ISBN: 978-3-95450-205-9 doi:10.18429/JACoW-Cyclotrons2019-TUP021

TOWARDS FLASH PROTON IRRADIATION AT HZB

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Abstract

The HZB cyclotron has been providing protons for eye-tumor treatment for more than 20 years. While it has been very successful using conventional dose rates (15-20 Gy/min), recent studies indicate that rapid irradiation with very high dose rates (FLASH) might be equally efficient against tumors but less harmful to healthy tissues. The flexible operation schemes of the HZB cyclotron can provide beams with variable intensities and time structures, covering a wide unexplored regime within the FLASH requirements (>40 Gy/s in <500 ms). This paper presents the results of the first FLASH beam production at HZB towards the establishment of an in-vivo clinical irradiation in the future.

INTRODUCTION

The cyclotron of Helmholtz-Zentrum Berlin (HZB) in Germany has been providing protons for the treatment of ocular tumors to more than 3600 patients since 1998, with a local tumor control of 96% five years after the treatment [1]. However, according to recent studies, side effects to healthy nearby tissues may be significantly reduced by using high dose-rate FLASH irradiation [2].

In short, the FLASH scheme utilizes much higher dose rates in much shorter irradiation times compared to conventional radiotherapy — regardless of the type of radiation being used. With its exact specifications not yet universally acknowledged, most studies categorize an irradiation of more than 40 Gy/s within 500 ms or less into the FLASH regime. Under these conditions, the normal cells appear to experience an equivalent dose of ~70% with respect to the dose received by the tumorous cells (1.4 dose-modifying factor), sparing thus selectively healthy tissues from radiation damage and enabling higher dose delivery to the tumor [3]. The underlying biological mechanism as well as the optimal irradiation parameters are still under investigation.

Different institutes worldwide are currently trying to test this new radiotherapy concept and prove its potential benefits. The first application to a human was recently conducted on a skin tumor using a 5.6 MV electron linac, which generated 15 Gy in 90 ms, delivered in 10 pulses of 1 µs each with a 100 Hz repetition rate [4]. Experiments with protons are also under preparation to be applied to small animals using a clinical system [5].

The HZB cyclotron, originally designed for ion experiments requiring various intensities and time structures, is nowadays an ideal machine for testing a broad unexplored regime of the FLASH radiotherapy — even in-vivo. Towards this direction, this paper demonstrates the first FLASH proton-beam production at HZB, the currently feasible parameters and finally the short- and mid-term plans of applying ocular proton irradiation on mice using the FLASH scheme for the first time.

MACHINE AND EXPERIMENTAL SETUP

The HZB cyclotron can be operated with two different types of injectors:

- A Tandetron (tandem accelerator), abbreviated as *TT*, which is routinely used for the medical operation due to its increased stability,
- a Van-de-Graaff accelerator, abbreviated as *CN*, which provides bunched beams of higher intensity and is equipped with a fast kicker (pulser) to selectively guide bunches within a specified time window into the cyclotron.

For the standard machine settings, the proton beam extracted from the cyclotron has a kinetic energy of 68 MeV, a repetition rate of 20 MHz and a bunch duration in the order of 5 ns when using the TT injector, or down to 1 ns when using the CN injector. These timescales are negligibly short for radiotherapy — even that of FLASH — meaning that the delivered beam is considered as approximately continuous (quasi-DC). Nevertheless, a pulsing scheme with a time window of at least 50 ns and a repetition rate of up to 2 MHz can be applied when using the CN injector. Regarding the average beam current at the end of the beamline, around 40 nA can be reached with the TT and 10 times more with the CN.

Considering the future plan of irradiating eyes of mice, whose tumors are typically located in a depth of 5 mm from the eye's front surface, a reduced proton energy will be needed at the irradiation target. Therefore, a 16 mm-thick aluminum plate was used as a range shifter between the exit port of the accelerator beamline and the target. In order to block the scattered protons downstream and irradiate only the desired area of the target (a circular field of ~9 mm diameter for mouse eyes), a holder for interchangeable round collimators of different diameter was placed in between. An Advanced Markus® ionization chamber [6], which is indicated for measuring high dose rates, was installed at the target position. A photo of this experimental setup can be seen in Fig. 1. Before and after measuring the dose rate, the dose monitor was replaced by a 12-bit CCD camera to capture the transverse profile of the beam with a resolution of 1280 × 1024 pixels and a scaling of 48 ± 2 µm/pixel.

The above setup was used to measure the delivered dose rate, range (Bragg-peak) and transverse distribution of the quasi-DC proton beam at the target for each injector.

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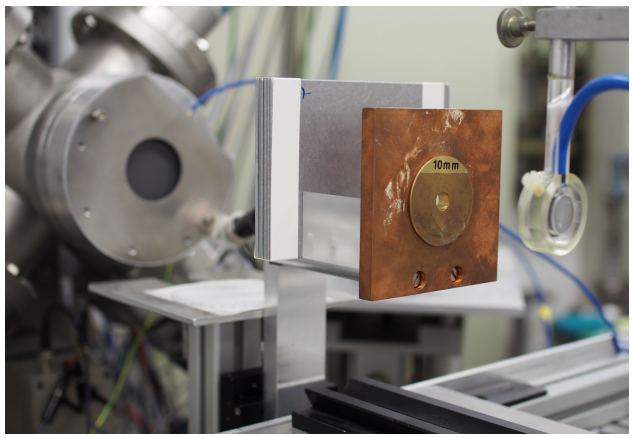

Figure 1: Photo of the experimental setup. The protons travel from left (vacuum beamline exit port) to right (dose monitor with blue cable) in air, while passing through an aluminum plate and a round bronze collimator.

MEASUREMENT RESULTS AND SIMULATION VALIDATION

After setting up the machine to the nominal operation parameters, the beam was centered with steerers and focused with quadrupoles at the target to a round transverse RMS width of ~1 mm, in the absence of the aluminum range shifter/scatterer. After inserting the aluminum plate, the dose rate at the target was recorded, while varying the average beam current with the accelerator's low-energy collimating slits and measuring it with a Faraday cup at the end of the vacuum beamline. The results from both injectors are plotted in Fig. 2. In these first measurements no statistical errors were recorded, but they were observed to be small due to the stability of the accelerator and the dose monitor.

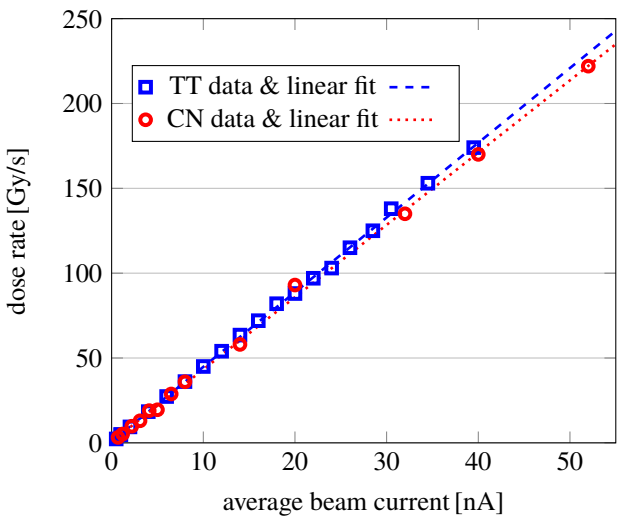

Figure 2: Measured dose rate at the target from each injector.

The measured dose rates indicate that the FLASH requirements can be covered to a wide extent by both injectors. The data show a good linearity with respect to the average beam current and a good accordance between the two injectors. As expected, higher intensities are available with the CN, which provided dose rates even higher that the plotted values (exceeding 1 kGy/s) not shown here due to very short measurement times as a precaution against damaging the involved components and triggering radiation-safety interlocks. Potential saturation and recombination effects of the dose monitor were not taken into consideration, which might imply that the presented data could be underestimated [7].

The measured values were already predicted by calculations and simulations using the LOOKUP code [8]. With the measured beam energy and transverse dimensions at the vacuum port as initial parameters, our experimental setup was simulated to deliver 22.84 MeV protons with an uncollimated transverse RMS width σ = 9.1 mm at the target. At this energy the protons have a mass stopping power S/ρ = 23.4 MeV·cm^2/g and a 5.4 mm penetration depth in water [9]. The dose rate $\dot{D}$ is given by:

$$\dot{D} = \frac{i_p}{A}\frac{S}{\rho}, \quad (1)$$

where i_p is the proton current at the detector's sensitive area A, which corresponds to a 2.5 mm radius in our case and collects only 3.7% of the total beam current for the expected σ, fairly uniformly. As a result, an i_p = 335 pA or a total average beam current of 9.1 nA is required for $\dot{D}$ = 40 Gy/s, in accordance with the measurements. In addition, σ was measured by the CCD camera to be 8.8 ± 0.4 mm.

As a further validation step, the dose monitor was put inside a water phantom and shifted in the direction of the beam in order to measure the Bragg peak. The resulting curve in Fig. 3 shows a good agreement with the simulation, measuring the distal 90% and 80% points at 5.4 mm and 5.6 mm respectively and a 1 mm sharp fall-off between 90% and 10% of the delivered dose.

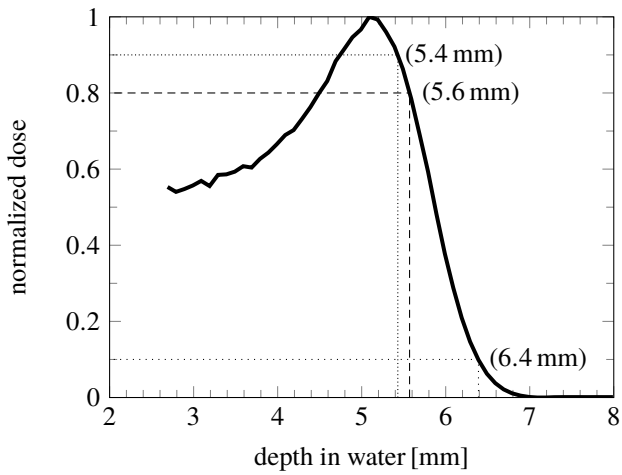

Figure 3: Measured Bragg peak with corresponding distal points in a water phantom for mouse irradiation.

At last, the transverse profile of the beam was captured at the target position after collimation through different apertures. It appeared that a 5 mm diameter aperture yielded a

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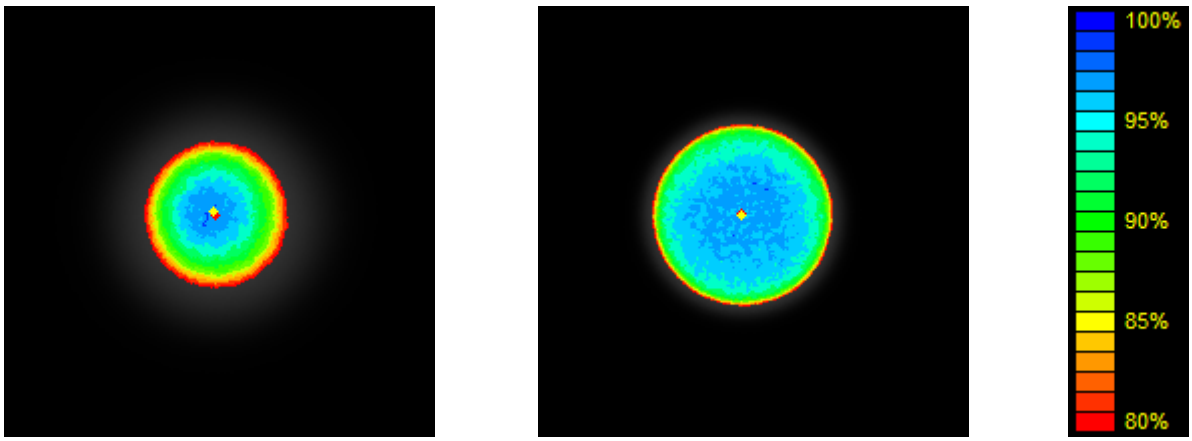

(a) Original setup with 5 mm aperture. (b) Modified setup with 7.6 mm aperture.

Figure 4: Measured normalized intensity of the transverse beam profiles at the target in grayscale, color-contoured between 80%–100%.

circular field of 9.2 mm as desired, but with a lateral width uniformity of 27% (Fig. 4a), which might not meet clinical standards. A much better uniformity of 6% was achieved for a similar field of 9.4 mm by moving the aluminum plate 19 cm upstream and using a 7.6 mm aperture (Fig. 4b). However this position shift reduced the proton intensity within the area of the dose detector by 82% with respect to the original setup using the same aperture, corresponding to an equal dose-rate reduction according to Equation (1). Even in this (far from optimized) case, a clinically acceptable FLASH beam can already be delivered to mice when reviewing Fig. 2.

OUTLOOK

The next steps towards clinical application include optimizing the setup for maximimum dose-rate delivery and lateral width uniformity, while applying an effective modulation scheme for a spread-out Bragg peak. For this purpose a number of components such as a fast transverse beam scanner, double or contoured scatterers and ridge filters are planned to be simulated and tested. From the machine side, a fast beam shutter that allows a precise dose delivery has to be developed and the efficiency of the existing beam diagnostics has to be verified for such short time scales. Moreover, the dosimetry of such intense beams has to be checked for limitations and potential correction models have to be applied. The forthcoming milestone is the first FLASH ocular irradiation of mice in collaboration with the Charité – Universitätsmedizin Berlin.

CONCLUSION

The HZB cyclotron is currently able to deliver FLASH proton irradiation with dose rates of more than 200 Gy/s and flexible pulsing schemes, qualifying as a powerful machine for the investigation of wide unexplored regimes of this promising radiotherapy technique. This first attempt already delivered a clinically usable beam for ocular irradiation of mice, which is under preparation together with Charité in Berlin. After an upcoming optimization of the involved components, further improvements of the reported performance and the first clinical results are expected to be published.

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