PAUL SCHERRER INSTITUT

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #19_03/2020

Dear Reader,

it is my distinct pleasure to present you with our first 2020 edition of SpotOn+. As stated several times in this newsletter and elsewhere, the magnitude of the clinical benefit for proton therapy is probably higher in children than for adults' patients because the former young patients are more sensitive to radiation therapy and protons decrease substantially the integral dose delivered to cancer patients. In this edition, Lim et al. report on the outcome of children with Neuroblastoma treated with PBS. The interest of this paper recently published in the Br J Radiol is not so much for the clinical outcome of these children (2-year overall survival of 94%) but more for the motion mitigation technique (i.e. re-scanning) used at PSI to treat some of these children. This is the first report that details the clinical implementation of re-scanning and routine delivery of this interplay effect-mitigation strategy for those patients with target motion. We made a number of interesting observations. First, maximum organ motion was actually rather low. Second, the 4D dose calculation demonstrated that volumetric rescanning (vRSC) decreased the dose deterioration, which was admittedly minimal. We concluded that children with ‹5mm organ motion could be safely treated with PBS proton therapy without vRSC. The second article assesses another dose-corruption motion mitigation technique, namely breath-hold (BH) vs. high-frequency percussive ventilation (HFPV) for the potential treatment of lung cancer with PBS proton therapy. This study was conducted after IRB approval jointly by ETHZ and PSI on 19 health volunteers who underwent 1.5 T MRI imaging. Dr Emert quantified the intra-fractional changes, the method being detailed in this Newsletter, using aforementioned imaging modality. Importantly, BH provided substantially more vessels-positional stability than did HFPV. Also of note, most (75%) healthy volunteers preferred BH over HFPV. It remains to be demonstrated if lung cancer patients with impaired respiratory function will also prefer non-HFPV strategy for motion mitigation effect on dosimetry, but BH provided a safe and efficient method within the framework of this study to mitigate respiratory motion during proton therapy. Lastly, Dr Albertini details PSI's Daily adaptive proton therapy (DAPT) paradigm for patients with nasopharyngeal/nasal cavity/para-nasal sinus cancers. With 625 simulated CTs with artificially filled nasal cavity and setup errors, her team showed that the narrow filed plan with reduced margins, due to the application of DAPT, could decrease between roughly 50% the integral dose, when compared to standard 4 –field 'Star' plans, for these challenging head and neck cancer patients, with no target dose compromise. PSI demonstrated that not only DAPT was feasible but also brought a clear dosimetric benefit for these patients. Noteworthy, it is foreseen that DAPT will be applied to selected patients in Q3 2020.

That being said, I wish you a good/much-awaited Spring time in this Covid-19 stricken world. Please stay tuned for our next edition of our newsletter 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

Early clinical outcomes of patients with paediatric neuroblastoma treated with proton therapy including motion mitigation strategy

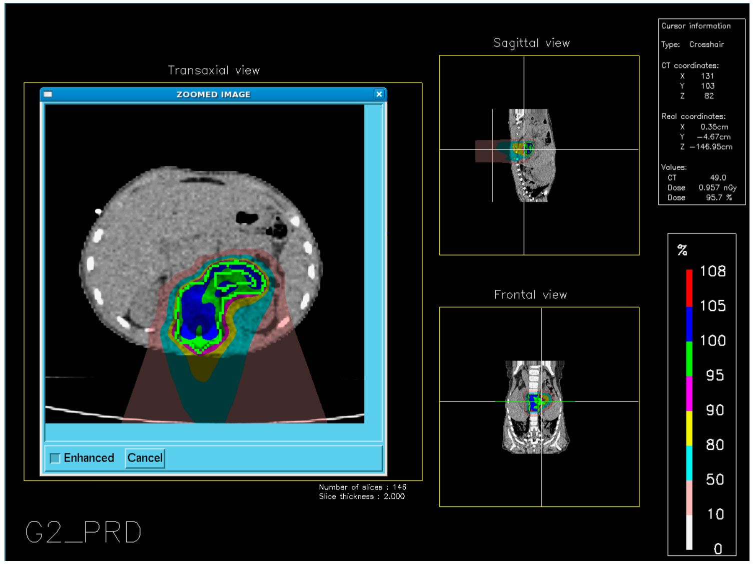


Figure: Beam arrangements and dosimetric plan for a 3.5year old boy presenting with a metastasized neuroblastoma of the adrenal gland.

Background

Neuroblastoma (NB) is the most common extracranial solid malignancy in children. The adrenal gland is a frequent primary site of this tumor and 90% of children are diagnosed under 5 years. Radiotherapy in the post-operative setting is important for loco-regional control, which impacts overall survival. Pencil-beam-scanning proton-beam-therapy (PBS-PT) is highly conformal but is prone to dose degradation from respiratory motion due to interplay effects. This effect is caused when the individual dynamic pencil beam spots are misplaced relative to the intended position due to motion, raising concerns on the safety and efficacy of PBS-PT. In this study, we report the outcomes of patients with NB treated with PBS-PT at PSI and describe our motion mitigation strategy using rescanning in a subgroup of our patients in the clinical setting.

Materials & Methods

Between March 2014 and April 2018, 19 children with histologically diagnosed NB (11 males/8 females) with intermediate-risk (n=3) and high-risk (n=16) were treated with PBS-PT. Anatomical sites of primary tumours were as follows: abdomen, n=5; adrenal, n=8; pelvis, n=2; thorax, n=3; head and neck, n=1. Median age at time of PBS-PT was 3.5 years (range, 1.2-8.6). Most children (89%) required general anaesthesia due to their young age. All patients except one (95%) received 21Gy(RBE). The other patient received 36Gy(RBE). All abdomen and pelvic tumours were planned with posterior or posterior oblique fields to avoid entry through bowel gas. Since August 2017, 4D treatment with volumetric rescanning (vRSC) was clinically available for use as our motion mitigation strategy. The vRSC technique treats the whole target volume (all energy layers) at each rescan. The number of rescans applied is guided by the magnitude of motion, respiration induced changes in heterogeneities, location and shape of target volume. 4D-dose calculations (4DDC) were carried out for clinical guidance when vRSC was new and for complex targets. Seven patients (37%) underwent a planning 4DCT scan for motion assessment and were treated with vRSC. Four anaesthetized children with ‹5mm motion had 4DDC to guide the number of vRSC in our cohort. The number of vRSC used were 2 (n=2), 4 (n=3) and 8 (n=2).

Results

With a median follow-up time of 14.9 months (range, 2.7-49.0), no local relapse was observed. The estimated 2-year distant-progression-free survival and overall survival is 76% and 94% respectively. PBS-PT was well tolerated and the acute Grade 2-4 toxicity rate was 11%. No late toxicities were observed. The mean result of maximum organ motion was largest in the cranial-caudal direction (3.2mm; range 1.9-5.9), followed by 1.2mm (range 1.0-1.6) in the left-right direction and 1.0mm (range 0.7-1.3) in the anterior-posterior direction. The mean deterioration or improvement of 4DDC plan compared with the 3D nominal plan for PTV-V95 were: 4DDC with no vRSC, -0.6%; 2 vRSC +0.3%; 4 vRSC +0.3% and 8 vRSC + 0.1%. Magnitude of dose degradation was minimal, with the largest observed deterioration of -1.9%. Dose deteriorations generally recovered to baseline with 2-4 vRSC application.

Discussion & Conclusions

This is the first series reporting the outcomes of paediatric patients with NB treated with PBS-PT and using vRSC in a subset of patients for motion mitigation. Excellent early outcomes are demonstrated with safe use of vRSC in the paediatric population. Children with ‹5mm organ movement undergoing PT for neuroblastoma located within the abdomen may not require rescanning as the interplay effects are minimal. The benefits of rescanning should therefore be carefully balanced with the disadvantages of increased treatment time.

This work was presented at the 51st Congress of the International Society of Paediatric Oncology (SIOP), Lyon in October 2019. The full paper has recently been published at Clinical Oncology (Lim PS et al.).

Medical-Physics News

Assessment of two different respiratory motion mitigation techniques for lung cancer treatment with pencil beam scanning proton therapy using MRI

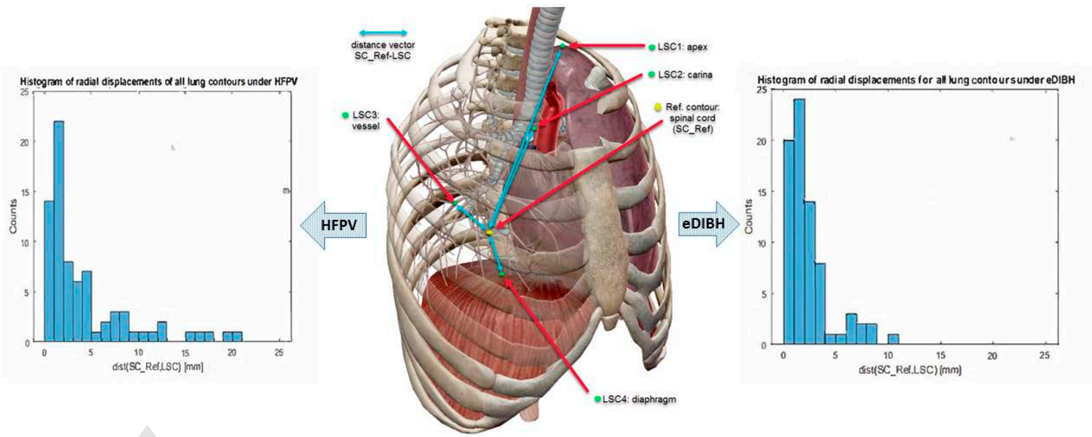
Introduction

Since 1996, proton therapy has been applied very successfully at the Paul Scherrer Institute to irradiate deep-seated, stationary tumors. In order to treat tumors, which move due to breathing, lung motion mitigation strategies are of critical importance and need to be implemented to ensure the precise irradiation of the moving target. Therefore, two motion-suppression techniques during apnoea were investigated in a clinical pilot trial (NCT03669341) with healthy volunteers: deep inspiration breath-hold enhanced via prior combined O2-hyperventilation (eDIBH) in comparison to high-frequency percussive ventilation (HFPV).

Main study objectives were applicability, effectiveness and reproducibility using MR imaging, and subject acceptance. The entire project was realized as a research collaboration between the Center for Proton Therapy at PSI and the Exercise Physiology Lab of the Institute of Human Movement and Sports at ETH Zurich.

Materials and Methods

Each of 19 healthy volunteers [58% men, age: (mean 48.5 ± stddev 5.0) years; BMI: (24.6 ± 3.3) kg/m2] performed two 1.5T MRI scans during four sessions at weekly intervals using both eDIBH and HFPV, accompanied by daily, home-based breath-hold training over a 3-week period. Each of the sessions begun with spirometrical and breath-hold duration measurements to document the physiological development of the participants. To quantify intra-fractional changes by MRI analysis, a lung-distance-metric was defined, consisting of one spatially invariant reference point (spinal cord) and four lung structure contours (LSC) with different breathing variabilities [apex, carina, vessel (as virtual tumor at varying locations), diaphragm] [Figure1]. Method acceptance rating [scale: 0-10 = positive-negative] and method preference by the participants were also evaluated.



Figur 1: Lung structure metric: reference and lung structure contours (spinal cord; LSCs: apex, carina, vessel; diaphragm) [mid] Histogram of maximum, radial displacements of all lung structure contours Δmax(LSC) under **HFPV** [left] and under **eDIBH** [right] for all subjects; LSC3 (vessel) represents a potential tumor and varies its location between subjects.

Results

Subjects achieved a breath-hold (BH) duration after completed training of (207±68) sec (max.: 423sec). This statistically significant increase over sessions ($p < 0.003$), especially between 1st and 3rd, stabilizes after 2-3 weeks, whereby the minimum time to reach the maximum BH duration takes about 7-10 days. The lung capacities reached after application of eDIBH and HFPV, which were derived from MRI imaging, using an in-house developed automated lung segmentation algorithm, stayed constant over BH training with no significant effect over sessions. With vessel locations, representing potential tumor locations, distributed over 6 out of 8 lung segments their largest absolute variation reached 3.4mm (eDIBH) compared to 13.1mm (HFPV). Therefore, eDIBH provided a four-times better positional stability of vessels and a twice better positional stability of diaphragm contours compared to HFPV. Around 80% of the subjects showed a significantly better intra-fractional lung motion mitigation under reproducible conditions with eDIBH. The ratings for the method acceptance by the subjects favored eDIBH (eDIBH: 1.1±0.9, HFPV: 2.2±2.3; breath-hold training: 2.2±2.1). Around 75% of the subjects preferred eDIBH to HFPV.

Conclusions

Although both methods were applicable and tolerated, our data suggest that eDIBH clearly outperforms HFPV in all investigated objectives. The technique provides an easy-to-handle, well-accepted, safe, effective, and efficient suppression of respiratory motion during proton therapy. Projecting the increase in breath-hold duration by eDIBH to patients, it appears realistic to treat lung tumors with a single eDIBH per irradiation field in Gantry2@CPT/PSI. This would allow the application of simplified 4D treatment strategies under 3D-like conditions. The clinical implementation of the eDIBH approach is foreseen in the near future.

This work has been presented at various international meetings, i. a. at the annual conference of the Particle Therapy Co-Operative Group (PTCOG) last year in Manchester. A full publication is in preparation.

For any further information, please refer to CPT

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Medical-Physics News

Daily Adaptive Proton Therapy enables dose reduction to normal tissue

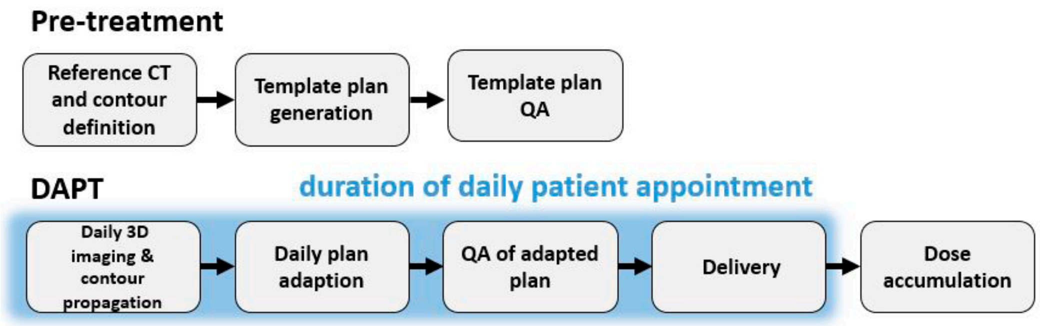

Figure 1: The DAPT workflow that will be implemented at PSI.

Patients with tumors involving the nasopharyngeal region can benefit from spot scanning proton therapy, as the tumor can be covered while high dose gradients allow the sparing of the organs at risk (OARs), in particular the optical structures and brainstem. However, if the patient anatomy along the proton beam changes, the resulting delivered dose is distorted. A fast plan adaption can mitigate these dose degradation resulting from anatomical changes.

The importance of plan adaptation is widely recognized. Therefore, at PSI we are implementing a daily adaptive proton therapy (DAPT) workflow. A scheme of this workflow is shown in Fig. 1. Before the treatment, a planning CT is acquired, structures are defined, and a template plan is optimized and checked with the standard clinical and physical QA. Each day, a low-dose CT is acquired with the CT-on rail while the patient is already in treatment position. Structures are propagated and a full re-optimization is done on the daily anatomy based on the template plan. After a fast clinical and automatized physical QA, the daily plan is delivered to the patient. After the delivery, the patient leaves the treatment room and the dose is reconstructed on the daily image using the delivery information from the machine logfile. In our first experiments, the time-span between the end of the daily CT acquisition and the start of the delivery was below 10 minutes. To reduce the need of correcting the daily structures, the DAPT workflow will be used firstly for patients treated in the upper part of the head (e.g. in the nasopharyngeal region), where the nasal cavities filling can change daily, where a rigid structure propagation is expected to be sufficient for most of the patients.

DAPT offers several benefits for these patients. Firstly, the patient can be treated with the plan optimized on the daily anatomy, thus improving the accuracy of the delivered dose. Secondly, the daily misalignments are included in the optimization process, so the margins of the planning target volume can be reduced. Finally, the DAPT approach allows the use of innovative, anterior field arrangements (Fig. 2). Such a field arrangement, although useful to reduce the dose to the normal tissue, is typically avoided, because the nasal cavity filling might change from day to day, resulting in a deterioration of the delivered dose. This is of course irrelevant if the plan is optimized on the daily anatomy. Therefore, DAPT combined with an adequate margin reduction and innovative field arrangements is a valid strategy to improve the dose conformity to the tumor and reduce the dose to the normal tissue. The plan optimized with the standard field arrangement and margin reduction (Fig. 2b) resulted in a normal tissue integral dose reduction of 26% in comparison to the standard optimized plan (Fig. 2a). The combination of smaller margin and the anterior field approach (Fig. 2c) resulted even in an integral dose reduction of 49%.

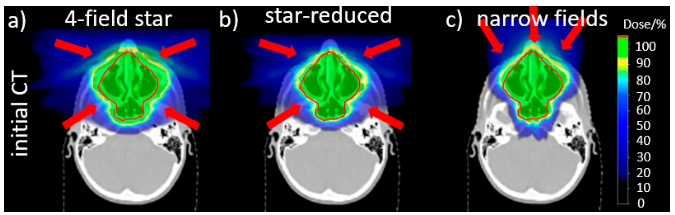

Figure 2: The clinical standard 4-field star plan (a), the star plan with reduced margins (b) and the narrow field plan with reduced margins (c) of one example patient. Red arrows show the field directions.

These results were confirmed by a planning study including 5 patients with up to 625 simulated CTs each, with artificially filled nasal cavities and simulated setup error. Evaluating all 5 patients, the innovative field approach reduced the integral dose to healthy tissue of the initial plan between 29% and 56%. Also, doses to OARs that did not overlap with the CTV could be reduced. For both field arrangements, CTV V95 of the simulated treatments were severely decreased without adaption (up to -34%) but could be restored with DAPT.

In conclusion, we could show that DAPT is feasible without prolonging treatment time and brings a clear dosimetric benefit for patients treated in the nasopharyngeal region.

Results of this project were published recently (Albertini et al.; Matter et al.; Nenoff et al.).

Imprint

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