

MiniBEE - MINIBEAM BEAMLINE FOR PRECLINICAL EXPERIMENTS*

J. Reindl[†], A. Rousseti, J. Neubauer, G. Datzmann¹, G. Dollinger
Universität der Bundeswehr München, Neubiberg, Germany

G. Kourkafas, J. Bundesmann, A. Dittwald, A. Denker², Helmholtzzentrum Berlin, Berlin, Germany

¹also at Datzmann Interact & Innovate GmbH, Munich, Germany

²also at Berliner Hochschule für Technik, Berlin, Germany

Abstract

Spatial fractionated radiotherapy using protons, so-called proton minibeam radiotherapy (pMBT) was developed for better sparing of normal tissue in the entrance channel of radiation. Progressing towards clinical use, pMBT should overcome current technical and biomedical limitations. This work discusses a preclinical pMBT facility, currently built at the 68.5 MeV cyclotron at the Helmholtz Zentrum Berlin. The goal is to irradiate small animals using focused pMBT with a sigma of 50 μm , a high peak-to-valley dose ratio at center-to-center distance as small as 1 mm and beam current of 1 nA. A first degrader defines the maximum energy of the beam. Dipole magnets and quadrupole triplets transport the beam to the treatment room while multiple slits properly form the transverse beam profiles. A high magnetic field gradient triplet lens forms the minibeam in front of the target station and, scanning magnets are used for a raster scan at the target. An additional degrader, positioned close before the focusing spot and the target, further reduces the energy, forming a spread-out Bragg peak. A small animal radiation research platform will be used for imaging and positioning of the target.

INTRODUCTION

Radiation therapy (RT) aims to maximize the delivered dose in the tumor while minimizing the dose to the normal tissues [1]. Proton beams can contribute to that goal due to their advantageous physical properties [2]. They deposit low dose at the entrance and the maximum dose is deposited in a well-defined range, based on their initial energy. Additional methods of protecting the healthy tissues are the temporal and spatial fractionation. The concept of Spatially Fractionated Radiation Therapy (SFRT) is the fragmentation of dose in space creating at the entrance a periodical pattern of regions with high (peak) and low (valley) doses [3]. Proton minibeam radiation therapy (pMBT) is an innovative treatment method which exploits the advantages of proton beams and spatial fractionation [4, 5]. Minibeams have a transverse beam size (σ) in the submillimeter range and they are delivered with an interdistance, which is called center-to-center (ctc) distance, in the millimeter range in order to cover the tumor laterally. In this way, the created alternated pattern of peaks and valleys in the entrance spares the healthy tissues. When proton beams transverse the matter they broaden due to multiple

Coulomb scattering (MCS) ending up to cover the tumor homogeneously (see Fig. 1).

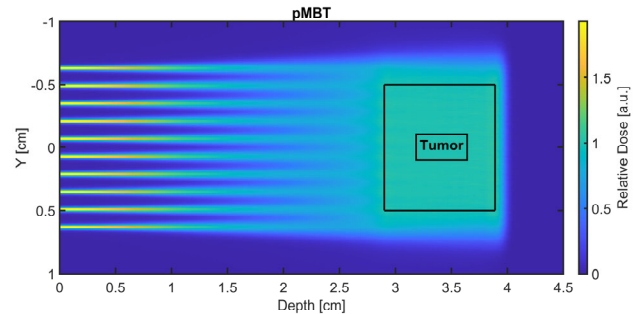


Figure 1: Simulated dose distribution of pMBT applying 68 MeV proton minibeam ($\sigma = 98 \mu\text{m}$ and ctc = 1.4 mm) in a water phantom assuming a tumor in 2.9 - 3.9 cm depth. The spread-out Bragg peak (SOBP) was obtained by positioning a range shifter close to the phantom.

The in-vivo studies conducted so far have highlighted the superiority of pMBT over conventional RT. One of the first proof-of-principle experiments, in which the right ear of the mice were irradiated with a broad proton beam or with an array of 16 minibeam ($\sigma = 180 \mu\text{m}$ and with ctc = 1.8 mm), showed that the acute side effects can be bypassed [6]. Another important in-vivo experiment investigated the dependence of side effects to the σ of the beam [7]. Also in this case, the right ear of the mice were irradiated with an array pattern of proton minibeam with different σ and the same ctc. The results showed that better sparing can be achieved with smaller beam sizes. Furthermore, a study in which rats with RG2 glioma were irradiated with pMBT or conventional RT schemes showed that rats irradiated with minibeam had better survival rate and less side effects [8]. All the aforementioned results gave a prominence to pMBT over conventional RT due to the better sparing of healthy tissue. However, the biological mechanisms underlying that phenomenon are not clear yet. A preclinical pMBT facility can contribute to intense and systematic research and tissue sparing effects have to be demonstrated on various tissues and beam settings in order to fully investigate the aspects and prospects of pMBT. In this paper we describe the concept of a preclinical proton minibeam radiotherapy facility for small animal irradiation at the Helmholtz-Zentrum in Berlin (HZB) [9].

BEAMLINE DESIGN

The proposed beamline concept should fulfill some constraints related to the beam energy, the beam energy degra-

* Work supported by German Ministry of Defence BMVg

[†] Judith.reindl@unibw.de

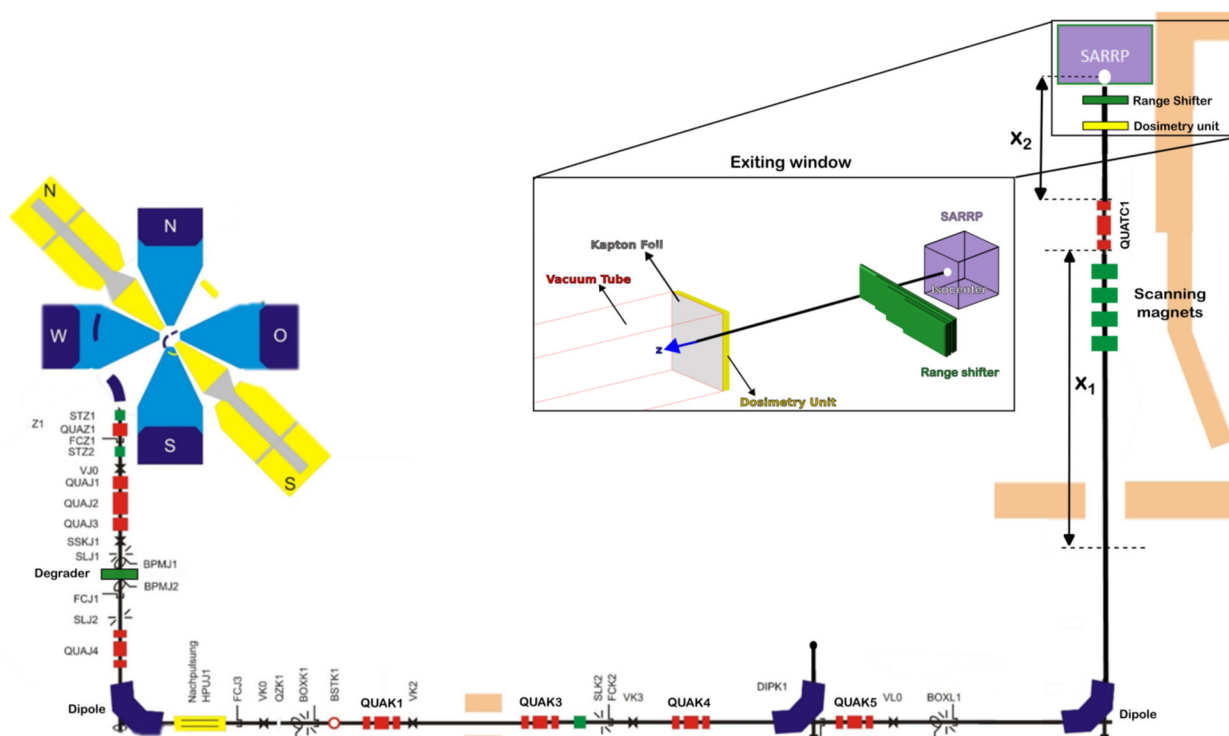


Figure 2: Layout of the pMBT beamline design at HZB. The beam goes from the left downwards to the right and upwards. Quadrupoles are shown in red, dipoles in blue and steerers in green.

dation and the beam dimensions in the target in order to be suitable for preclinical experiments in animals. The proposed beamline design is demonstrated in Fig. 2. The cyclotron at HZB generates a 68 MeV proton beam which has a maximum penetration depth ~ 4 cm (in water), appropriate for small animal experiments. The energy can be degraded by a "Hybrid range shifter system" in a twostep process. Firstly, the beam energy, as extracted from the cyclotron will be reduced by a degrader, defining the maximum penetration depth. Then, a range shifter placed a closed to the target will further degrade the energy, creating a SOBP to fully cover the tumor. After the first energy degrading, the beam can be transported towards the target room by using a set of two 90° dipole magnets and four quadrupole triplets (QUAK1, QUAK3, QUAK4, QUAK5). Downstream of the second dipole magnet a focusing system is situated consisting by one quadrupole triplet (QUATC1), with high magnetic field gradient, and two drift lengths (x_1 , x_2). The drift length x_1 is the distance between the focus plane of the second 90° dipole magnet and the QUATC1 and x_2 is the distance between the QUATC1 and the isocenter. In order to achieve the demagnification of the beam's size, the drift length x_1 is almost five times larger compared to x_2 ($x_1 \approx 5 x_2$). Upstream of the QUATC1, two sets of scanning magnets are placed aiming to have raster-scanning application of the minibeam in the target. In the last part of the beamline, the beam is extracted by the exiting window, which consists of the vacuum tube and

a Kapton foil. Right after there is a dosimetry unit and then the beam transverse a few cm of air and its energy is further degraded, when it is necessary, until the target. For the accurate positioning and imaging of the animal, a small animal radiation research platform (SARRP, Xstrahl GmbH, Ratingen, Germany) will be used. The suggested beamline aims to generate proton pencil minibeam with a transversal size of $\sigma=50 \mu\text{m}$, etc ~ 1 mm, for raster-scanning application and beam current ~ 1 nA.

BEAMLINE SIMULATION

In this work, we performed preliminary beamline simulations for the presented minibeam beamline concept (see above). All the simulations have been done using Trace 3-D [10], which is a first-order beam dynamic code. The starting point of the simulations, named "SLJ1", is after the beam extraction from the cyclotron (see Fig. 2). The beam parameters at SLJ1 are known from measurements that have been already conducted in HZB. The measurements have been performed at a current of 22 nA, but more than 100 nA are easily available with the same beam parameters. The beam is transported from SLJ1 until the isocenter, which is located in the SARRP, using only the 90° dipole magnets and the quadrupole triplets, as it is illustrated in Fig. 3. In Table 1 the transversal beam parameters (beam size: σ and beam divergence: σ') are presented for

Content from this work may be used under the terms of the CC-BY-4.0 licence © 2023. Any distribution of this work must maintain attribution to the author(s), title of the work, publisher, and DOI

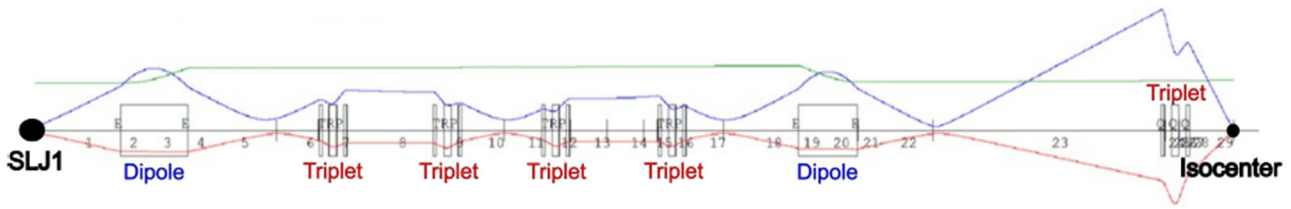


Figure 3: Beamline simulations in Trace 3-D: The simulations include only the magnetic elements (dipole magnets and triplets) starting after the beam extraction from the cyclotron (SLJ1) until the isocenter (SARRP).

both SLJ1 and the isocenter. These preliminary results demonstrate that the suggested setup can achieve a beam size demagnification of $\sim 1/4$ in the isocenter in both axes.

Table 1: Beam Parameters at SLJ1 and at the Isocenter

	SLJ1	Isocenter
σ_x	800 μm	220 μm
σ_y	480 μm	118 μm
σ'_x	3.67 mrad	9.83 mrad
σ'_y	1.19 mrad	4.84 mrad

CONCLUSION

The presented beamline concept can properly reduce the beam size in the isocenter by a factor of ~ 4 . In the next steps, the slits should be positioned to properly shape the transversal phase spaces to meet the desired beam parameters. In addition, it is crucial to study the effects of the degrader in the beam current and the beam size. For all these purposes, programs which also include Monte Carlo simulations are going to be used to properly simulate the beam transport and its interaction with materials. The results will contribute to a fully comprehensive investigation of the beamline and finally, to the construction of the MiniBEE facility.

REFERENCES

- [1] Radiation Oncology Physics: A Handbook for Teachers and Students, IAEA, Vienna, Austria, 2005.
- [2] R.R. Wilson, "Radiological use of fast protons," *Radiology*, vol. 47, no. 5, pp. 487–491, 1946. doi:10.1148/47.5.487
- [3] J.A. Laissue, H. Blattmann, and D.N. Slatkin, "Alban Köhler (1874-1947): Erfinder der gittertherapie," *Zeitschrift für Medizinische Physik*, vol. 22, no. 2, pp. 90–99, 2012. doi:10.1016/j.zemedi.2011.07.002
- [4] O. Zlobinskaya *et al.*, "Reduced side effects by proton microchannel radiotherapy: Study in a human skin model", *Radiat. Environ. Biophys.*, vol. 52, no. 1, pp. 123–133, 2013. doi:10.1007/s00411-012-0450-9
- [5] Y. Prezado and G. R. Fois, "Proton-minibeam radiation therapy: A proof of concept", *Med. Phys.*, vol. 40, no. 3, p. 031712, 2013. doi:10.1118/1.4791648
- [6] S. Girst *et al.*, "Proton Minibeam radiation therapy reduces side effects in an in vivo mouse ear model", *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 95, no. 1, pp. 234–241, 2016. doi:10.1016/j.ijrobp.2015.10.020
- [7] M. Sammer *et al.*, "Proton Pencil minibeam irradiation of an in-vivo mouse ear model spares healthy tissue dependent on beam size," *Plos One*, vol. 14, no. 11, 2019. doi:10.1371/journal.pone.0224873
- [8] Y. Prezado *et al.*, "Tumor control in RG2 glioma-bearing rats: A comparison between Proton Minibeam therapy and standard proton therapy," *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 104, no. 2, pp. 266–271, 2019. doi:10.1016/j.ijrobp.2019.01.080
- [9] A. Denker *et al.*, "Status of the HZB Cyclotron", in Proc. Cyclotrons'1), Cape Town, South Africa, Sep. 2019, pp. 253-255. doi:10.18429/JACoW-CYCLOTRONS2019-TUC02
- [10] K.R. Crandall, Trace 3-D Documentation, Los Alamos National Laboratory, Los Alamos, NM, USA, 1987.