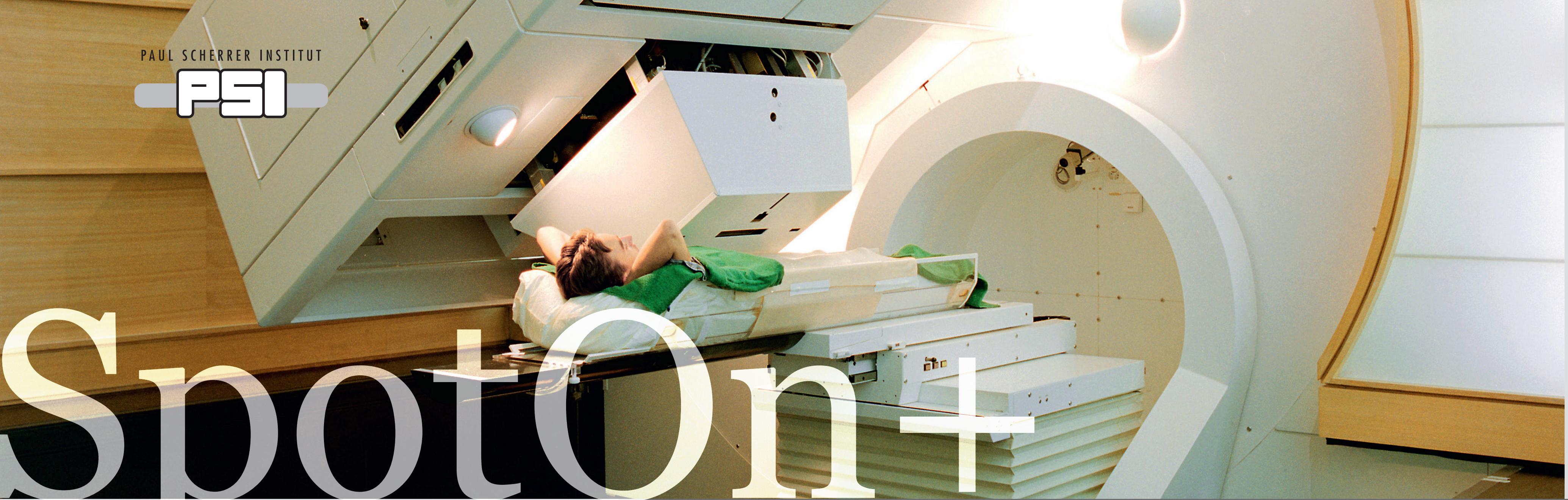


SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #16_12/2018

Dear Reader,

on December 4th, as planned, our Gantry 1 has delivered the last fraction of proton radiation therapy to a patient. This treatment unit has been used clinically during 22 years with no significant mechanical failures. As a reminder, Gantry 1 was the first pencil-beam scanning Gantry in the world, which has been routinely used for the treatment of cancer patients. Although the paradigm of spot scanning delivery was described by a Japanese group in the 1980s, the group of Eros Pedroni conceptualized, designed and finally supervised the construction of this unit with a non-isocentric design which makes it still parenthetically in 2018 one of the most compact gantry in the world. It was also this unit that delivered the first ever intensity-modulated proton therapy planned by the team of Tony Lomax. It has been the showcase of the knowhow of PSI in the field of proton therapy and has been displayed in numerous papers, congresses and symposiums (with or without the knowledge of PSI!) as the quintessence of the impact of PSI in this field. This gantry has been now replaced by the Gantry 3 (collaboration between USZ-UZH), which started successfully treatment of patients this summer. The transition has been nearly perfect and I must thank all CPT's collaborators to have made the changeover as smoothly as possible with no decrease in patient's throughput. Congrats to all of my collaborators.

The first article of this edition details the outcome of large sacral chordoma patients, most of them treated on Gantry 1, after proton therapy and hyperthermia in the framework of a collaboration with the Kanton Spital Aarau (St. Bodis). With this combined modality paradigm, a mean decrease of tumor volume of 50% was achieved, quite a remarkable achievement for this slow responding/radio-resistant tumor. Overall, two third of patients presented with a partial radiological response. In the second article, Robert Poel presents a dosimetric analysis using CFR-PEEK for proton therapy. Titanium surgical implants generate substantial artefacts on radiological studies. This will substantially hamper the delineation process and corrupt the translation of Hounsfield units to stopping power. Moreover, the manually correction of these artefacts is labor-intensive. PSI has shown that the use of carbon-based decreases by a factor of four the target volume receiving less than 95% of the prescribed dose (data not shown). As radiation-oncologist, we need to convince our fellow surgeons that, when possible, polyetheretherketone material should be used for radiotherapy delivered to extra cranial bone tumors, be it with protons or photons, the latter mainly for delineation issues.

Lastly, Ye et al. has assessed the impact of 4D plan optimization with or without motion mitigation strategies for the delivery of pencil-beam scanning proton therapy. Our group observed that 4D plan optimization could reduce the dose to normal tissues. Incorporating rescanning into 4D optimization was also beneficial for achieving dose optimization/robustness. At PSI we use for selected patients with target/organs at risk motion such mitigation strategies and/or 4D dose optimization.

That being said, I wish you a merry 'Xmas and Happy new year. Please stay tuned for our next edition in 2019 of our magazine for some results stemming from our ongoing clinical/research program.

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

Radio-Oncology News

Proton therapy and hyperthermia in large inoperable sacral chordomas

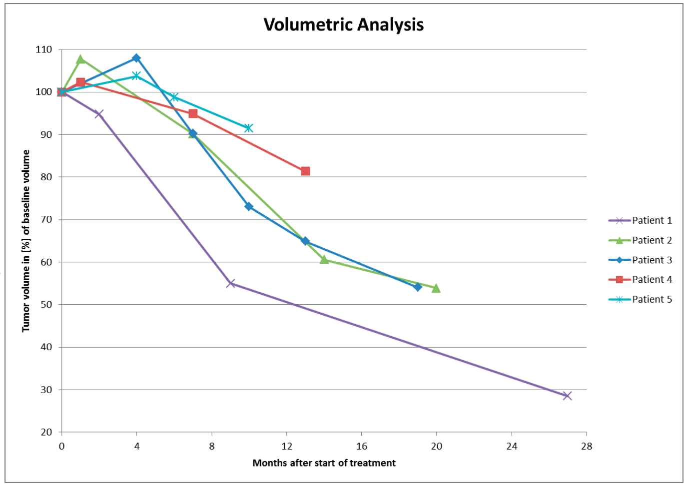


Figure 2: Volumetric tumor response relative to tumor volume at treatment start.

Objectives: Large inoperable sacral chordomas show unsatisfactory local control rates even when treated with high dose proton therapy (PT). Improving the efficiency of the primary treatment is therefore of paramount importance. As we commented in the December 2017 issue, the combination of hyperthermia and irradiation showed promising results in selected tumor types, including soft tissue sarcomas. The aim of this study is assessing feasibility and reporting early results of patients treated with Pencil Beam Scanning (PBS) PT and concomitant hyperthermia (HT).

Methods: Patients with inoperable, non-metastatic, biopsy-proven chordoma in the sacral region received HT in addition to definitive PT. PBS Intensity Modulated PT was administered utilizing PSI's 250 MeV cyclotron. Target volume definition was performed on a 3D high resolution planning CT, matched with a planning MRI. Prescribed dose was 70 Gy(RBE) in 28 fractions of 2.5 Gy(RBE), delivered 5 times weekly over 5½ weeks. HT was delivered weekly at Kantonsspital Aarau, using either the Sigma 60 or the Sigma-Eye applicators of the deep hyperthermia unit. The HT treatment planning was carried out using SigmaHyperPlan software by segmentation and creation of a grid model of the various body tissues according to their dielectric properties (e.g. tumor, muscle, bone, fat) followed by simulation of the electric fields. Temperature during HT application was monitored on the skin, in the rectum, gluteal fold and the urinary bladder. Toxicity was assessed according to CTCAE_v4. A volumetric tumor response analysis was performed.

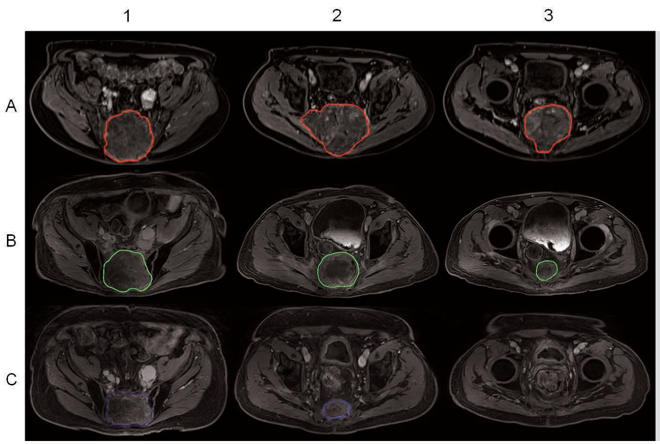


Figure 1: Tumor response in patient 1. (A) baseline, (B) 9 months and (C) 27 months after treatment. Columns represent the (1) cranial, (2) middle and (3) caudal aspects of the tumor. Disease is no longer found in the caudal region 27 months after treatment due to tumor response.

Results: From May 2016 to October 2017, five male patients referred from centers in Switzerland (n = 2) and the United Kingdom (n = 3) were treated with the combined PT and HT approach with a common treatment protocol. Median patient age at diagnosis was 67 years (range, 57–72) and median baseline tumor volume was 735cc (range, 369–1142). All patients completed PT and received a median of 5 HT sessions (range, 2–6), either just before (n = 4) or after (n = 1) PT. One patient had to stop HT after 2 sessions due to pain in the sacral area, thereby making it difficult to maintain the position during the hyperthermia treatment sessions. Median follow-up (FU) was 18 months (range, 9–26). At last FU, no patient was diagnosed with neither local nor distant recurrence. In the volumetric analysis, we found that all but one patient presented with an initial increase in tumor volume on the first FU MRI, always followed by tumor shrinkage below pre-treatment volume in further FU imaging. Overall, the median tumor shrinkage was 46 % of reference (range, 9–72). According to the revised RECIST criteria, 3 patients (67 %) showed a partial radiological response. All acute toxicities resolved completely. One patient presented with a late grade 3 iliac fracture. Another patient presented with late grade 2 local fibrosis and grade 1 skin hyperpigmentation. Grade 1 rectal bleeding was observed in 1 case.

Conclusions: Combining PT and HT in large inoperable sacral chordomas is feasible and causes acceptable toxicity, providing proactive pain control during treatment. Volumetric analysis shows promising early results, warranting confirmation in the framework of a prospective trial.

These results have been submitted for publication in a peer-reviewed journal.

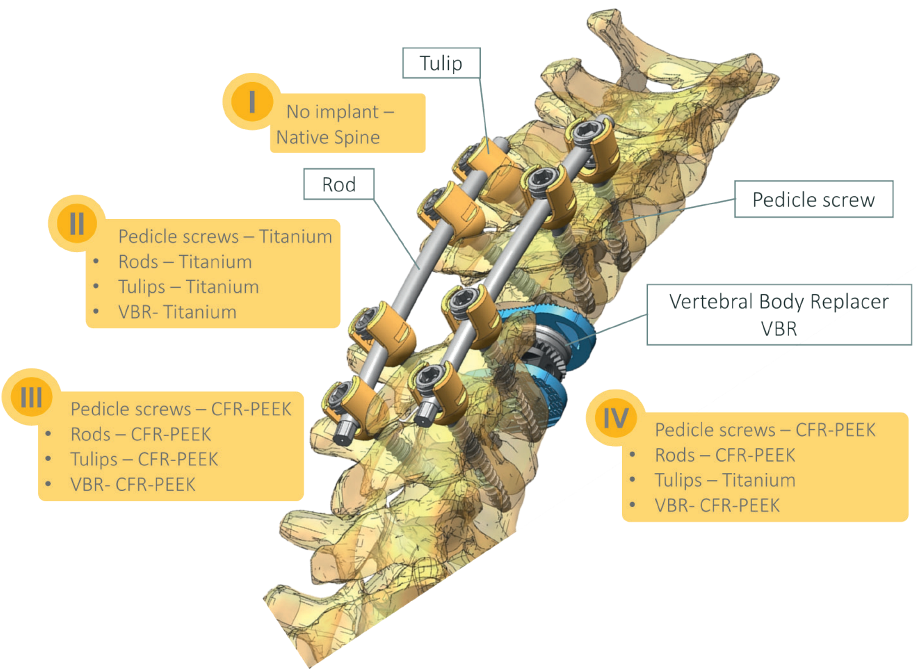
For any further information, please refer to

Dr. Sébastien Tran, CPT
Tel.: +41 56 310 35 04
sebastien.tran@psi.ch

Prof. Dr. N.R. Datta, KSA
Tel.: +41 62 838 95 59
NiloyRanjan.Datta@ksa.ch

Medical-Physics News

CFR-PEEK vs Titanium spinal implants in radiotherapy: A phantom study



Design schematic of the interchangeable insert of the phantom. The 4 different inserts exist of: A native spine (case I), a full titanium implant (case II), an implant completely out of CFR-PEEK (case III) and a hybrid implant where the tulips are made of titanium (case IV).

Radiotherapy, including proton therapy, is often given adjuvantly after surgery. In diseases involving the bones, such as chordomas and chondrosarcomas which are often treated at our institute, the surgical resection might lead to instability, for example in the spine. In these cases the spinal instability is redressed by titanium implants.

Unfortunately, titanium is a hard and dense material which will lead to several difficulties in the planning and delivery of a radiotherapy treatment. Planning and dose calculation is based on the density mapping retrieved with a CT scan. For proton therapy these Hounsfield units (HU) are then correlated to proton specific stopping powers to correctly calculate the exact energy deposition of the protons. A titanium implant, due to its density, saturates the HU on a CT hence causing artefacts and thus compromising the correct density mapping. Especially in proton therapy where the majority of energy is deposited in the Bragg peak a correct representation of the stopping power is of utmost importance for correct dose calculation. As a consequence the artefacts have to be corrected manually which is time-consuming and subsequently lead to a higher level of uncertainty in the dose calculation.

The second issue is the big difference in density between titanium and human tissue. Dose calculation algorithms are based on water equivalent densities and therefore specific proton interactions as multiple coulomb scattering and non-elastic interactions are not taken into account. The consequence is that the dose of proton beams shooting through these structures, especially distally of the metal, are not correctly simulated by the dose calculation. Besides, the large density difference makes the constructed plans less robust in case of setup errors and/or anatomical changes.

Nowadays, carbon fiber reinforced polyetheretherketone (CFR-PEEK) implant materials are available. The advantage of this implant material is that it has a density equivalent to human tissue and therefore does not cause artefacts and there are no unaccounted proton interactions expected. Theoretically this would solve the challenges currently present with titanium implants. CFR-PEEK is therefore likely to be the ideal material to use for stabilization when radiotherapy is anticipated.

To show this theoretical advantages in a scientific way and to promote the use of CFR-PEEK implants we have set up a study together with two collaboration partners: Icotec AG, a Swiss spin-off company of ETH and one of the two worldwide manufacturers of CFR-PEEK implants and Inselspital Bern covering the photon part of the research.

A unique anthropomorphic torso phantom was designed with an interchangeable spinal part that represents 4 different cases: No implant, an implant made totally out of titanium, a prototype implant made fully of CFR-PEEK and a clinically approved hybrid implant (see image). With this phantom we were able to mimic and compare treatment of these 4 different cases and subsequently verify the dose distribution within the target by means of GafChromic film. To compare the differences of the 3 different implant configurations and the reference case without an implant, we have performed a standard clinical workup of simulation, contouring, artefact correction, plan optimization and delivery. Our colleagues in Bern performed the same protocol for the clinical photon plans. Preliminary results show the potential of CRF-PEEK material use in radiotherapy. A meeting will take place soon with all collaboration partners to present and discuss first results.

For any further information, please refer to CPT

Robert Poel
Tel.: +41 56 310 34 11
robert.poel@psi.ch

Medical-Physics News

Towards a more robust 4D plan optimization for PBS-based moving tumor treatments

Plan quality can be compromised for mobile tumour treatments using pencil beam scanning (PBS) proton therapy, due to the detrimental effects of intra-fractional motion on dose deposition. As a complement to the classic motion mitigation approaches, such as rescanning, gating, tracking or combinations of these, 4D plan optimization is a process that can inherently include motion into the pencil beam weight optimization in order to generate 'motion-robust' 4D plans by itself. In this presented study, we would like to evaluate this promising technique systematically using 4DCT-MRI datasets of liver tumour patients, as well as to investigate the possibility of increasing plan robustness by directly incorporating rescanning into the 4D plan optimization.

Using nine 4DCT(MRI) datasets of liver tumors (PTV:100–400 cc), 3D plans were generated on the end-of-exhalation phase of the 4DCT using geometric Internal Target Volume (gITV: encapsulating PTVs at all 4DCT phases). 4D dose calculation was performed by considering regular and irregular motion patterns (range: 8–20 mm; period: 3.3–6.3 s) with and without rescanning (x5 layered). In addition, 4D, directly optimized plans, which accurately take into account beam delivery dynamics and organ motion, were calculated to the PTV (on reference CT) without expanded gITV. The robustness of optimized 4D plans were assessed by recalculating the optimized 4D plans under variable motion scenarios with motion phase delays up to 1 s (in 50 ms intervals). All re-calculated 4D plans were quantified and compared using homogeneity index (HI) of D5–D95 in the PTV as well as V10 %, V20 % and V60 % in the healthy liver (liver-PTV).

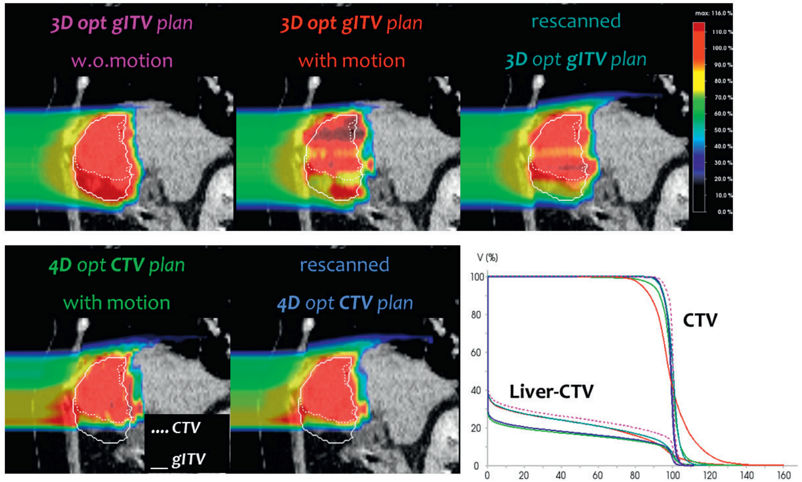


Figure The effectiveness of 4D plan optimization (with and without rescanning) for mitigation organ motion (amplitude over 20mm) incl. respective dose-volume-histogram (DVH) plots. Colors in DVH plots are corresponding to those used by sub-figure of each scenario.

Independent on the motion pattern (regular or irregular), amplitudes (up to 20mm) or periods (either fast or slow breathers), interplay effects could be effectively mitigated using 4D plan optimization alone, where HI in the PTV being ‹15 % can be achieved. Furthermore, combining 4D optimization with rescanning, can additionally improve optimized plan quality, by reducing HI in the PTV to within 5 % of static 3D plans. For the 'best-case' rescanned 4D plans, 4D optimization could be able to provide "zero-motion-margin" for 4D treatments (in Figure), resulting in pronounced reduction of dose to the healthy liver (median 5 % for V10/20/60 % indexes). However, optimized 4D plans, especially those without rescanning, have been shown to be extremely sensitive to variations of the presumed (during the optimization) and actual motion conditions during delivery. Nevertheless, the robustness of 4D optimized plans can be substantially increased by combining optimization with rescanning. The comparable plan quality (within 5 %) can be achieved for rescanned 4D optimized plans, even allowing for motion phase shifts of up to 500ms between optimization and delivery. The resulted 4D plan robustness is in contrast to the less than 200ms motion phase shifts that were observed to degrade plan quality for 4D plans optimized without rescanning.

4D plan optimization can substantially minimize ITV margins, therefore reducing dose to normal issues. Incorporating rescanning into 4D optimization is beneficial for achieving such goals, thanks to the significantly increased 4D plan robustness with respect to motion variations.

This work was presented on the annual meeting of the European Society for Radiotherapy & Oncology (ESTRO) 2018. A full publication is in preparation.

For any further information, please refer to CPT

Dr. Ye Zhang
Tel. +41 56 310 5834
ye.zhang@psi.ch

Imprint

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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