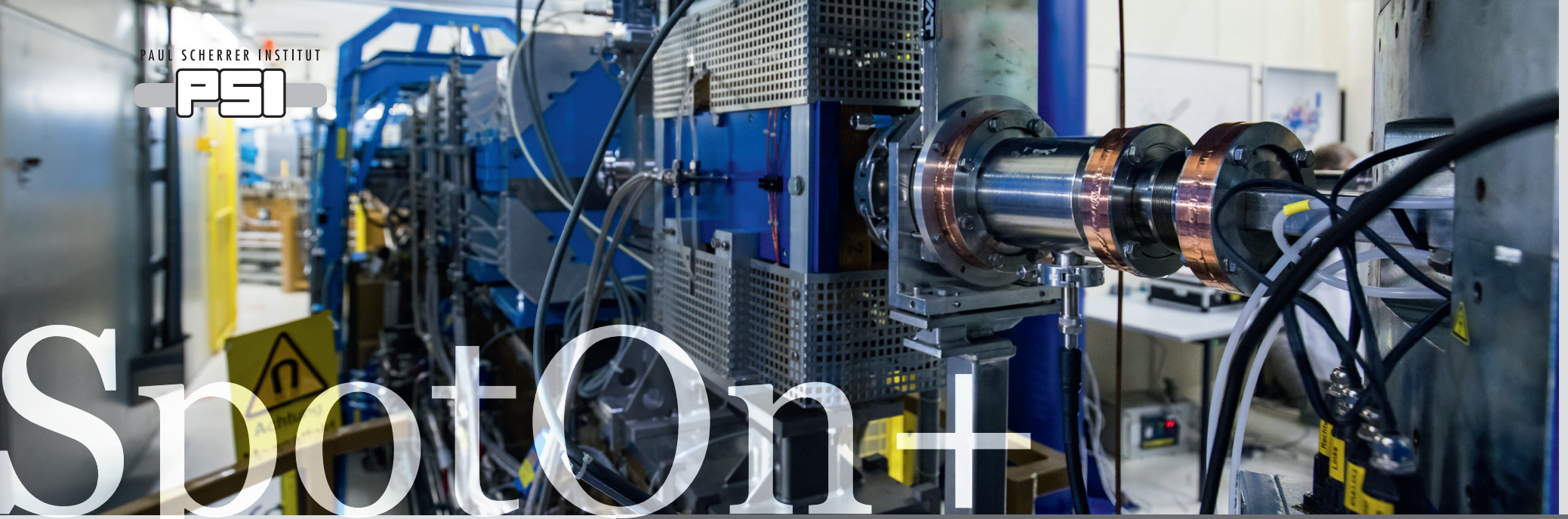

PAUL SCHERRER INSTITUT

PSI

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #12_8/2017

Dear Reader

Welcome to this summer edition of SpotOn+. As of July 17th, the clinical program at PSI has successfully resumed as planned when the COMET cyclotron went back on line two weeks prior to this date. We are now having a full patient throughput with anesthesia patients mostly treated at Gantry 2. This choice has been self-evident in the light of the speed of the radiation delivery with this treatment unit which has consequently decreased the sedation time for children. Cases can be referred to PSI by contacting the head of the clinical team (Dr. Marc Walser; marc.walser@psi.ch) or myself (damien.weber@psi.ch). The next big task on our list is the clinical commissioning of our new treatment Unit (Gantry 3) that will start this late summer. On the picture above you can see the coupling point of the beam line (on the left hand side) with the G3. It is foreseen that the first patients should be treated by the end of this year. A dedicated SpotOn+ edition will be proposed soon to our readers and a symposium will be scheduled in Q2 2018 at PSI. Additional information will be given to the radiation oncology community in a not too distant future.

If there is one category of patients who will benefit from protons, it is surely children, adolescents and young adults (AYA). In this edition, we report our results of proton therapy for EWING sarcomas for these challenging patients. With a follow-up of approximately 50 months, only 16% of children/AYA experienced a local failure. Importantly only 2 (7%) patients experienced significant (i.e. grade 3) late toxicity due to the decrease in radiation delivery to tissues in vicinity of the target volume. Despite the numerous negative prognostic factors presented by a substantial number of patients, the survivorship at five years (>80%) was excellent. The second article of this edition deals with advanced MRI techniques (i.e. functional imaging) used for proton therapy planning purposes, with or without a SIB delivery paradigm. The reader has to go beyond the rather tedious list of acronyms (DWI, DTI, DSC, ASL), to acknowledge the interest of imaging for radiation delivery in general and protons in particular. Our group has shown that 'functional sparing' was possible using dedicated MRI sequences that may benefit ultimately a selected number of brain tumor patients. Finally, the last article details the clinical commissioning of advanced proton delivery techniques that include motion-mitigation strategies such as re-scanning, with or without gating. The former has been now applied routinely in patients for which tumor and/or OAR's motion is a clinical concern, with the first patient treated this summer. The end-to-end testing showed that spatial displacement of the measured dose was acceptable with a standard deviation of 0.0–0.3 mm. We are excited in the prospect of introducing optical tracking in addition to the above-mentioned motion-mitigation strategies. As of 2017, we are the only proton therapy center worldwide proposing combined motion-mitigation strategies, including rescanning techniques, to alleviate the interplay-effect inherent to PBS delivery to moving target volumes.

That said, I would like to thank you for reading this Newsletter and wish you a good start after the summer recess. Stay tuned on SpotOn+ to have the latest clinical/research reports on our center.

Yours sincerely,
Prof. Dr.med. Damien Charles Weber
Chairman of CPT, Paul Scherrer Institute

Radio-Oncology News

Pencil-beam scanned protons for the treatment of patients with Ewing sarcoma

Introduction

Ewing sarcoma (EWS) is a highly malignant small round-cell tumour of the bone and/or soft tissue, most commonly found in male adolescents and young adults (AYA) with a highest incidence in the 10–15 years range. The therapeutic strategy for these challenging tumours consists on multimodal treatment involving chemotherapy and local therapy, the latter consisting of surgery and/or radiotherapy (RT), resulting in a 5-year survival of approximately 60–75% for non-metastatic EWS. The advantage of pencil-beam scanning (PBS) over passive-scattering proton radiation therapy is that dose distribution may be possibly optimized and the production of neutrons decreased, thus decreasing the probability of radiation-induced secondary cancers. To the best of our knowledge this analysis presents the first results on the long-term outcome of children and AYA treated with PBS proton therapy (PT). As such, we have evaluated the outcome of these patients and have assessed the major prognostic factors for this locally invasive tumour.

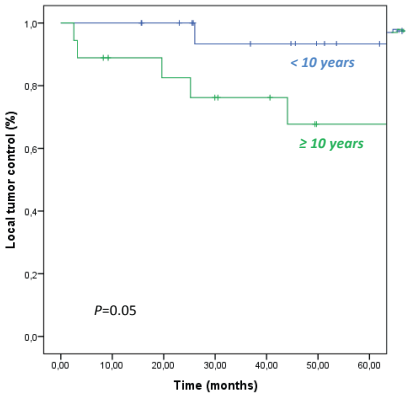

Figure 2: Local tumor control as a function of age of EWS patients treated with PT.

Materials and Methods

To identify the study cohort, we selected all paediatric and adolescent/young adult (AYA) patients aged ≤ 39 years with at least 9 months of follow-up (FU). We excluded 3 cases with FU ‹ 9 months and another case aged › 39 years. Thirty-eight patients (median age at diagnosis: 9.9 years, range: 0.4 – 38.9 years) form the basis of this report. A total of 24 male and 14 female patients received a median dose of 54.9 GyRBE (range: 45.0 – 69.6 GyRBE). Thirteen (34%) patients were anesthetized during PT. Children were sedated with propofol under spontaneous breathing. Size of the tumour ranged from 1.7 to 24 cm (median: 6.7 cm). Most common primary site was axial/pelvic (n = 27; 71%). Four patients (11%) presented with metastasis at diagnosis. Twenty (53%) patients had chemo-PT only. Median follow up was 49.6 months (range, 9.2–131.7). Local control (LC), distant metastasis-free survival (DMFS), toxicity-free survival and overall survival (OS) were determined from the first day of PT. Univariate analyses were performed to identify prognostic factors.

Results

With a median follow up of 49.6 months and 50.5 months for the surviving patients, 6 (15.8%) patients experienced local failures after a median time of 22.4 months. Seven (18.4%) patients developed distant metastasis 2.5-56.1 months (median, 19.2) after PT. Two patients presented with concomitant local and distant failure, 2 other patients presented with sequential local and distant failure and 3 patients with distant metastasis only. The 5-year actuarial rate of local control (LC), distant metastasis-free survival (DMFS) and overall survival (OS) were 81.5%, 76.4% and 83.0%, respectively. All local recurrences occurred in field and in patients with non-extremity primaries. Six patients died, all of tumour progression. Age ‹ 10 years was a favourable factor for LC (P = 0.05) and OS (P = 0.05) of borderline significance, but was significant for DMFS (P = 0.003). Tumour volume ‹ 200 ml was a significant prognostic factor for DMFS (P = 0.03), but not for OS (P = 0.07). Metastasis at diagnosis was a strong predictor of local failure (P = 0.003). Acute toxicity was limited to grade 1–2 skin erythema or mucositis. Only 2 (6.9%) grade 3 late toxicities were observed. The 5-year actuarial rate of grade 3 toxicity-free survival was 90.9%.

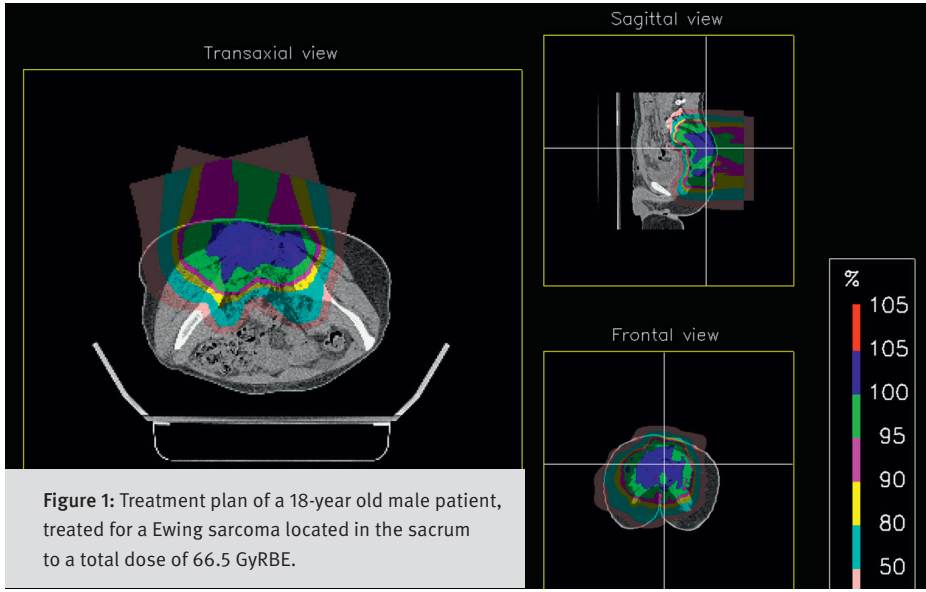

Figure 1: Treatment plan of a 18-year old male patient, treated for a Ewing sarcoma located in the sacrum to a total dose of 66.5 GyRBE.

Conclusions

These preliminary data suggests that the outcomes of children and AYA with EWS were good and PT was well tolerated with very few late adverse events. The local and distant tumour control for older patients with large pre-PT tumour volumes remains problematic in these challenging patients.

The results were recently published (Weber al. 2017) and will be presented at the 49th Congress of the International Society of Paediatric Oncology (SIOP) in October in Washington.

Reference

Weber et al. Pencil beam scanned protons for the treatment of patients with Ewing sarcoma 10.1002/pbc.26688

Medical-Physics News

Shaping proton therapy dose with DTI and DSC MRI data: functional SIB and avoidance proof of concept study

External beam radiation therapy is, together with surgery and chemotherapy, a standard first (radical) or second line therapy for many brain cancer indications. In particular, ions (e.g. protons and carbon) are attractive because of their ability to control dose deposition at a precise location in space due to their Bragg peak characteristic, allowing improved sparing of organs at risk. In addition, proton pencil beams used in combination with Intensity Modulated Proton Therapy (IMPT) allow for flexible planning of dose and sharp dose gradients even in the most complex geometries. Nonetheless, radiation-induced damage to healthy tissues in the form of early, delayed or late neurocognitive toxicity can substantially affect patient quality of life. Current treatment planning typically ignores functional structures, such as white matter neural networks or hypoxic/aggressive sub-areas of tumours. However advanced MR imaging techniques, such as diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion with Dynamic Susceptibility Contrast (DSC) or Arterial Spin Labelling (ASL) MRI and MR-Spectroscopy (MRS) provide the possibility to more precisely characterize brain lesions and functional regions to aid the treatment planning process.

In this work, we investigate the potential of incorporating cortico-spinal tract structures (DTI_CST), determined using DTI, and relative Cerebral Blood Volume (rCBV), thought to correlate with tumour aggressiveness and identified using T2* DSC perfusion imaging, into treatment planning for IMPT. The goal is to spare dose to the DTI_CST structures whilst boosting dose to the rCBV. For an example oligoastrocytoma (WHO II) patient (Figure 1), four treatment plans have been calculated. i) A uniform dose PBS proton plan, ii) a Simultaneous Integrated Boost (SIB) plan based on a rCBV, iii) a uniform plan modified with DTI_CST guided functional sparing and iv) both SIB and DTI_CST functional sparing. Dose constraints for the DTI_CST plans were defined either on the tract structures as a whole volume or by splitting them into upper, middle and lower portions, as the middle portion overlapped with the PTV.

Resulting plans and DVHs are shown in Figure 2. For the rCBV-SIB plan (ii), mean and max doses in the cochlea were reduced by 3% and 5% respectively c.f. the uniform plan, max dose to the brainstem by 3% and dose to the central and lower DTI_CST by 2%. Using an alternative field arrangement, the CST-centre could be better spared (mean dose -5%), but at the cost of increased mean/max dose to the cochlea (3% and 5% respectively). For the DTI_CST sparing plan (iii), CST_centre mean (61% vs 103%) and maximum (70% vs 103%) doses were substantially reduced c.f. the uniform plan (i), and max dose was reduced by 5% and 2% in the brainstem and cochlea respectively. This was however at the cost of a reduced V90 to the CTV (91.3% vs 100%). With different constraints for the different DTI_CST portions, mean and max dose to CST_centre could be reduced to 52 and 56% respectively. Similar results were found for the SIB_DTI plan (iv).

In conclusion, it has been shown that IMPT plans can be generated to account for constraints on MRI defined functional volumes. Although this is only a first proof of concept, we think that introducing functional information into the plan and along the treatment course will help to exploit the flexibility of pencil beam scanned proton therapy further.

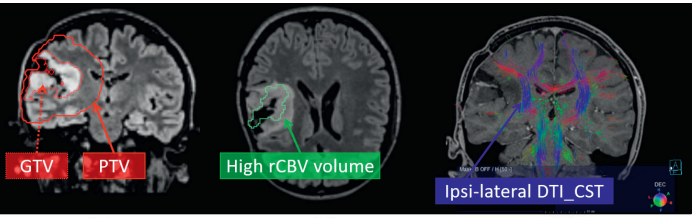

Figure 1: Case presentation. (a) T2 FLAIR MRI with overlaid GTV and PTV contours. (b)T2 FLAIR MRI overlaid with volume with elevated rCBV (correlating with aggressiveness. (c) DTI tractography, note how the ipsilateral DTI_CST is next to the tumour area

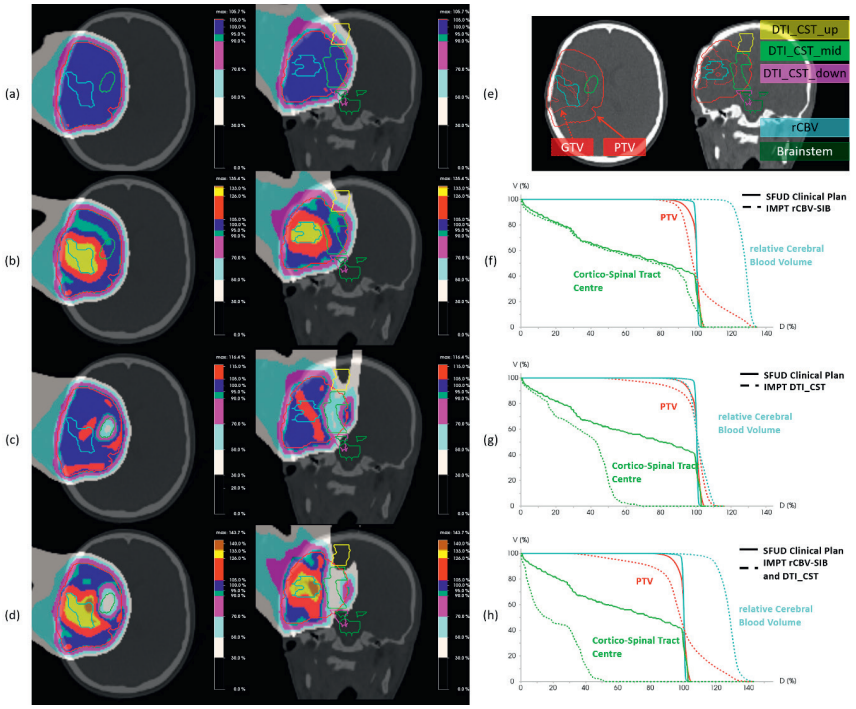

Figure 2: Plan Comparison. (a) clinical SFUD plan; (b) IMPT rCBV-SIB plan and (f) DVH comparison SFUD vs IMPT rCBV-SIB; (c) IMPT DTI_CST sparing plan and (g) DVH comparison SFUD vs IMPT DTI_CST; (d) IMPT with rCBV-SIB and DTI_CST sparing plan and (h) DVH comparison SFUD vs IMPT with rCBV-SIB and DTI-CST sparing; (e) Structures used during plan comparison.

This project was presented at the BiGART conference in Aarhus, Denmark in June this year.

For any further information, please refer to CPT,

Dr. Marta Peroni
Tel. +41 56 310 4037
marta.peroni@psi.ch

Medical-Physics News

Clinical commissioning of rescanned pencil beam scanning treatments of moving targets

In the spring 2017, CPT PSI has performed commissioning of the clinical procedure for the treatment of moving targets with pencil-beam scanning on Gantry 2. This included treatment planning with 4D dose calculation (4DDC), patient-specific verifications extended by measurements with a 2D ionization chamber array mounted on a moving platform, and end-to-end testing using a dynamic anthropomorphic phantom.

Treatment planning approach and 4D dose calculation (4DDC)

Single field uniform dose (SFUD) plans were optimized on the mid-ventilation phase extracted from a 4DCT dataset of each thoracic patient, with primary anatomical target motion below 8 mm in superior-inferior direction, delivering V95%=100% to PTV.
Static plans created for the mid-ventilation phase were subject to 4DDC, which simulates the interplay between motion of anatomy derived from 4DCT and time structure of delivering pencil beam sequence, taking into account handling of all spots by treatment control system of Gantry 2 for the given rescanning regime (figure 1). In the 4DDC, 8 rescans were found to provide full and homogeneous CTV coverage for all cases, independent of starting phase (fluctuations of V95% and D5%–95% under 2%).

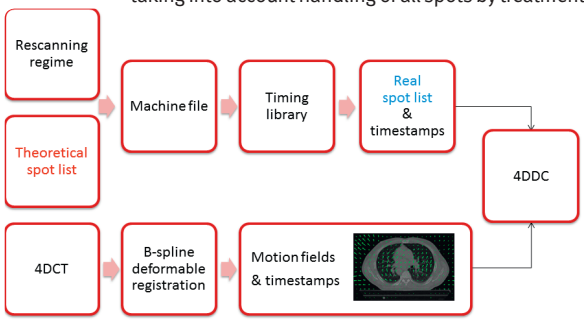

Figure 1: Schematic diagram of the 4D dose calculation.

Dosimetric verification

Each rescanned field was measured at proximal and distal depth using a 2D-chamber array as stationary and also moving (figure 2) under different motion scenarios:

- nominal (8mm motion),
- random fluctuations in amplitude and period
- scaled in amplitude to exceed the clinical inclusion criteria (>10mm).

Gamma score (GS) (3% dose difference /3 mm distance-to-agreement) was 100% for all static measurements and >98.5% for all fields tested with nominal patient motion. Average GS reduced however to 97.8% (1SD=2.9%) in the presence of moderate motion fluctuations, and was not clinically acceptable for amplitudes >10mm (average GS=76.9%) (figure 3).

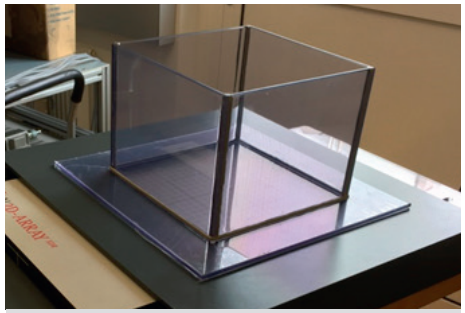

Figure 2: A 2D ionization chamber array mounted on a moving platform placed under a "bridge" which holds a water phantom.

End-to-end test

The whole clinical treatment workflow, including 3-DOF patient positioning based on image registration of the averaged 4DCT with a slow, pre-treatment in-room CT, was verified using an anthropomorphic breathing phantom and radiochromic films positioned at 2 planes in the tumour. Spatial displacement of measured dose distributions were 1.4mm (1SD=0.3mm) in the left-right direction and 1.5mm (1SD=0.0mm) in the cranio-caudal direction. Dose inhomogeneity in the CTV was <9%.

Conclusion and outlook

It was theoretically and experimentally verified that rescanning can be safely applied clinically to mitigate motion with irregularities in moving-target treatments for amplitudes ≤ 8mm. Optical tracking system is currently under integration at Gantry 2 to allow treatment of targets moving more than 8 mm in the regime of gated rescanning. This system will be commissioned for the clinical use by the end of this year.
This work was presented at the 56th annual conference of the particle therapy co-operative group (PTCOG) mid of May this year in Yokohama, Japan.

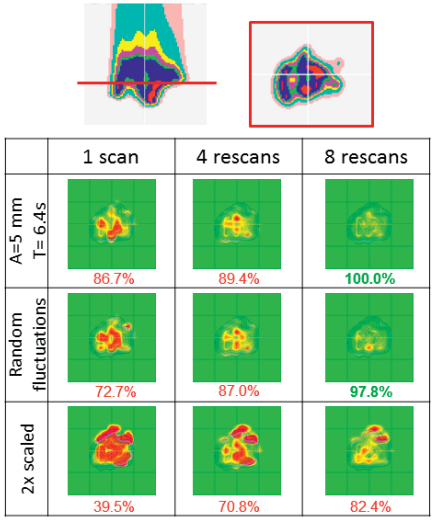

Figure 3: An example of gamma analysis for a patient treatment field. The gamma score improves with increased number of rescans and dose distribution remains robust also in case of fluctuations of amplitude and period.

For any further information, please refer to CPT,
Dr. Jan Hrbacek
Tel. +41 56 310 37 36, jan.hrbacek@psi.ch

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Editor
Dr. Ulrike Kliebsch

Chairman
Prof. Damien C. Weber

Chief Medical Physicist
Prof. Tony Lomax

Design and Layout
Monika Blétry

Contact

Center for Proton Therapy
CH-5232 Villigen PSI
protonentherapie@psi.ch
www.protonentherapie.ch
Tel. +41 56 310 35 24
Fax +41 56 310 35 15

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