ACCELERATOR RESEARCH FOR PROTON THERAPY

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Abstract

Proton therapy is a powerful tool in the fight against cancer. The number of accelerators has increased tremendously over the last years. Patients are treated now at over 125 facilities world-wide, which is an excellent example of an extremely successful technology transfer from fundamental research to healthcare. Depending on the tumour species, local tumour control can reach very high levels, e.g. more than 96% for uveal melanoma. To minimize side effects and maintain tumour control, new treatment modalities like FLASH or minibeams are investigated. For FLASH, dose rates should be higher than 40 Gy/s with treatment times below 0.5 s. Minibeams aim for spatial fractionation of the beam. Experiments on cells, organoids and animals have been promising. These new irradiation forms create challenges for the existing and future accelerators: Developments in beam delivery, beam adaptation, and dosimetry are necessary. This paper describes changes on control system, beam shutters, and beam scattering systems which allow now irradiation times of 10 ms with a precision in dosimetry of better than 3% for a Spread-Out Bragg Peak at HZB. The set-up of a target station for minibeams will be presented.

INTRODUCTION

80 years ago, R.R. Wilson described the radiobiological use of fast protons for tumour treatment [1]. From today's point of view the first patients were treated very shortly after. Groundbreaking work was performed at Lawrence Berkeley Laboratory [2]. In the beginning, patients were treated at accelerators originally built for nuclear and particle physics [3]. Since 1985 the Particle Therapy Co-Operative Group (PTCOG) fosters the development of particle therapy [4]. In 1990 the first hospital-based accelerator was installed at Loma Linda [5]. Research comprised, among others, the development of more compact accelerators and the development of new beam delivery techniques, e.g. pencil beam scanning [6]. The field then evolved rapidly, with dedicated and commercial accelerators taking over (Fig. 1) [7].

Proton therapy is now a mature technique, with turnkey solutions available on the market, which broadens its use. However, the number of patients treated with protons is still very small compared to the number of patients treated with electron linacs. These ready-to-use solutions fulfil the requirements of the medical device regulations or comply with FDA, an intricate set of rules and regulations which became more complex over the years. Now it is more difficult to implement modifications as companies prefer their standardized, certified products.

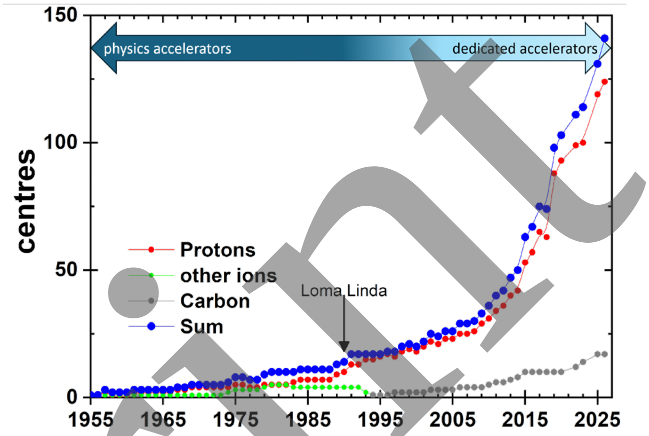

Figure 1: Centres world-wide performing particle therapy. Since installation of the first hospital-based accelerator in 1990 (Loma Linda), the number of facilities increased exponentially [3].

Albeit for some types of tumours like uveal melanomas very high local tumour control rates of more than 95% can be achieved [8], there is still room for improvement. The wish is to maintain the tumour control while reducing the side effects. Two potential techniques are discussed in the community: FLASH beam delivery, which is defined as high dose rates of at least 40 Gy/s in less than 0.5 s. The other technique is the spatial fractionation, where instead of a homogenous field a set of tiny needle beams is applied.

ACCELERATORS

About 50% of the accelerators used for clinical particle therapy as listed by the PTCoG [3] are cyclotrons, 21% synchrocyclotrons and 29% synchrotrons. Cyclotrons – and even more so synchrocyclotrons – are far more compact than synchrotrons. However, they both provide protons with a fixed energy. An interesting new design is an energy variable cyclotron without the magnetic iron [9]. The average beam intensity of synchrotrons is lower than with cyclotrons and synchrocyclotrons, which may present special challenges when considering FLASH irradiations. On the other hand, they often provide both proton and carbon therapy, and permit energy changes without large beam losses.

Besides these well-established accelerator types, there are further developments. A cyclotron is under construction in Caen, France, which shall provide protons, helium and carbon ions [10-12]. Several projects involve the use of proton linacs [13-16] or FFAGs [17-19]. Albeit these projects are very interesting from the viewpoint of an accelerator physicist, none of them treats patients up to now. The same is valid for the development of FFAG Gantries [20, 21] which could be much lighter than the conventional versions. Effects playing a role is consideration of costs, necessary manpower, and, most important, that the devices have to be certified according to medical device regulations.

Ocular tumour therapy is a special field with special requirements to the accelerator. An expert summary by the PTCoG-Optic group summarises the parameters of the accelerators employed in ocular therapy [22]. Only the cyclotrons with an energy around 70 MeV provide distal-dose fall-offs of 1 mm or less which is optimal for eyes, being a small organ with critical organs nearby. From the viewpoint of a medical physicist a cyclotron with the “right” energy for ocular tumour therapy is desirable [23]. However, this tumour is comparatively scarce and only few accelerators can deal with the world-wide occurrence, making the field unattractive for large commercial companies.

For this reason, most of the accelerator development, which will be applied to patients in the nearer future, will be focused on the beam delivery for either FLASH or minibeams. In the following sections we will concentrate on changes on HZB’s accelerator for further therapy development. However, the problems encountered are representative.

The HZB cyclotron provides a proton energy of 68 MeV, ideal for ocular treatments with the eye having a diameter of about 25 mm. Due to the low energy spread, an extremely sharp distal dose fall-off (90% to 10%) of less than 1 mm is achieved which permits better reduction of side effects, e.g. loss of vision (Fig. 2).

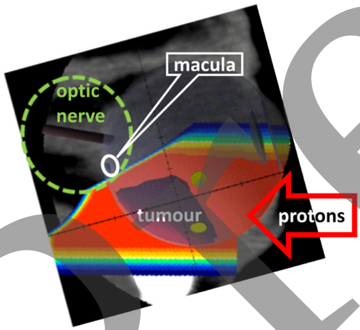

Figure 2: Treatment plan for an ocular tumour. The sharp distal fall-off of the dose permits sparing of optical nerve and macula.

The intensity of the extracted beam is high enough to ensure treatment times of less than a minute per fraction for conventional treatment. More than 5000 patients have been treated with a local tumour control of 96% and an eye retention rate of 95% [24].

FLASH

Irradiations on animals using an electron linac showed fewer side effects when using FLASH irradiations [25]. This started very active research including the field of proton therapy [26, 27] with already first patients being treated in exceptional studies [28, 29].This technique poses new challenges for the accelerator [30]: A ±1.5% dose precision is still required by the medical physicists for these short irradiation times as well as beam intensities considered high for a medical accelerators, especially when the Spread-out Bragg Peak (SOBP) is applied rather than using a shoot-through mode.

Control System

The first step taken at HZB towards this direction was to compensate the delay between addressing the beam stop and its real closure. A 10 kHz feedforward control of the dose delivery was implemented using an FPGA controlled by LabVIEW. The FPGA reads the analogue signals from the two ionisation chambers and the Faraday Cup (FC) in front of the experiment and triggers the shutters [31].

Shutter

The first FLASH experiments at HZB were performed using the mechanical shutter also used for therapy [32]. The reason for having irradiation times of 200 ms were the relatively long opening times of 10 ms and closing times of 5 ms. As there are hints that shorter irradiation times are necessary for the FLASH effect [33], a new electrical shutter was developed and installed [34]. Together with the changes in the control system, irradiations within clinical specifications are feasible down to 10 ms (Fig. 3).

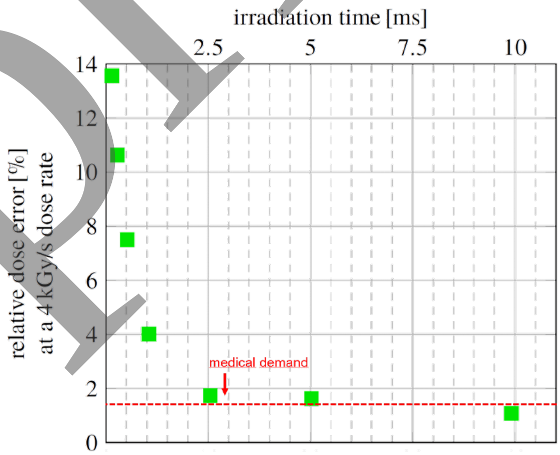

Figure 3: Relative dose error as a function of the irradiation time at a dose rate of 4 kGy/s. The precision limit wanted by the medical physicists is represented by the dashed red line.

Scattering System

Treatment times in ocular tumour therapy are short compared to other tumours and vary between 30 s to 60 s. For this reason, a passive scattering system is used to adapt the beam to the tumour. Standard beam intensities at HZB are 25 nA of extracted proton beam which are reduced to about 5% by the patient-specific beam shaping: range shifter and modulator wheel. Hence, a dual scattering system [35] was developed which consists of a first scattering foil and a second scatterer which may consist of up to 4 concentric rings [36]. A Python GUI optimizer was developed which permits the calculation of the irradiation field (Fig. 4) including the design parameters of the scatterers and their position. With this system, the transmission to the treatment room could be increased by a factor of 10. Field sizes of 30 mm in diameter can be achieved.

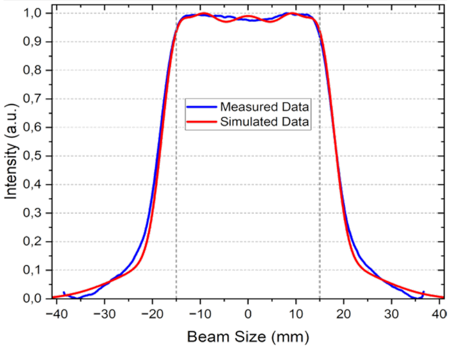

Figure 4: Simulated and measured intensity profiles after the dual scattering system. The simulated and experimental data match well.

SPATIAL FRACTIONATION

Spatially fractionated proton irradiation, particularly proton minibeam radiation therapy (pMBRT), has emerged as a promising approach to improve the therapeutic window of proton therapy. Here the proton radiation is applied in small beams of several ten to several hundred micrometre beam size (σ). Figure 5 shows the different ways of how to apply proton irradiation. The dose in the entrance of the beams can be much higher than the prescribed tumour therapy [37].

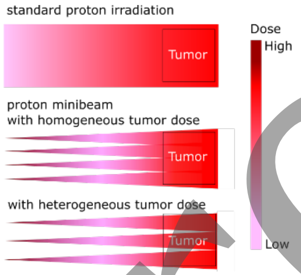

Figure 5: schematic view of different types of proton irradiation. Top: Standard proton irradiation with homogeneous irradiation of healthy tissue and tumour. Middle: Proton minibeam irradiation with spatial fractionation pattern in healthy tissue and homogeneous tumour coverage. Bottom: Proton minibeam irradiation with spatial fractionation in healthy tissue and tumour.

Previous pre-clinical studies in mouse-ears or rat brains have demonstrated enhanced normal tissue sparing while maintaining tumour control, even at high peak doses, suggesting that spatial dose modulation can fundamentally alter tissue responses to irradiation [38-40]. Specifically, spatial fractionation has shown potential to reduce acute [39, 41] and late toxicities [42, 43], enable dose escalation, and possibly modulate anti-tumour immune responses [44]. These encouraging findings have stimulated growing interest in combining pMBRT with other emerging concepts such as ultra-high dose-rate (FLASH) irradiation and immunotherapy [45].

Despite these advances, many key questions remain unresolved before clinical translation can be achieved. The biological mechanisms underlying normal tissue sparing and tumour response are still incompletely understood, and the influence of parameters such as beam size, centre-to-centre spacing, valley dose, dose rate, energy, irradiation geometry, and fractionation schemes requires systematic investigation [46]. Importantly, many of these parameters are strongly interdependent in clinical beam delivery systems, making it difficult to isolate their individual biological contributions. For this reason, dedicated research beamlines are essential for advancing the field. Such platforms must provide energies optimized for pre-clinical research, precise dosimetric control, and the flexibility to independently vary relevant irradiation parameters in a highly reproducible manner. This enables systematic studies that are critical for establishing mechanistic understanding and identifying optimal treatment configurations for future clinical applications. In this context, the MiniBEE beamline [47] at Helmholtz-Zentrum Berlin represents pioneering work in proton spatial fractionation research. It provides a 68 MeV proton beam with a range of approx. 4 cm, perfectly suited for performing pre-clinical investigations in mice and rats. The dedicated experimental platform consisting of a Small Animal Radiation Research Platform (SARRP, X-Strahl) together with a specifically designed magnet setup for focussing allows for proton dedicated minibeam studies, including flexible beam shaping and integration with complementary irradiation modalities, such as x-ray irradiation. In the current setup the MiniBEE will allow to provide beams with sizes as low as 50 µm and beam currents of max. 2 nA. This results in a dose-rate of 270 Gy/s in the entrance and 50 Gy/s at the end of range [48]. MiniBEE enables, as the world's first beamline of that kind, comprehensive investigations into the physical and biological foundations of spatially fractionated proton therapy.

HELIUM BEAMS

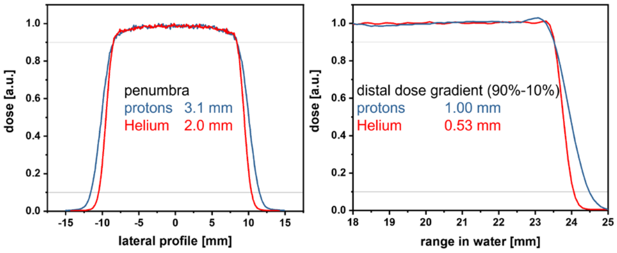

Figure 6: Monte Carlo simulations for intensity profiles and dose distributions for HZBs treatment room for protons (blue) and Helium (red).

Monte Carlo simulations using TOPAS [49] have been performed for the treatment nozzle at HZB for 70 MeV protons and 280 MeV Helium ions (Fig. 6). These two ion species have the same range, but He ions provide an improvement in the penumbra from 3.1 mm to 2 mm at the same beam nozzle and a sharper distal fall-off, 0.53 mm instead of 1 mm. Especially for ocular tumours, where relevant dimensions are about a magnitude smaller compared to other tumours, this improvement offers a further potential to reduce side effects as demonstrated in an in silico planning study [50]. Measurements with 45 MeV molecular H_2^+ ions and 90 MeV He^{2+} ions showed that a change in the RF of the cyclotron is sufficient to switch between the two beams within 30 minutes [51].

A cyclotron being able to provide both ion species at 70 MeV/u is not available on the market. Furthermore, beam intensities of such a cyclotron should allow also FLASH irradiations. For this reason, a first sketch for a superconducting cyclotron was developed with the help of AIMA development [52].

CONCLUSION

Proton therapy is a well-established and growing field of accelerator application in medicine. Several companies provide turnkey and certified solutions to the needs of the hospitals. The fact that exciting and innovative accelerator ideas cannot yet be found in clinical routine, shows the hurdles to be overcome: costs, reliability, and requested staff, as accelerator specialists are not present in hospitals. Regulatory work should be considered as early as possible when starting planning to avoid later delays.

Besides completely new accelerator designs, changes in beam delivery pave the way to novel techniques in cancer research like FLASH irradiations and minibeams. At HZB, the control system, shutters and scattering system have been modified, successfully tested, and employed for experiments. With these improvements, FLASH irradiations of human eyes with an SOBP are technically possible. Again, before application on humans, the devices must be medically certified.

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