTRON

E-POSTER VIEWING

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Background and Aims: Proton pencil beam scanning (PBS) technique is the most popular method for modern proton therapy facilities. However, this technique require careful monitoring and periodic control to guarantee safety and high quality of treatment procedure. In this study, we investigated self-made 2D scintillation based detection system for periodic quality assurance for proton therapy on Protom synchrotron systems.

Methods: Dosimetry system based on scintillating (luminescent) screen, mirror and CCD camera in compact waterproof box with entrance window diameter of 5cm. This format was used to avoid significant deformation of window in water measurements. Beam size depending depth in water and Bragg peak position were investigated compared with EBT3 film and PTW Bragg peak chamber measurements. Scintillator linearity with number of particles and image quality was evaluated.

Results: Preliminary results have shown that such simple 2D detection system is suitable for quality assurance and commissioning of proton PBS facilities. In comparison with EBT3 films scintillation detector showed a good agreement in beam size measurements but with much faster data acquisition. Bragg peak estimation in water phantom is possible when this detection system placed on special positioner with high accuracy moving device.

Conclusions: Presented 2D scintillation based detection system appears as a cheap and accurate tool for beam setting, commissioning and periodic quality assurance checks for proton facilities. This detector can be used in water and air single beam measurements as fast time sparing alternative of EBT3 films.

EPV017 / #292

MICRODOSIMETRY OF FLASH BEAMS: TOO GREAT A CHALLENGE?

E-POSTER VIEWING

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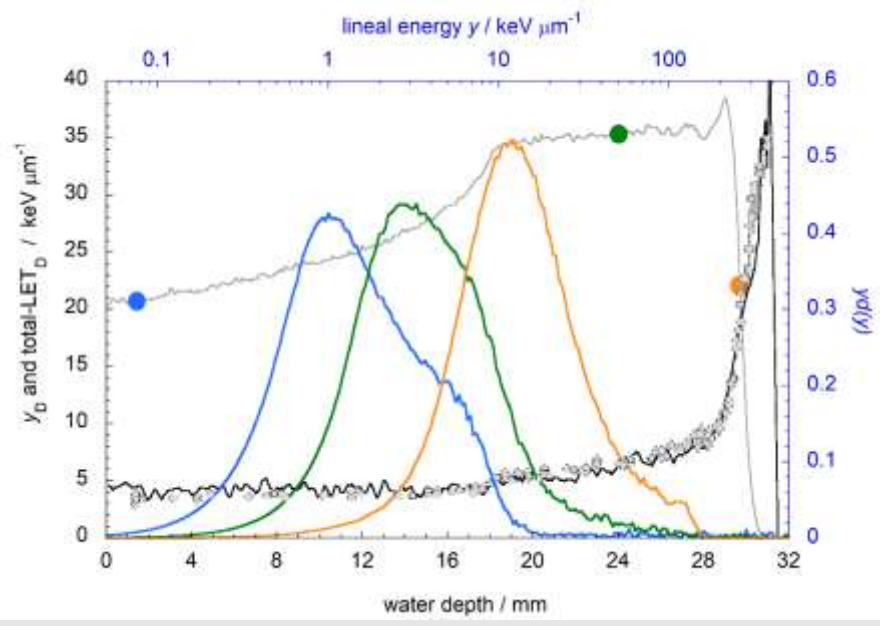
Background and Aims: The challenge of a fast and accurate in-phantom monitoring of radiation quality is common to both conventional (low dose-rate) and FLASH proton beams. Microdosimetry is a valuable technique towards this aim, since it measures the stochastic distribution of energy deposited in microscopic volumes by single events, which is related to the biological effectiveness of the radiation field. The present contribution discusses the possibility of applying microdosimetry to FLASH proton therapy.

Methods: Being a single-event technique, microdosimetry is intrinsically insensitive to dose and dose-rate. Tumour control probability (TCP) seems also not to be sensitive to dose-rate effects, but depends on the radiation quality of the proton beam, which is strongly correlated to the single-track energy deposition stochastics. In general, the maximum event rate sustainable by gas and solid state microdosimeters is about 10^4 Hz, far below the typical levels in flash radiotherapy. However, considering that TCP also does not depend on dose rate, it is possible to perform microdosimetric measurements at a reduced dose-rate.

Results: The figure shows microdosimetric measurements performed at different depths in the CATANA clinical facility (Catania, Italy), with a miniaturized tissue-equivalent proportional counter. The dose-mean value of microdosimetric spectra was found to be equal to the calculated dose-averaged LET (Linear Energy Transfer).



Conclusions: The microdosimetric characterization of FLASH proton therapy facilities can already be performed with existing detectors, provided that the fluence rate can be reduced to about 10^6 s^{-1} cm^{-2}. New detectors should be developed to reach FLASH therapeutic dose rates.

EPV018 / #294

PYTRIP - A FREE AND EXTENSIBLE RESEARCH TREATMENT PLANNING TOOLBOX FOR PROTON AND ION RADIOTHERAPY

E-POSTER VIEWING

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Background and Aims: Recent years brought developments in treatment planning with variable RBE for protontherapy. Commercial treatment planning systems (TPS) are costly products and hard to adapt to the modern data science programming environment. We aim at providing a suitable data science toolbox for research in treatment planning, based on the TRiP98 TPS and freely available libraries.

Methods: Our research TPS is composed of: a core library PyTRiP and a graphical user interface (GUI) pytripgui. Both projects are implemented in the Python programming language. The core library is capable of handling DICOM and VOXELPLAN formats. GUI was migrated to PyQt5 framework. Project management follows best practices in an Open-Source environment: code is hosted on public infrastructure (github), tasks and issues are being properly traced, code is being formally reviewed before adapting any new changes. An automatic test suite running after any change in the code ensures high code quality.

Results: The TRiP98 optimization engine runs locally or remotely and can be accessed from Windows, Mac or Linux operating systems. PyTRiP extends TRiP98 with new features such as empirical models of variable RBE in proton therapy, DVH/LVH calculations, native DICOM support, and handling of TRiP98 data formats. The GUI supplements TRiP98 by a plotting tool, capable of handling CT scans, dose, LET and RBE.

Conclusions: PyTRiP provides a powerful toolbox for research in treatment planning. The usage of python programming language makes it easy to connect with modern data science programming environments. Graphical user interface aids users in visualization and calculation of treatment plans for research purposes.

EPV019 / #300

THE LASER-HYBRID ACCELERATOR FOR RADIOBIOLOGICAL APPLICATIONS (LHARA)

E-POSTER VIEWING

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Background and Aims: The 'Laser-hybrid Accelerator for Radiobiological Applications', LhARA, is conceived as a novel, uniquely flexible facility dedicated to the study of radiobiology. The technologies that will be demonstrated in LhARA have the potential to allow particle-beam therapy to be delivered in a completely new regime, combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates. LhARA will be a hybrid accelerator system in which laser interactions drive the creation of a large flux of protons or light ions that are captured using a plasma lens and formed into a beam. The laser-hybrid approach will allow the exploration of the vast "terra incognita" of the mechanisms by which the biological response is modulated by the physical characteristics of the beam. I will describe outline the state of the art in laser-driven ion acceleration, describe the motivation for LhARA, present the status of its development, and summarise the programme upon which the LhARA collaboration has embarked to drive a step-change in clinical capability.

Methods: The LhARA facility has been simulated using a variety of codes. A prototype of the principal focusing element has been exposed to a beam.

Results: Teh results of teh simulation of the LhARA facility will be presented. The spatial distrbution of the beam at the endstations has been estimated and the instantaneous and average dose rates have been calculated.

Conclusions: The LhARA initiative has the potential to deliver the required to deliver automated proton- and ion-beam therapy at FLASH rates in a variety of spatial and spectral configurations.

EPV020 / #305

BIOLOGICAL EFFECTIVENESS OF THERAPEUTIC PROTON BEAMS FOR COMPLEX ABERRATIONS

E-POSTER VIEWING

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Background and Aims: Higher biological efficiency of proton beams in induction of complex aberrations as compared with photon irradiation may lead to underestimation of genetic damage when routine cytogenetic analysis is applied. Thus, in the present study the 24-color FISH analysis was used to assess the complexity of chromosome aberrations in human lymphocytes induced by photons and proton beams.

Methods: Chromosome aberration spectra induced in human lymphocytes of healthy donors after exposure to Co^{60}-γ-rays, 150 MeV and spread out Bragg peak (SOBP) proton beams have been assessed by multicolor Fluorescent In Situ Hybridization (mFISH). Recorded structural aberrations were subdivided into chromosome- and chromatid breaks, simple and complex exchanges.

Results: Biological efficiency of proton beams at given dose (isodose effect) was evaluated by means of the relative dose effectiveness (RDE) for several radiobiological outcomes: the number of aberrations per cell, the number of breakpoints per cell, the percentage of breaks participating in total breakage and from mean number of breaks per complex. Aberration spectra for 3 Gy protons revealed that ~20% of aberrations is of complex type. While routine metaphase analysis resulted in similar aberration spectrum for photons and fast protons (RDE at 3 Gy ~ 1.1), it has increased significantly (1.51±0.08) for SOBP protons when the ratio of breakpoints was taken into account.

Conclusions: The mFISH method revealed higher RDE values (in respect to routine analysis) for therapeutic proton beams due to the detection of complex aberrations. Proton trucks produce more clustered DNA damage in respect to homogenous photon exposure.

EPV021 / #150

TARGETING CD47 FOR IMPROVEMENT OF PARTICLE THERAPY OUTCOMES TOWARD HYPOXIC TUMORS: IN VITRO MODELING

E-POSTER VIEWING

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Background and Aims: Particle therapy with proton or carbon ion beams is thought to be a very effective modality to treat solid tumors. Importantly, the curative effects of proton and carbon ion beams are partly due to the post-irradiation stimulation of phagocytosis and immunogenic death of irradiated cancer cells. Importantly, cancer cells residing in the hypoxic tumor regions can express CD47 at their surface that allows them to evade the attacks of phagocytes and cytolytic T-cells; therefore, the hypoxia-induced CD47 can decrease the efficacy of particle therapy. The aim of our study was to develop a simple model system to test various approaches and agents for targeting the CD47 expression/signaling in the hypoxia-adapted cancer cells.

Methods: Several tumor cell lines (carcinomas, gliomas, lymphomas) were cultured in 25 cm2 flacks under hypoxic conditions when the normal atmosphere was replaced by nitrogen. The hypoxia-associated induction of carboanhydrase-9, CD47, HIF-1alpha, HSPs and GRPs was analyzed using real-time PCR, immunofluorescence staining/microscopy and immunoblotting.

Results: We have developed a simple test-system which enables to have samples of hypoxia-adapted cancer cells expressing CD47 at their surface. These cell samples can be used for the in vitro experiments to find suitable agents for suppressing the CD47 expression/signaling in hypoxic tumors. Our findings suggest that some inhibitors of HIF-1alpha, HSF1, HSP70 or GRP78 as well as anti-CD47 antibodies may abolish the CD47-mediated evasion of hypoxia-adapted cancer cells from phagocytosis or immunogenic cell death following the particle beam treatments.

Conclusions: CD47 is a promising target for increasing the efficacy of particle therapy toward hypoxic tumors.

EPV022 / #108

CHARACTERIZATION OF OSL AND TL DOSIMETERS WITH DATA COLLECTED AT THE MT25 CYCLIC ELECTRON ACCELERATOR

E-POSTER VIEWING

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Background and Aims: The Microtron MT25 is a cyclic electron accelerator with a Kapitza resonator. Pulsed high-current electron beams are produced and accelerated in a radio-frequency cavity. The electron beams have energies of up to 25 MeV, pulse length of 3.5 μs, repetition rate of 423 Hz, and a maximum current of 30 μA.

Methods: Within the scope of the 18HLT04 UHDpulse EMPIR project, Thermoluminescence (TL) and Optically Stimulated Luminescence (OSL) detectors were irradiated at the Microtron MT25. The detectors were placed on a Plexiglas phantom and enclosed in a lead and iron bunker, to shield them from the intense background radiation. Two separate irradiations were performed: with and without an 8 cm thick polyethylene moderator placed before the phantom. GAFchromic™ films and plastic nuclear track detectors were, as well, included in the experimental setup.

Results: Preliminary results are presented. The responses of the different detector technologies are compared amongst each other.

Conclusions: Experiments performed with conventional radiation beams, such as the one at Microtron MT25, allow to characterize the dosimeters in known and controllable radiation fields. In turn, this allows to develop models and predict their behavior in complex radiation fields, such as those of laser-driven accelerator and FLASH facilities. This project 8HLT04 UHDpulse has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.

EPV023 / #262

ENHANCING CANCER CELL SURFACE EXPRESSION OF CALRETICULIN: A POTENTIAL TOOL FOR PARTICLE THERAPY

E-POSTER VIEWING

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Background and Aims: The anti-tumor effects of proton or carbon ion therapy are partly realized via the stimulation of phagocytosis of survived cancer cells which begin to expose calreticulin on their surface after being irradiated with the particles. In vivo, calreticulin is expressed on the cancer cell surface in response to the irradiation and then recognized by phagocytizing macrophages as a specific signal 'eat me'. Therefore, co-treatments somehow increasing the cancer cell surface expression of calreticulin can improve the outcome of particle therapy. The present study was aimed at experimental finding of ways to enhance the post-irradiation of expression of calreticulin at the surface of survived tumor cells.

Methods: Cells of several lines derived from human or murine malignancies were in vitro subjected to various kinds of drug treatments or stressful preconditioning prior to or after irradiation. The levels of cancer cell surface expression of calreticulin were quantified by means of immunofluorescence staining/flow cytometry analysis.

Results: We examined a possibility to manipulate the cancer cell surface expression of calreticulin by stressing the target tumor cells or affecting their protein transport/export machinery with certain inhibitors and drugs. According to our observations, pre- and post-irradiation treatments of cancer cells with hyperthermia or some inducers of endoplasmic reticulum stress, inhibitors of autophagy and calcium chelators or ionophors may significantly elevate the level of calreticulin expression on the cancer cell surface.

Conclusions: There are clinically applicable ways to artificially enhance the cancer cell surface expression of calreticulin; such an approach may be used to increase the efficacy of particle therapy.

EPV024 / #172

DOSEPIX: A FAST X-RAY SPECTROMETER

E-POSTER VIEWING

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Background and Aims: The 16x16 pixel detector Dosepix is a photon-counting hybrid pixel detector with a pitch of 220 micrometers developed in a collaboration of CERN and the Erlangen Centre for Astroparticle Physics for the application of dosimetry. In this contribution, the features of Dosepix are utilized for spectrometry tasks.

Methods: Charges created by energy depositions of ionizing radiation in the 300-micrometer thick silicon sensor are integrated by a charge sensitive amplifier for each pixel. A discriminator generates a digital pulse whose duration corresponds to the deposited energy. It is measured digitally as time-over-threshold (ToT) and further processed in the pixel-electronics. A binning state machine is used to gain spectrometric information about the deposited energy of the impinging radiation. It consists of 16 energy channels whose edges are individually configurable. Once the ToT of an event is registered, the corresponding channel is incremented, i.e. an energy histogram is continuously filled per pixel. The read-out of the pixel matrix takes place column-wise to avoid dead time. i.e. only the currently read column cannot detect events while the remaining columns are still taking data.

Results: Dosepix detectors are utilized as a spectrometer. It can record energy spectra of high photon flux sources with at most 256 x 16 energy bins for even short exposures. Simulations and measurements of various sources are presented and compared to each other to show the capabilities of Dosepix.

Conclusions: The Dosepix detector is a promising candidate for spectrometry tasks. Setups involving the detector can be used for the quality assurance of radiation sources.

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PJ-34 IMPROVES THE EFFECT OF IONIZING RADIATION IN MDA-MB-231 BREAST CANCER CELLS

E-POSTER VIEWING

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Background and Aims: Radio-resistance causes a major problem for improvement of outcomes of breast cancer patients treated with radiation (IR). The important role of poly (ADP-ribose) polymerases (PARPs) prompted the development of potent inhibitors and use them as radio-sensitizing agents. Thus, the aim of the present study was to investigate the possible role of PJ-34, one of the PARP inhibitors, in radio-sensitivity of MDA-MB-231 human triple negative breast cancer cells.

Methods: MDA-MB-231 cells were treated with PJ-34 in different concentrations (1 and 10 μM) and exposed to IR (2 and 4 Gy) one hour later. The radio-sensitizing effect of PJ-34 was elucidated using MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) assay 71 hours after the IR. The evaluation of the cell cycle phase distribution was performed using Muse™ Cell Analyzer (Merck Millipore) 47 hours after the IR.

Results: We observed that PJ-34 at concentration of 10 μM effectively inhibited the proliferation of MDA-MB-231 cells compared to IR alone. Moreover, the results revealed that the same concentration of PJ-34 significantly enhanced IR-induced cell cycle arrest at the G2/M phase in comparison to IR alone.

Conclusions: Our data suggest that PJ-34 can effectively increase the radio-sensitizing effect of MDA-MB-231 cells. Further research will be required to clarify these findings. Acknowledgements: This work was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no 730983 (INSPIRE).