PAUL SCHERRER INSTITUT

PSI

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #9_8/2016

Dear Colleagues

This summer's edition of our SpotOn+ Newsletter is dedicated to children treated with proton therapy. Children are exquisitely sensitive to radiation therapy, possibly by a factor of at least 10 when compared to adults, as the survivors of the atomic bomb or other nuclear accidents, for that matter, have undisputedly shown. As such, it is of paramount importance to decrease the integral dose as much as reasonably possible in these young patients. This is best achieved with protons, as there is virtually no 'exit' dose with proton therapy in contrast to any photon radiotherapy technique. Protons have the advantages of being often more conformal (the full dose deposition occurs in a modulated narrow zone called the Bragg Peak) and, simultaneously, homogeneous in comparison to conventional radiotherapy. Additionally, protons can be scanned through the tumor volume (i.e. pencil beam scanning or PBS), as advocated and pioneered by PSI 20 years ago. This active delivery paradigm permits both spatial refinement in dose deposition and a decrease in neutrons delivered to the patient (approximately 20 times fewer), when compared to passive-delivery proton therapy. Moreover, many juvenile cancer patients present a germline mutation that may confer susceptibility to a feared long-term side effect of radiation therapy, namely radiation-induced cancers. PSI's experience with PBS proton therapy is detailed in this issue by Dr D. Leiser in the framework of an active collaboration with Inselspital Bern. Over 80 children with rhabdomyosarcoma have been treated successfully at PSI with a 5-year local control rate of 79%. This issue also contains the plan robustness evaluation for the treatment of children with ependymoma. Finally, Dr M. Frei-Welte explains how anaesthesia is routinely performed at PSI, with a complication rate of less than 0.1% reported in the literature. Anaesthesia of young children on the PSI campus is only possible due to the active collaboration with the Children's Hospital Zürich (Kispi). To date, over 250 children have been successfully sedated in Villigen. Considering the published success rate observed in our paediatric cohort and the dosimetric advantages of protons, should every Swiss child with cancer be treated with proton therapy? Probably not. It is my belief, however, that protons should be considered for each paediatric case in a multi-disciplinary tumor board evaluation (MDTB). Failing to do so would result in suboptimal radiation treatments for some of these children. As health professionals and care givers, we owe it to our patients to provide the best possible therapeutic strategy. Unfortunately, MDTB discussions rarely consider proton therapy which, understandably, puzzles the pediatric medical oncologists managing these children. PSI is in the process of creating agreements with the Children's Hospitals of Zurich and Bern. This is a tedious but unavoidable administrative process aimed at optimizing collaboration between centers. For obvious reasons such agreements cannot be negotiated with all 10 SPOG Centers. An alternative solution is our weekly Virtual Tumor Board (info @ protonentherapie@psi.ch), during which every physician can present a case. It is disquieting to see that the proportion of children treated with protons at PSI has steadily decreased over time: in 2010 and 2015, the children/adults ratio was 0.45 and 0.26, respectively. This substantial decrease in ratio in Switzerland is in complete contrast of what is happening in countries such as the US or within the EU. In the US, a proton center dedicated exclusively to children was recently inaugurated in Memphis, TN. I will finish this editorial by quoting Hermann Suit who stated that 'there is no medical reason to irradiate healthy tissues'. This quote will hopefully reap some interest from radiation oncologists managing children with cancer.

Yours sincerely,

Prof. Damien Charles Weber, Chairman of CPT

General

Paediatric Anaesthesia at the Center for Proton Therapy (CPT) at PSI, Villigen

A cooperation exists between the Center for Proton Therapy (CPT) at PSI and the Children's Hospital Zürich, Department of Anaesthesia since 2004 (lead anaesthetist: Dr. Martina Frei-Welte), to facilitate treating young children under deep sedation / anaesthesia.

By the end of April 2016 a total number of 251 children aged 0.84 to 9.29 years (mean 3.55 years) have undergone proton radiation therapy (PT) under deep sedation.

The anaesthesia facility is integrated in the Center for Proton Therapy, with a dedicated waiting room for children, the anaesthesia induction and emergence room and a 3-bed recovery room.

Anaesthesia is carefully induced, using Midazolam and Propofol to maintain spontaneous respiration. During positioning and control scans, as well as during transportation and during PT, anaesthesia is maintained by continuous infusion of Propofol. Propofol is a short acting hypnotic that allows quick adjustment to the sedation requirements of the child and fast recovery after cessation of Propofol infusion. Vital sign monitoring consists of intermittent, non-invasive blood pressure measurement, ECG and pulse oximetry. The nasal prongs for oxygen application also allows measurement of exhaled CO_2, the most important means by which the quality of spontaneous breathing is measured.

A child being prepared for induction of sedation.

Before induction of anaesthesia, a child must have been fasting; i.e. a last light meal four hours and last drink of clear fluid two hours prior to sedation. This minimizes the risk of pulmonary aspiration of gastric contents. Daily fasting is one of the major worries for these children, as most of them are already in a reduced physical condition and additional weight loss in the course of radiotherapy must be avoided. Scheduling them at the same time every day helps the families to organize an acceptable feeding rhythm.

Parents and other family members (even siblings) are allowed to accompany the child during induction of anaesthesia. All children are supplied with a long-term central venous catheter, either a Port-a-Cath or a Broviac/Hickman catheter, through which intravenous anesthetics are administered. Daily use of the central venous catheter increases the risk of infection and therefore requires highly sterile manipulation techniques. Under our strict regime, no increased infection rate has thus far been observed.

Anaesthesized child in treatment position, fixed with bite-block to the table.

Since 2011 we counted 8 central venous catheter infections in 130 children affording antibiotic therapy and/or catheter removal. There was no implication on proton radiation therapy.

Potential complications of deep sedation/anaesthesia during PT are airway related problems, such as obstruction, bronchospasm, laryngospasm, apnea, especially if the child has a concurrent respiratory infection. The anaesthesia team is well trained in handling these problems by mask ventilation, suctioning, inhalation, insertion of an oropharyngeal or nasopharyngeal airway.

In a retrospective review of 9'328 anaesthesia records for children undergoing proton radiation therapy under deep sedation with Propofol and spontaneous respiration Owusu-Agyemang et al found a complication rate of 0.05 % [1]. A retrospective analysis of the anaesthesia records at PSI is in progress.

In the recovery room children are monitored by pulse oximetry until fully awake. Parents support the anaesthesia team by caring for their conscious but sleepy child in the recovery room. As soon as the children are fully awake they are allowed to eat and drink and/or leave for home.

Reference: [1] Owusu-Agyemang P et al. *Non-invasive anesthesia for children undergoing proton radiation therapy.* 10.1016/j.radonc.2014.01.016

Radio-Oncology News

Clinical Outcomes of Children with Rhabdomyosarcoma treated with Pencil Beam Scanning Proton Therapy

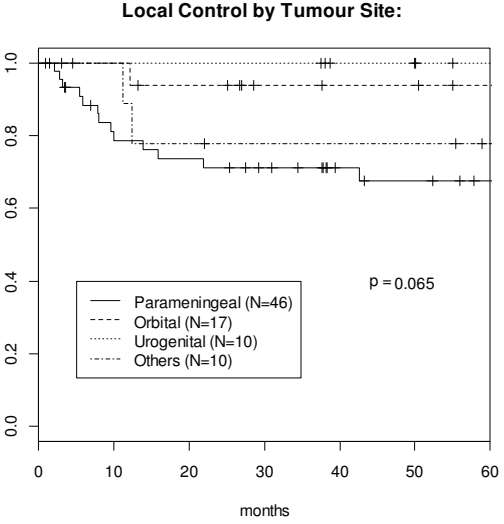
Introduction: Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children accounting for approximately 4.5 % of all pediatric cancers. Epidemiologically, a bimodal age distribution can be observed, with a peak between 2 and 6 years and subsequently 10 and 18 years of age. Children with RMS are treated with a combination of surgery, chemotherapy and radiation therapy. Proton therapy (PT) delivers no exit dose to the patient when compared to photon techniques and thus decrease the integral dose delivered to the child, potentially decreasing long term radiation-induced adverse events. The purpose of this study is to evaluate the clinical outcomes of children with RMS treated with pencil beam scanning PT at PSI and to assess the Quality of Life (QoL) of these patients. Moreover, prognostic factors for tumor control were evaluated in the cohort of patients.

Methods and Materials: Eighty-three RMS (embryonal, *n*=74; 89 %) patients treated from January 2000 to December 2014 were eligible for analysis. Median age was 4.5 years (range, 0.8-15.5). All children received systemic chemotherapy according to prospective protocols. Patients had low- intermediate- and high-risk disease in 24 %, 63 % and 13 % of cases, respectively. Median total dose delivered was 54 Gy(RBE). The median number of fractions was 30. Dose per fraction was 1.8 Gy(RBE) for 74 patients (89 %) and 2 Gy(RBE) per fraction for 9 (11 %) other patients. Health-related QoL was evaluated by the parents using the well established PedQoL questionnaire up to 3 years after PT. It is a multidimensional instrument covering 8 domains (self-esteem, emotional functioning, body image, cognition, physical functioning, peers and family social functioning and subjective well-being).

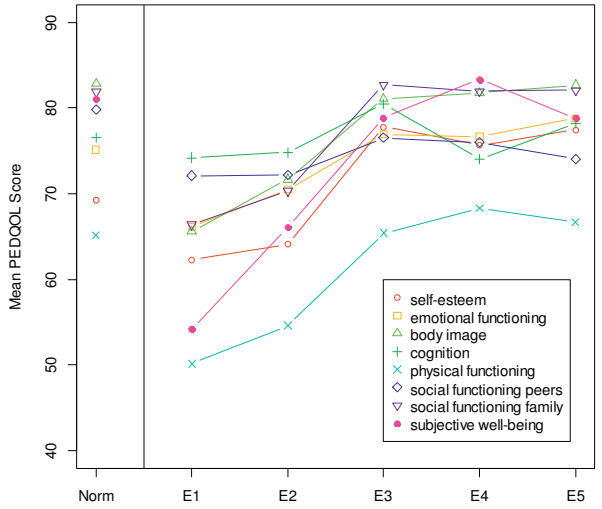
Results: PT was well tolerated and no treatment interruption was observed. No acute grade › 3 toxicity was observed. After a median follow-up time of 55.5 months (range, 0.9–126.3) the cumulative incidence of local failure was 16 (19 %). Fourteen (88 %) patients presented with in-field local failures and two (12 %) others presented with marginal local failures. Four patients (25 %) presented with distant failures associated with local failures. No distant only failures were observed. The 5-year local control rate was 78.5 % (CI95 %: 69.5–88.5 %). The estimated local control rates were 67.5 %, 93.8 %, 100 %, and 77.8 % for the parameningial RMS, orbital RMS, urogenital RMS and other RMS subgroup, respectively (p=0.065, Figure 1). Significant predictors for local failure were Group/Stage, tumor location and size. Fourteen patients (16 %) died, all of tumor progression. The 5-year overall survival was 80.6 % (CI95 %: 71.8–90.0). The 5-year incidence of grade 3 toxicity for ocular and non-ocular was 18.4% (CI95 %: 9–29%) and 3.6 % (CI95%: 1–12 %), respectively. Of note, all grade › 3 late toxicity was experienced in patients with tumor recurrence. One patient presented with a radiation-induced malignancy. In the QoL analyses parents rated the QoL of their children lower than the norm group at the start of proton therapy (E1). The rating improved after two months after end of PT (E2). Two years after end of PT (E4) all but 3 domains reached higher or normative level. The improving is more pronounced within the first year after PT and then reaches a plateau.

This evaluation was done in a cooperation between Inselspital Bern and PSI by a resident staying one year at PSI. The results were recently published (Leiser et al. 2016) and will be presented at the 58th annual meeting of the American Society for Radiotherapy and Oncology (ASTRO) end of September in Boston.

Reference: Leiser et al. *Tumor control and Quality of Life in Children with Rhabdomyosarcoma treated with pencil beam scanning Proton therapy* 10.1016/j.radonc.2016.05.013



Local tumour control as a function of tumour site. The p-value of 0.065 was calculated using a long-rank tet.



QoL Scores over time compared to a norm population. Higher scores mean better QoL. Time points: E1=baseline before PT; E2=2 months after PT; E3=one year after PT; E4=two years after PT; E5=three years after PT.

Medical-Physics News

Different margin concepts for paediatric Ependymoma patients – analysis of plan robustness for pencil beam scanned proton therapy

Paediatric treatments are one of the best indications for proton therapy due to the reduction in integral dose for the healthy tissue. For those patients the margins are dictated by variation in daily setup and range uncertainties. Margins reduction could improve the healthy tissue sparing and this could potentially be achieved with new treatment planning opportunities, improved delivery accuracy and the use of robust optimisation to decrease organs at risk (OAR) doses while assuring good and robust target coverage.

In this study we evaluated the robust planning for eight paediatric Ependymoma patients treated with pencil beam spot scanning proton therapy up to 59.4 GyRBE (four series treatment). PTV was defined as a 5 mm isotropic expansion of the CTV. Additionally two different PTVs were defined: one with reduced margins (isotropic CTV expansion of 2 mm) and one with beam specific margins (BSM) of 2 mm and additional 3 mm distally (see figure 1); robust optimisation option (minmax optimisation) was tested as well.

All the treatment plans were generated in RayStation 4.8.102 (RaySearch Laboratories, Sweden), and they were all optimised using three fields approach from posterior/cranial directions. The dose was computed for all the series (dose levels of 30.6 GyRBE, 50.4 GyRBE, 54 GyRBE and total dose of 59.4 GyRBE) with the single field optimisation option, and with robustness optimisation considering 2 mm set-up and ±3.5% range errors. This optimisation was performed in two ways: i) on CTV only and ii) on CTV, brainstem and chiasma. The results were evaluated considering PTV coverage, described by $D_{2\%}$, $D_{98\%}$, D_{median}, mean dose to the body (healthy tissue) and $D_{2\%}$ for brainstem, chiasm and other OARs depending on their relative position to the CTV.

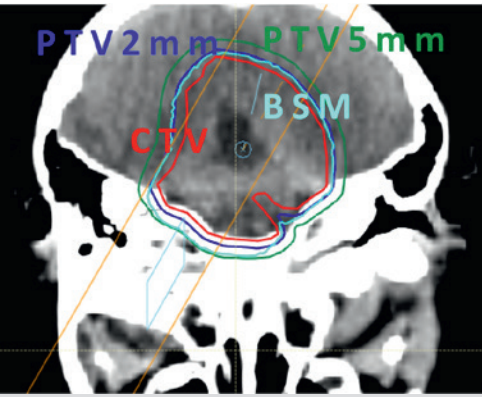


Figure 1: Visualisation of different margin concepts for patient1.

In Figure 2 and 3, you can see dose distributions and dose volume histograms for the plans optimised with the different margin concepts for one representative patient. CTV coverage is preserved very well for all the cases while the lowest dose to critical organs is reached with robust optimisation only for the targets. BSM, 2 mm isotropic margins and robust optimisation considering both target and OARs present with similar DVHs.

If we focus on the 2nd series plan (from 30.6 GyRBE till 50.4 GyRBE), the CTV coverage is very good as described by those dosimetric parameters: CTV_{D50} = 30.6 GyRBE, CTV_{D2} ‹107% of D_{pres} and CTV_{D98}›95% of Dpres. Those were achieved for all margin concepts, and none of these values was disturbed by any perturbations. Main advantages were found for the OARs such as the chiasm , where the $D_{2\%}$ values were reduced, compared to the 5 mm margins, by 17.4%, 12.8% and 39.7% for 2 mm, BSM and robust optimisation, respectively. Robust optimisation and small margins of 2 mm resulted in a reduction of the mean dose to the brainstem. Shifts in cranio-caudal and anterior-posterior directions caused biggest dose perturbations.

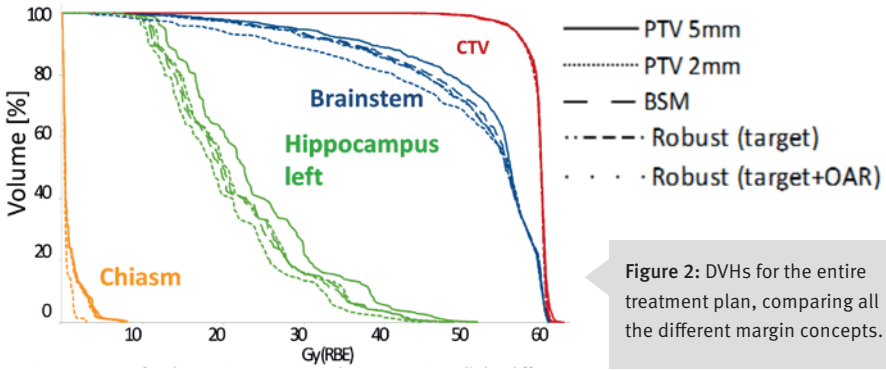


Figure 2: DVHs for the entire treatment plan, comparing all the different margin concepts.

The results of this work show that treatment plans were robust against set-up and range errors independently of the margin concept. Margins of 2 mm are sufficient to guarantee a good CTV coverage, while the dose to selected OARs can be reduced applying robust optimisation.

The use of robust optimisation requires a careful inclusion of relevant OARs to guarantee the robustness of the treatment plan not only for the target but also for the adjacent tissue. Robust analysis on a voxel by voxel basis will be included to eliminate the fractionation effect.

This work was performed by a guest scientist under PSI staff supervision. The results were presented at the 55th annual conference of the particle therapy co-operative group (PTCOG) end of May in Prague.

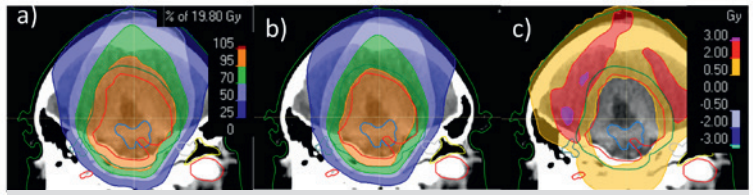


Figure 3: Dose distributions for 2nd series plan for a representative patient
a) 5 mm isotropic margin, b) robust optimization for CTV, brainstem and chiasm, c) dose-difference map.

Imprint

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