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PRECLINICAL PROTON MINIBEAM RADIOTHERAPY FACILITY FOR SMALL ANIMAL IRRADIATION *

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Abstract

Compared to classic proton therapy, proton minibeam radiation therapy (pMBT) further spares normal tissue. To fully study this potential with small animal experiments focused minibeams with a σ of 50 µm, a beam current of 1 nA and approx. 4 cm proton range (water) is needed. We present a preclinical pMBT beamline concept based on the 68 MeV cyclotron of the Helmholtz-Zentrum Berlin (HZB). The beamline was designed in first-order using the beam dynamic code TRACE 3-D. The maximum beam energy is defined by a first degrader after the cyclotron. A second degrader placed close before the target further reduces the energy, forming a spread-out Bragg peak in the target. Along the beamline, various slits shape the transverse beam profiles. A high magnetic field gradient triplet lens focuses the beam on the target while scanning magnets rasterscan it over the target. A small animal radiation research platform (SARRP) is used for positioning and imaging of the target. This beam-line concept fulfills all the basic needs for the planned small animal minibeam irradiation studies. The results will contribute to the construction of a preclinical pMBT facility for small animals at HZB.

INTRODUCTION

Radiation therapy (RT) aims to maximize the delivered dose in the tumor while minimizing the dose to the healthy 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).

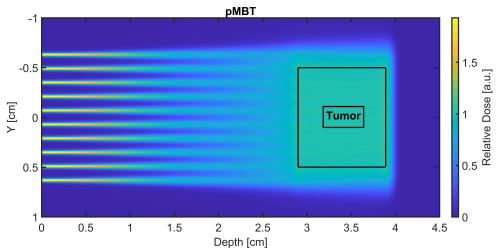

Figure 1: Simulated dose distribution of pMBT applying 68 MeV proton minibeams (σ =98 µm and ctc = 1.4 mm) in a water phantom assuming a tumor in 2.9 - 3.9 cm depth. The spread-out Bragg peak (SOBP) was obtained by positing a range shifter close to the phantom.

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 minibeams (σ=180 µm 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 minibeams 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 minibeams 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 Helmoholtz-Zentrum in Berlin (HZB) [9].

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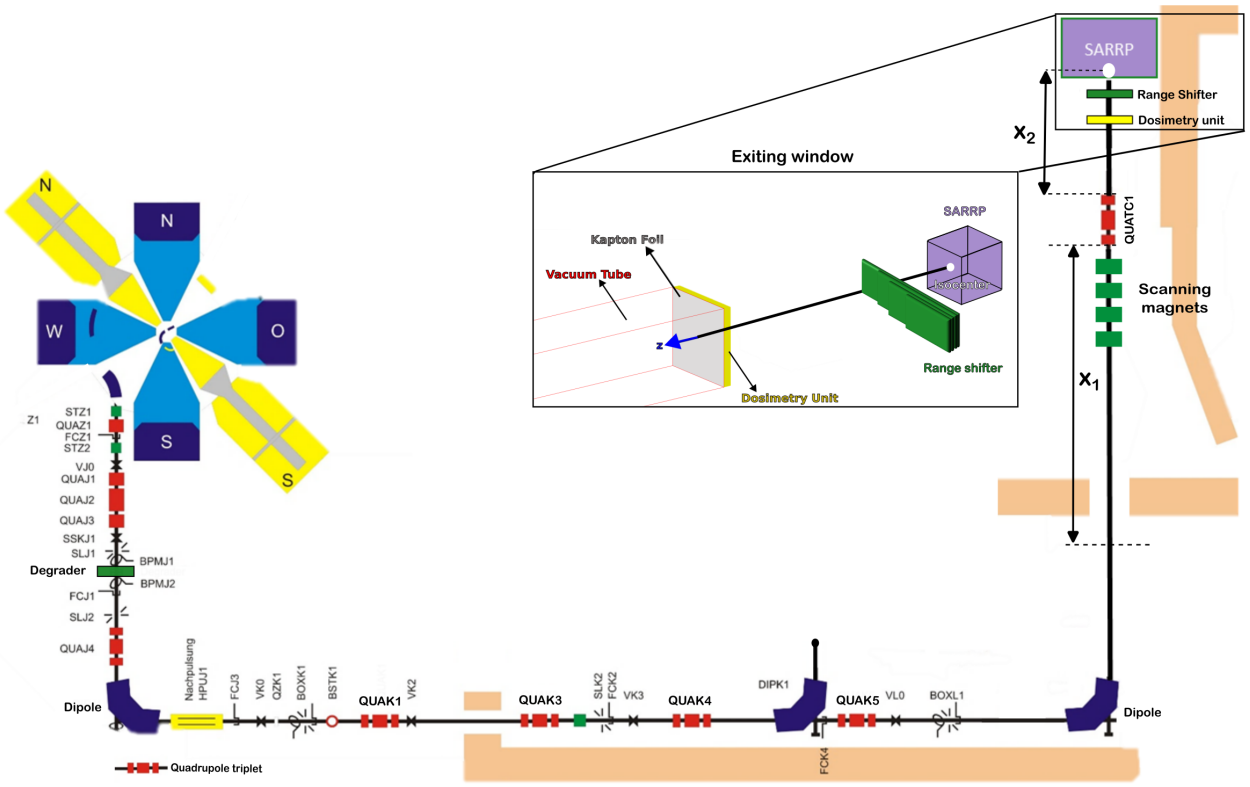

Figure 2: Layout of the pMBT beamline design at HZB. The beam goes from the left downwards to the right and upwards. Quadrupoles are shown in red, dipoles in blue and steerers in green.

BEAMLINE DESIGN

The proposed beamline concept should fulfill some constrains related to the beam energy, the beam energy degradation 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 two-step 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 ($x_1 \approx 5 \cdot x_2$). Upstream of the QUATC1, two sets of scanning magnets are placed aiming to have raster-scanning application of the minibeams 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 minibeams with a transversal size of σ=50 µm, ctc ~ 1 mm, for raster-scanning application and beam current ~ 1 nA.

BEAMLINE SIMULATIONS

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).

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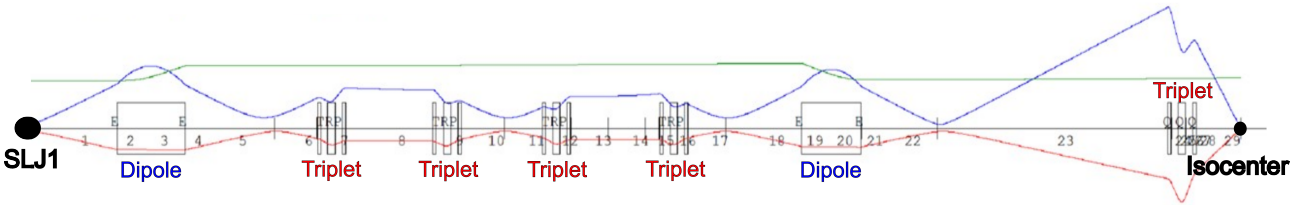

Figure 3: Beamline simulations in Trace 3-D: The simulations include only the magnetic elements (dipole magnets and triplets) starting after the beam extraction from the cyclotron (SLJ1) until the isocenter (SARRP).

The beam parameters at SLJ1 are know from measurements that have been already conducted in HZB. The measurements have been performed at a current of 22nA, 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 both SLJ1 and the isocenter. These preliminary results demonstrate that the suggested setup can achieve a beam size demagnification of ~ 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
$\sigma_{x'}$	3.67 mrad	9.83 mrad
$\sigma_{y'}$	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 preclinical pMBT facility for small animal irradiation.

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