White Paper
P-Cure Proton Therapy Solution

Jon Feldman[1] and Alexander Pryanichinikov[2, 3*]

[1]Sharett Institute of Oncology, Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel
[2]Division of Biomedical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[3]P-Cure Ltd./Inc, Shilat, Israel

Abstract

Proton therapy is an advanced form of radiation therapy that effectively treats tumors while minimizing side effects. However, access to this novel treatment is currently limited to large, well-funded clinics. A significant global challenge is to make proton therapy available to a broader range of patients. P-Cure was founded to address this challenge and create a new proton therapy system that is affordable, minimally burdensome on hospital infrastructure, and suitable for most patients. P-Cure has always emphasized individualized approach and patient comfort during treatment. Initially, we developed an innovative patient positioning system with a vertical CT scanner, allowing diagnosis and treatment in the same room. This pioneering system was first installed at the Northwestern Medicine Proton Center (Warrenville, IL, USA) in 2016 and has since become an integral part of clinical practice. The next crucial step was the development of a proprietary proton therapy solution, including a proton source. After years of development, P-Cure successfully launched the first serial clinical unit in Shilat, Israel. In March 2023, specialists from Hadassah Medical Center (Jerusalem, Israel) began treating the first in Middle East patients with proton beams. The unique technologies, the result of extensive development efforts, has resulted in a bladeless radiation system and one of the world's most compact proton therapy system, allowing it to be place in a standard linacc vault. This breakthrough significantly expands the accessibility of proton therapy, paving the way for a new era in radiotherapy and revolutionizing cancer treatment worldwide.

Introduction

Proton therapy has gained significant recognition as a preferred mode of radiation treatment for cancer in recent years. Protons offer a notable physical advantage over photons commonly used in standard radiation therapy, primarily due to the distinctive depth-dose distribution they exhibit. Protons can precisely deliver the maximum dose at the Bragg peak, allowing for high doses to be targeted at tumors while minimizing impact on healthy tissue. Even a limited number of proton fields can achieve superior dose distribution compared to the most recent advanced techniques like Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) in standard radiation therapy. Proton beams show exceptional effectiveness in treating tumors located near critical organs like the optic nerves [1], [2] or the brain stem [3]. Notably, proton therapy stands as a highly effective treatment option for patients with head or neck cancer [4]. Extensive clinical trials have substantiated the efficacy of proton therapy in treating various cancers [5], [6], especially in pediatric cases [7].

*Corresponding author: alexander.pryanichnikov@p-cure.com
Published: December 1, 2023

Global challenge is to reduce the cost

Radiotherapy, either alone or in combination with other cancer treatments, accounts for approximately half of cancer treatment protocols and is the most cost-effective approach to cancer therapy. However, despite its considerable physical benefits and proven clinical efficacy in most cases, the substantial capital investment required to establish and maintain a modern proton therapy center is a significant hurdle. To generate precise medical proton beams, energy-intensive and large accelerator facilities are essential. The prevailing standards for accurate prone radiation delivery require expensive and complicated beam delivery systems such as gantries.

P-Cure proton therapy vision

P-Cure developed a new commercially viable generation of proton therapy facility including proton accelerator, beam delivery system and patient positioning system.

It uses a compact variable energy proton synchrotron as a replacement for isochronous cyclotrons or synchrocyclotrons to reduce both construction and maintenance expenses. Our innovative synchrotron possesses a lower weight and power consumption compared to the previous generation accelerator. The system can treat patients with multiple energies directly from the accelerator without necessitating

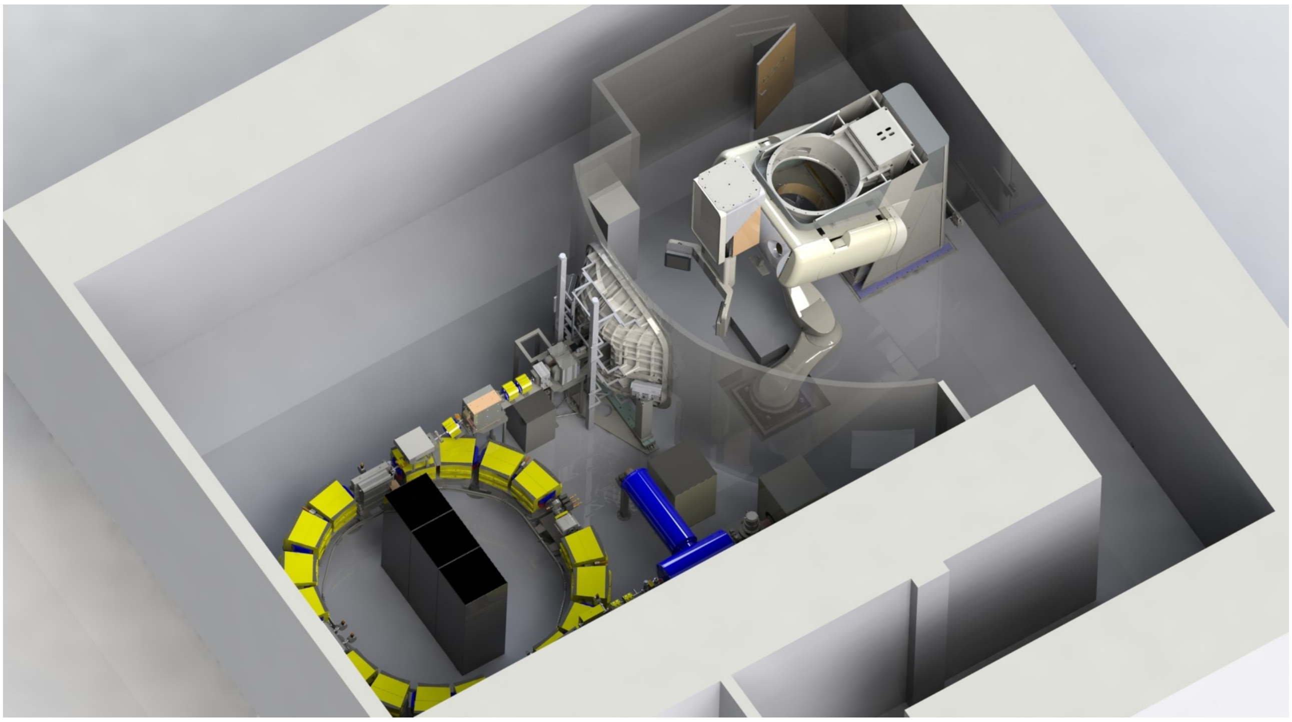

Figure 1: *Render of P-Cure proton therapy facility in Shilat, Israel. The total required footprint for the system is 12 × 7.5 m and can be further reduced based on clinical requirements*

beam degraders or collimators, resulting in superior proton beam quality, reduced background radiation, and subsequently, more streamlined facilities with decreased shielding requirements.

Another innovation involves treating patients in a rotating upright, sitting, or semi-seated position, bypassing the need for an expensive rotating proton gantry. Combination of vertical CT, six degree-of-freedom robot, adjustable patient positioning system (ranging from nearly horizontal to upright) and motion management techniques for upright and semi-upright treatment have made low-cost proton therapy solution feasible.

The first cost-effective proton therapy system, which combines a modern compact synchrotron with an innovative patient positioning system developed by P-Cure Ltd, has been successfully installed at the P-Cure Clinical and Development Center in Shilat, Israel.

Methodologies

P-Cure Proton Therapy Solution: Accelerator

Proton beam therapy enables precise radiation delivery by controlling the depth of penetration of the radiation by adjusting the energy of the proton beam. Stable beam position and energy are essential to concentrate the dose on the target while minimizing the impact on normal tissues. The P-Cure proton therapy facility features a modified Prometheus compact proton synchrotron which provides reliable and precise proton beam.

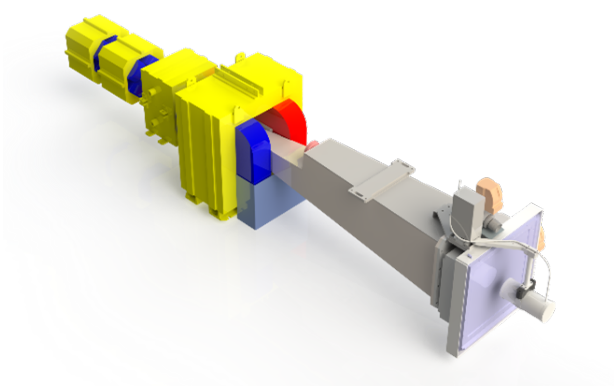

Figure 2: *Beam delivery system and extraction nozzle*

This medical accelerator includes a hydrogen ion source, tandem accelerator, main synchrotron, and beam extraction and transfer lines. The synchrotron accelerates the protons to the clinical energy range of 70-250 MeV in less than 1 second. 1800 proton energies ranging every 0.1 MeV are available for treatment. This system is the most compact for proton accelerators in clinical usage, with a synchrotron diameter of 5 meters and a weight of 15 tons. It also boasts remarkably low power usage, averaging about 20 kW in stand-by mode and approximately 110 kW

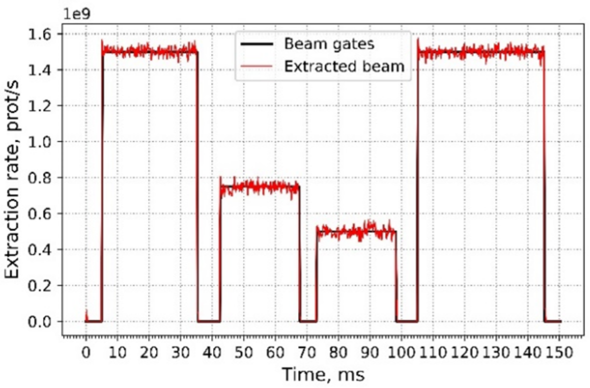

Figure 3: *Example for an intensity- and time- and energy-modulated proton beam treatment*

Figure 4: *The P-ARTIS system installed in P-Cure Research and Clinical Center, Shilat, Israel*

during treatment at maximum beam energy.

P-Cure Proton Therapy Solution: Beam delivery system

The synchrotron proton beam is extracted during a specific beam gate into the beam delivery system. The beam delivery system handles beam transport and formation of a pencil beam. It integrates crucial devices such as bending magnets, focusing quadrupoles, scanning magnets, a fast magnetic shutter, a dose monitoring system, an external Faraday cup, lasers, and an external range shifter for energy adjustments below 70 MeV.

The dose monitoring system provide the important beam information like beam coordinates, beam energy and dose every 200 µs. In the case of any emergency the irradiation can be stopped within 50 µs.

The current configuration of the beam delivery system allows to use 32 cm × 32 cm irradiation field in the isocenter. This value can be extended up to 40 cm × 40 cm. The maximum extraction rate is 2.4×10^9 protons/second with total amount of protons per cycle is 2.0×10^9.

The size of pencil beam varies from 7.6 to 2.7 mm at the isocenter position.

P-Cure Proton Therapy Solution: P-ARTIS

The Patient Robotic Positioning and Imaging System (P-ARTIS©) immobilizes, positions and images patients. It includes a patient positioning system with a convertible carbon X-ray transparent chair, a vertical 4DCT imaging system for patient planning and adaptation, and an orthogonal 2D X-ray imaging system for patient position verification at the isocenter.

P-ARTIS uses Leoni Orion, a six-degree-of-freedom robotic system approved for particle therapy. It's calibrated for loads up to 180 kg, extendable to 240 kg. The vertical 4DCT uses Philips Brilliance Big Bore with respiratory motion kit. The 2D orthogonal imaging system is designed with two 150 kV orthogonal X-ray sources positioned on either side of the beam delivery system and ceiling-mounted retractable 30 cm × 30 cm flat detectors. P-ARTIS supports specific positions: loading, imaging, and treatment at isocenter during proton irradiation and insurances patient positioning accuracy within ± 0.5 mm.

P-Cure Proton Therapy Solution: Treatment planning system

The treatment planning system (TPS) plays a crucial role in determining the treatment approach for proton beam therapy. Its primary function is to formulate an optimal irradiation plan that concentrates the necessary dose on the affected target. This involves defining the irradiation angles for the P-ARTIS robot to achieve multidirectional irradiation, minimizing damage to normal tissue in the process. TPS uses CT images stored on an image server to locate the target area, develop an appropriate irradiation plan, and calculate the dose distribution. The range of protons, irradiation angles and the choice of irradiation equipment is automatically calculated based on information such as the depth of the target obtained from the converted to water equivalent thickness CT images, and the shape of the target. The dose distribution is calculated based on the obtained irradiation parameters.

The P-Cure Research and Clinical Center uses RayStation (RaySearch Laboratories AB, Stockholm, Sweden) for beam modeling and treatment planning. The RayStation TPS features two dose calculation algorithms: a pencil beam algorithm and a Monte Carlo algorithm.

Figure 5: *RayStation 10B modified for P-Cure proton therapy solution.*

Discussion

P-Cure Proton Therapy System has already been installed in Shilat Research and Clinical Center. As this system becomes more widespread, it can require further refinement and enhancement to respond to the needs of medical staff. And the facility's adaptability and modularity set the stage for potential future expansion and improvements.

Figure 6: *P-Cure proton therapy facility in Shilat, Israel during the construction phase*

There are four key areas that stand out for potential upgrades. Firstly, exploring an increase in beam energy up to 330 MeV and implementing an ultra-low intensity extraction mode for proton radiography and proton CT. Secondly, ongoing efforts aim to enable stepwise beam acceleration within one cycle, potentially allowing for the extraction of multiple beam energies in a single acceleration cycle, reducing irradiation time by more than a factor of two. Thirdly, to support the extraction of protons at various energies for proton FLASH therapy, currently in early clinical trials, a modernized beam injection system is in development to enhance captured beam current and subsequent extraction while maintaining extraction speed. Lastly, mini-beam proton therapy has demonstrated promising clinical outcomes with tissue sparing. Additionally, as part of ongoing research on mini-beams, there are plans to manufacture and implement a collimator array for mini-beam delivery without necessitating structural beamline modifications. This collimator array will attach to the beam delivery system in place of the range shifter and move into the beam during treatment.

Conclusion

P-Cure proton therapy solution, particularly the one operational at the P-Cure Research and Clinical Center in Shilat, Israel by Hadassah Medical Center team has been examined and demonstrated. The ongoing work to refine and enhance this system as it becomes more prevalent exists at the convergence of the fields of medicine and engineering. The aim is to foster even closer connections between medical and engineering technologies in this domain, with the ultimate goal of developing a proton beam therapy system that boasts high standard of this field but also not expensive and ease of use.

References

[1] Eva Biewald et al. "Feasibility of proton beam therapy as a rescue therapy in heavily pre-treated retinoblastoma eyes". In: *Cancers (Basel)* 13.8 (2021), p. 1862.

[2] Marina Marinkovic et al. "Clinical outcomes after international referral of uveal melanoma patients for proton therapy". In: *Cancers (Basel)* 13.24 (2021), p. 6241.

[3] Stephanie G C Kroeze et al. "A prospective study on health-related quality of life and patient-reported outcomes in adult brain tumor patients treated with pencil beam scanning proton therapy". In: *Cancers (Basel)* 13.19 (2021), p. 4892.

[4] Anna Lee et al. "Evaluation of proton therapy reirradiation for patients with recurrent head and neck squamous cell carcinoma". In: *JAMA Netw. Open* 6.1 (2023), e2250607.

[5] Miao-Fen Chen et al. "Effect of proton therapy on tumor cell killing and immune microenvironment for hepatocellular carcinoma". In: *Cells* 12.2 (2023), p. 332.

[6] Yang-Gun Suh et al. "Proton beam therapy versus photon radiotherapy for stage I non-small cell lung cancer". In: *Cancers (Basel)* 14.15 (2022), p. 3627.

[7] E C Fortune IV et al. "Outcomes following proton radiotherapy for pediatric salivary gland tumors". In: *Int. J. Radiat. Oncol. Biol. Phys.* 114.3 (2022), e479.