PAUL SCHERRER INSTITUT PSI

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: # 25_03/2022

Dear Reader,

Welcome to this first 2022 edition of our SpotON+ Newsletter. Uni- or bi-lateral brain necrosis (particularly so of the mnesial aspect of the temporal lobe [see Fig.]) is a classical treatment-induced complication of radiation therapy of brain and skull base tumors treated with high-dose (i.e. › 70 Gy) radiation. If this adverse event happens, it will have a substantial objective and subjective impact on the patient's daily activities and overall QoL. Ch. Schroeder and A. Köthe from CPT have both assessed ca. 300 patients treated with › 60 GyRBE proton radiation, a substantial number of them with long-term follow-up (median, › 5 years). Approximately 75% of these patients were treated for skull-base chordomas and chondrosarcomas. Roughly, 10% of these challenging patients presented with high-grade CTCAE temporal lobe necrosis (median time to event, 20 months), of which ca. 40% were bilateral events. In assessing the most robust parameters associated to the incidence of these events (utilizing a bootstrapping analysis paradigm) prescription dose, age, arterial hypertension, together with D1cc [Gy] and V40Gy [%] in the temporal lobe, were most frequently associated with an event. After cross-correlation analysis however, the first three parameters alone were found to be the most predictive. As a result of this, we are routinely assessing these factors into the clinical decision making and planning process so as to decrease the likelihood of this complication. The second article by Giovannelli et al. is an important contribution for PBS beam and delivery time reduction. In sum, energy modulation is an important concept for range variation in order to conform proton radiation dose to the target volume. Energy modulation however takes time and is a major factor contributing to dead time during PBS proton therapy. As such, modulating the energy without re-tuning the magnets (i.e. modifying the beam acceptance) could save precious treatment delivery time. PSI's team present the experimental characterization of the beam properties within the momentum acceptance of the PSI Gantry 2, which can exploit the former to the full. Using a modified control system, a median energy switching time of ‹30 ms could be achieved. Based on ionization chamber array measurements, the clinical plan irradiation (glioma case) resulted in high gamma pass rates at 1%, 1 mm when compared to conventional delivery settings. In summary, these investigations experimentally show that fast energy changes can be achieved, whilst preserving clinical beam quality. The last article by Maradia et al. tackles the issue of higher transmission and thus higher intensity at the isocenter to also reduce treatment times. The group have redesigned the beam optics of Gantry 2 to transport higher emittance beams without the need of any mechanical modifications to the gantry beamline. This re-design could be key to treating moving tumors by delivering high-intensity proton treatments, allowing ultimately to deliver a complete field within a single breath-hold.

That being said, I hope that this newsletter was of interest to you and I stay tuned for the next edition in 4 months' time.

Sincerely,
Prof. Damien C. Weber,
Chairman Center for Proton Therapy,
Paul Scherrer Institute

Radio-Oncology News

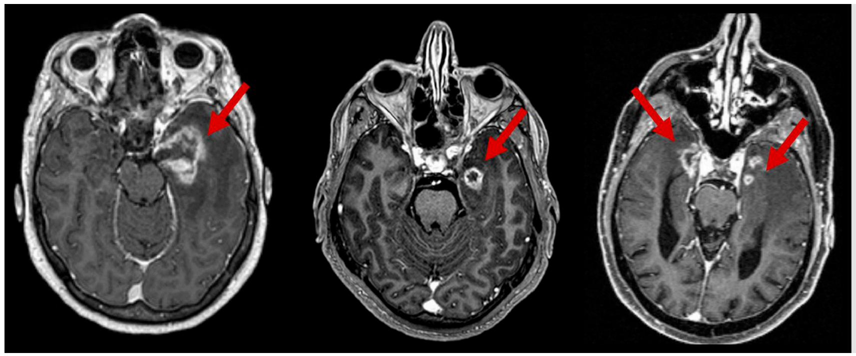
NTCP modelling for high-grade temporal lobe radionecrosis in a large cohort of patients receiving pencil beam scanning proton therapy for skull base and head and neck tumors

Background

Radionecroses (RN) are well-documented side effects following high-dose radiation to the brain, especially for patients with radio-resistant tumors in the vicinity of critical structures, such as skull-base chordoma, chondrosarcoma or cancers of the head and neck region. For these tumors, the temporal lobes are especially at risk given the close anatomical proximity of the target volumes. High-grade temporal lobe RN (TRN) can severely reduce the patients' quality of life post-treatment, which is why it is important to understand the risk factors and drivers behind this side effect, so that treatments can be adapted accordingly wherever possible. Especially in the field of proton therapy, large datasets for TRN are scarce. Therefore, this study was aimed at developing a normal tissue complication probability (NTCP) model integrating clinical as well as dosimetric factors to predict high-grade TRN in patients with skull base or head and neck tumors treated with proton therapy.

Methods and Materials

A dataset of 299 patients treated with a prescription dose of at least 60 GyRBE at PSI and a follow-up of at least 4 months (median 60.5) was used for evaluation and model development. The database included skull-base chordoma (61.5%), skull-base chondrosarcoma (24.4%), adenoid cystic carcinoma (8.4%) and other head and neck primaries (5.7%). Patients with TRN of grade 2, defined as showing moderate symptoms and an indication for corticosteroids, or higher were considered as high-grade (CTCAE v5.0). For the modeling procedure, 11 clinical and 26 dosimetric parameters were considered as possible contributors to the incidence of TRN. The modeling procedure itself consisted of a cross-correlation analysis followed by a penalized logistic regression (LASSO) fit including bootstrapping and cross-validation.



Axial T1 with contrast MRI of three different patients treated with proton therapy showing uni- and bilateral radiation necrosis (red arrows) of the temporal lobe

Results

A total of 75 (25%) patients developed a RN of any grade of the brain tissue after proton therapy. Out of these, 27 (9%) presented high-grade TRN including 11 patients with bitemporal necrosis. Overall, 38 out of 598 temporal lobes were affected with a median time to incidence of 20 months. The 1-, 3- and 5-year rates of high-grade TRN were 1.3%, 8.0%, and 9.0%. The most robust parameters associated to the incidence of TRN following the bootstrapping analysis were prescription dose (PD), age, V40Gy [%], arterial hypertension (HBP) and D1cc [Gy] in the temporal lobe (TL). After cross-correlation analysis, the best performing model was based on age, PD, D1cc and HBP. Good calibration (Hosmer-Lemeshow test p-value 0.45) on our dataset and an AUC-ROC of 0.79 for the patient-wise model were observed. The final model was given by:

$$NTCP_{TRN} = 1 - \left(1 - NTCP_{TL_{left}}\right)\left(1 - NTCP_{TL_{right}}\right)$$

with

$$NTCP_i = \frac{1}{1 + e^{23.25 - 0.031*Age - 0.204*PD - 0.06*D1 - 0.584*HBP}}$$

Discussion

A NTCP model was developed allowing for a quantification of the patient-specific risk for high-grade TRN. Given the imbalanced nature of this cohort and the low percentage of patients with an event, a large focus during the modelling process was on the robustness of the final model. The model providing the best fit in this analysis includes both clinical (Age, HBP) and dosimetric risk factors (prescription dose, D1cc [Gy] of the temporal lobes). This NTCP model could be integrated into a clinical decision making process by allowing on one hand for comprehensive patient counseling through a quantification of their specific risk for this side effect, on the other by assigning patients to high and low-risk groups (proposed threshold: 7.5% for each temporal lobe) and optimizing treatments accordingly. For example for high-risk patients, treatment plans could be optimized prior to therapy to favor the reduction of D1cc within the TL, decreasing the risk for high grade TRN. However, before safe clinical integration, the model requires external validation to ensure generalizability as well as to minimize the risk for overfitting and statistical anomalies.

The research leading to these results has received funding from the Strategic Focal Area "Personalized Health and Related Technologies (PHRT)" of the ETH Domain.

The full paper has recently been published (Schröder and Köthe et al. 2022).

Physics News

Beam properties within the momentum acceptance of a clinical gantry beamline for proton therapy

Pencil beam scanning (PBS) is nowadays the standard delivery technique in proton therapy. It allows even the most complicated geometries to be treated precisely by scanning a thin pencil beam through the target laterally and in depth. To change the lateral position of the spots, the beam is deflected transversally using sweeper magnets, while beam energy is controlled to adjust the spot position in depth.

Transporting beams of different energies requires tuning of the magnetic field in several magnets along the beamline, and this regulation causes dead time during treatment delivery. Depending on the technology used, energy changes can take from seconds to hundreds of milliseconds in operating facilities. Fast energy changes shorten the treatment time, which in turn is beneficial for patient comfort and operating costs. In addition, PBS is particularly vulnerable to organ motion. If less time is needed to scan the target volume, motion mitigation and online adaptation of the beam settings can be implemented more efficiently.

The momentum acceptance defines a range (or band) of energy within which the beam energy can be modulated without re-tuning the magnets, thus overcoming the main source of dead-time in treatments delivery. Although conventional beamlines have a finite momentum acceptance of the order of few percent by design, this is not typically exploited for energy modulation, while priority is given to optimal beam properties. Distortions in the energy spectra can in fact alter critical beam parameters and thus have an impact on treatment quality. In this study, a standard upstream energy degradation system is used to control the beam momentum within acceptance under realistic clinical settings, requiring no hardware modification of the beamline. We present the experimental characterization of the beam properties within the momentum acceptance of the PSI Gantry 2 facility and use this means of regulating energy to deliver an exemplary clinical plan, originally prepared for the treatment of a cranial glioma.

For beam energies within the acceptance, depth-dose curves were only marginally distorted gamma (1%, 1mm) › 90%. The impact on the beam size was limited and errors in the lateral spot position within the clinical tolerance. Using dedicated correction models for fine range control and compensation of beam intensity losses, a median energy switching time of 27 ms could be achieved. Based on ionization chamber array measurements, the clinical plan irradiation resulted in high gamma pass rates at 1%, 1 mm when compared to conventional delivery settings (Fig. 1), while allowing about 45% reduction of the energy switching time when regulation could be performed within acceptance (Fig. 2).

In conclusion, provided that range and transmission losses introduced by the distortion of the beam spectra are compensated for, fast energy changes could be achieved under experimental settings while preserving clinical beam quality. The use of a standard upstream degrader allows for fast energy changes in clinical treatments, with negligible distortions in the delivered dose distribution. Moreover, it does not require modification in the beamline hardware, therefore, being potentially applicable in any running facility, not only in the cyclotron-based ones but also in treatment centers using synchrotrons. Facilities with slow energy switching time can particularly profit from such a technique for reducing dead time during treatment delivery.

The research leading to these results has received funding by the SNF. The full paper has recently been published (Giovannelli et al 2022).

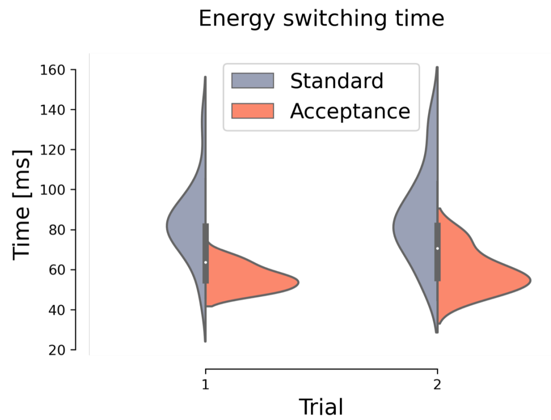


Fig. 2: Distribution of energy switching times during the delivery of a treatment in standard clinical settings and while making use of beamline acceptance. Data from two consecutive irradiations.

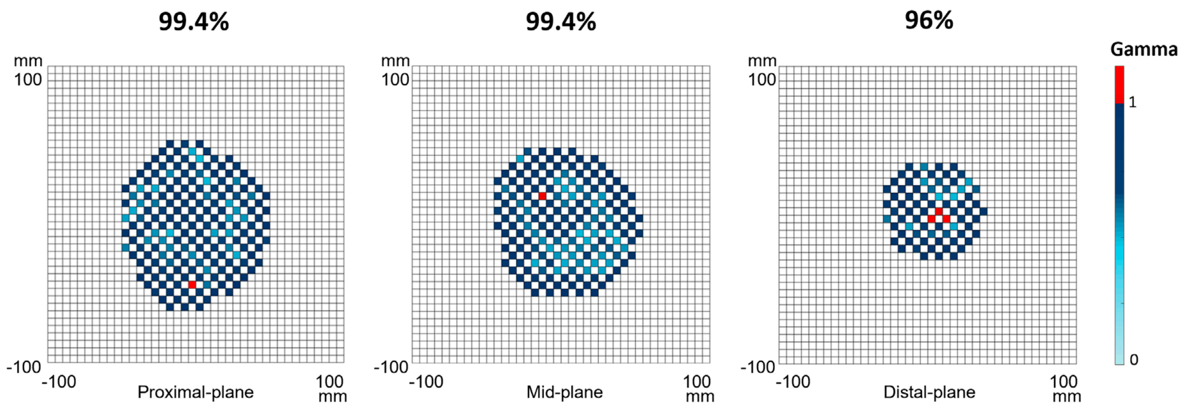


Fig. 1: Gamma analysis at 1%/1mm for three measurement planes in a treatment field. Results of energy regulation within acceptance are compared with reference data from standard delivery settings.

Physics News

Increase of the transmission and emittance acceptance through a cyclotron-based proton therapy gantry

In proton therapy, the gantry, as the final part of the beamline, has a major effect on beam intensity and beam size at the isocenter. Most of the conventional beam optics of cyclotron-based proton gantries have been designed with an imaging factor between 1 and 2 from the coupling point (CP) at the gantry entrance to the isocenter (patient location) meaning that to achieve a clinically desirable (small) beam size at isocenter, a small beam size is also required at the CP. In this study, we showed that such imaging factors are limiting the emittance (at CP, emittance = beam size * beam divergence), which can be transported through the gantry. We, therefore, propose the use of large beam size and low divergence beam at the CP along with an imaging factor of 0.5 in a new design of gantry beam optics to achieve substantial improvements in transmission through gantry and thus increase beam intensity at the isocenter.

To this purpose, the beam optics of our gantry have been re-designed to transport higher emittance (transporting higher emittance means transporting higher number of protons) without the need of any mechanical modifications to the gantry beamline. Finally, the new beam optics have been tested with measurements performed on our Gantry 2 (Figure) at PSI.

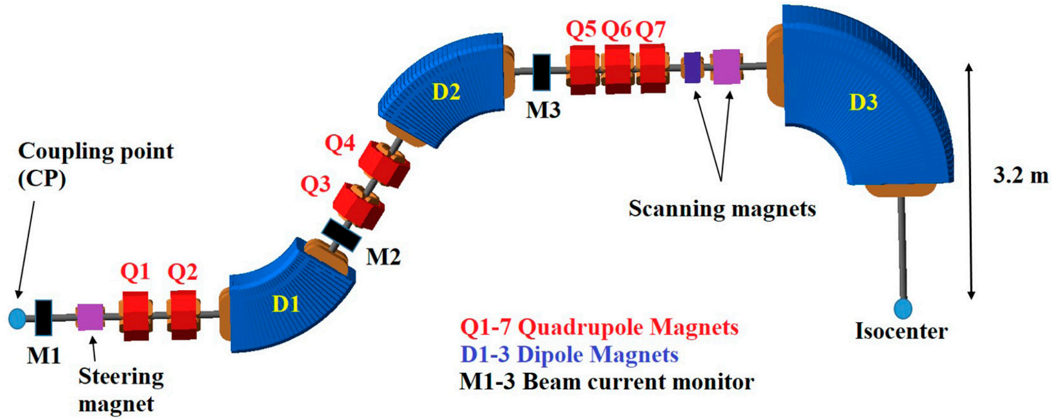


Figure: PSI's Gantry 2 layout in Monte Carlo simulation code BDSIM.

With the new beam optics, we have shown that for a fixed emittance value, it is possible to maximize proton beam transmission through a gantry by using a small divergence value and large beam size at the coupling point (CP), together with de-magnifying beam optics imaging from CP to the isocenter. Additionally, we have shown that the use of large beam sizes and low divergence at the CP allows the transport of larger emittances through the gantry while achieving reasonable transmission (>50%) of even low energy beams through the gantry. By transporting 100 π*mm*mrad emittance through the beamline and gantry, it is possible to achieve almost 6 nA beam current (800 nA from cyclotron) at the isocenter for 70 MeV beam in combination with asymmetric emittance selection collimators. In addition, the studied beam optics with point-to-point imaging gives the flexibility to change the beam size at the isocenter, without changing the gantry beam optics simply by adjusting the beam size at the CP. Such achromatic optics allow beam transport with different momentum spread so that in treatment planning one can balance intensity against fall-off of the dose distribution.

These new beam optics could give the flexibility to choose different beam sizes and intensities of the beam based on the clinical requirement without making a significant change in the beamline or gantry. It could reduce the difficulties to treat moving tumors and could enable the treatment with certain motion mitigation techniques efficiently and effectively. High intensity could allow to deliver a field within a single breath-hold. It could also help to reach the dose rates required for FLASH irradiations. Altogether, this will increase the possibilities to treat new indications in current and future proton therapy facilities.

In summary, we have developed a new gantry beam optics which, by selecting a large beam size and low divergence at the gantry entrance and using an imaging factor of 0.5 (2:1), increases the emittance acceptance of the gantry, leading to a substantial increase in beam intensity at low energies. We expect that this approach could easily be adapted for most types of existing gantries.

This study has recently been published (Maradia et al 2022).

Imprint

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