PAUL SCHERRER INSTITUT PSI

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #13_12/2017

Dear Reader,

it is my distinct pleasure to present you with our latest issue and last 2017 edition of SpotOn+. I would like to take the opportunity of this newsletter to inform you that after the elective shutdown of our cyclotron this summer we have resumed our full clinical patient throughput. In this edition, we report the assessment of the prevalence rate of brain necrosis in children treated for a brain tumor at PSI. As you know, the brain necrosis-issue has been looming in the radiation Oncology for quite some time. We decided late 2016 to analyze our results in children treated with PBS protons. This is a large cohort (170+ patients) composed of young to very young patients (median age, 3.3 years) treated with PBS protons. This joint Inselspital/PSI assessment was made scrupulously with a neuro-radiologist looking for brain necrosis (BN) and/or white matter changers, regardless if the patient was symptomatic or not. Roughly 60% of BN were asymptomatic and identified only on routine MRI scans. All save one were observed within a 2 years period. Interestingly, ependymoma histology was a risk factor, among others, for this radiation-induced complication. It is fair to say, that we observed a low prevalence of symptomatic BN and these data are in line with other modern photon series. The second article describes the remarkable radiological (see figure) and clinical response observed in a patient with advanced sacral chordoma treated both with hyperthermia (delivered at KSA, Aarau) and proton therapy. PSI and KSA have engaged in a fruitful clinical collaboration and these two institutions are currently piloting a prospective protocol for non-resectabale sarcoma (STS). Proton therapy was delivered with a SIB paradigm. We have treated four additional patients and the (very) initial results seem promising. As such, we are considering launching a clinical protocol with possibly the active international collaboration with the Sarcoma Unit of University College London Hospital, UK. One clinical observation of paramount importance during the treatment of these challenging patients was the importance of pain control during and immediately after the combined therapeutic modalities. Last but not least, treatment time is of critical importance in photon and proton therapy alike. Shortening radiation delivery times, by reducing the number of proton spots (i.e. pencil beams) while maintaining dosimetric plan quality may present a number of advantage, including but not limited to patient comfort, intra-fractional patient motion, shorter anesthesia duration for sedated children and patient throughput to name a few. In this issue, Francesca Belosi reports the results of a joint study performed with the Erasmus MC Cancer Institute, Rotterdam, Netherlands by Steven van den Water, PhD. The investigators looked at a planning of a sino-nasal malignancy with both a standard and a reduced number of spots. For the spot-reduced plan, the number of spots was minimized using the 'pencil beam resampling' technique as described in the article. Interestingly, the number of spots could be reduced from 26,069 in the clinical plan to 1,540 in the spot-reduced plan, a roughly 95% decrease with no plan corruption. Moreover, the spot-reduced plan was found to be clinically deliverable and importantly the delivery time per field was shortened on average from 56 s to 20 s (i.e. 65% reduction in delivery time). Interestingly, the spot-re¬duced plan was less sensitive to rigid setup and range errors, with a target mean dose reduction of < 0.5% in the worst case scenario, compared to a > 2.0% reduction for the standard spot plan. These results are interesting but should be confirmed by other simulations. Definitively, delivering non-standard spot plans may be clinically advisable. With this last controversial report, I would like to take the opportunity to wish you all a very merry 'Xmas and happy new year for 2018.

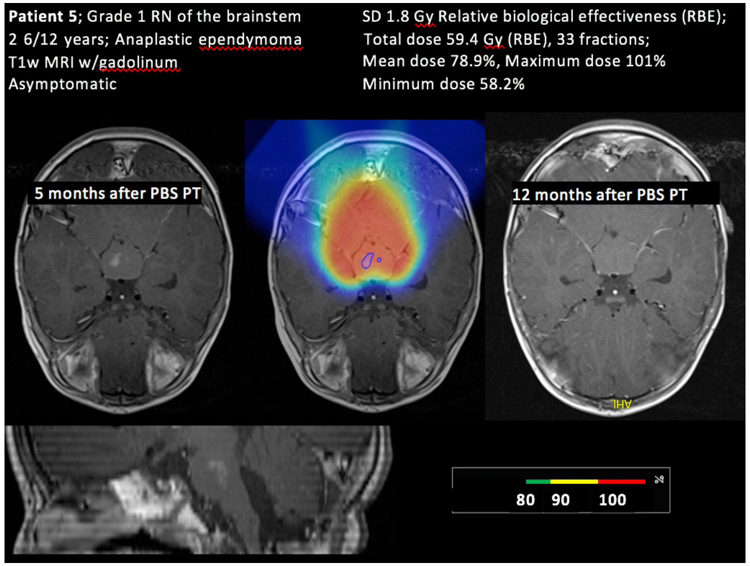
Yours sincerely,

Prof. Dr.med. Damien Charles Weber

Chairman of CPT, Paul Scherrer Institute

Radio-Oncology News

Pediatric Patients with Brain Tumors treated with Pencil Beam Scanning Proton Therapy: complications of brain necrosis and whiter matter lesions



Introduction

Successful treatment of brain tumors in children often requires an interdisciplinary strategy. In addition to surgery, chemotherapy and radiotherapy are essential pillars in the overall concept. Compared with conventional (photon) radiotherapy, proton therapy (PT) offers the physical advantages of a reduced entrance dose, the absence of an exit dose and thereby provides a highly conformal dose distribution in the target volume, and a reduced radiation dose to adjacent healthy tissue. These advantages of protons over photons led to an increased use of PT in pediatric brain tumors. Parenchymal brain alterations such as radiation necrosis (RN) or white matter lesions (WML) are feared complications occurring after radiotherapy. Usually this is treated with steroids, but more recent data suggests that anti-VEGF agents such as bevacizumab may also be effective since it was established that RN might be mediated either by an ischemic response or oligodendrocyte damage, while white matter lesions (WML) might be the result of the radiation-induced inflammation, causing progenitor cells to differentiate into glial cells instead of neurons. Although histopathology can be used to establish a diagnosis of RN or WML, more commonly a clinicoradiologic diagnosis of radiation necrosis is used to avoid surgical morbidity and potential complications. Some authors have reported a very low prevalence of RN (0.6 %) after PT, whilst others have reported a high rate (43%) of this feared complication. This might be related to mostly non-specific imaging techniques or differences in clinical terminology leading to varying estimates of toxicities caused by treatment induced brain lesions. However, limited data exist regarding RN or WMLs after PT in pediatric patients. Further investigation of MRI-parenchymal brain alterations in pediatric patients with a brain tumor is required to understand the incidence, timing, clinical significance and risk factors of RN and WMLs in children treated with PT. As such, the purpose of this study was to assess the rate of RN and WMLs in a cohort of brain tumor children treated with pencil beam scanning (PBS) PT.

Materials and Methods

Between 1999 and 2015, 171 pediatric patients (<18 years) were treated with PBS PT. Median age at diagnosis was 3.3 years (range, 0.3-17.0) and the median delivered dose was 54 Gy (RBE) (range, 40–74.1). Radiation necrosis and WML were defined as a new area of abnormal signal intensity on T2-weighted images or increased signal intensity on T2-weighted images, and contrast enhancement on T1 occurring in the brain parenchyma included in the radiation treatment field, which did not demonstrate any abnormality before PT. Radiation necrosis and WML were graded according to the Common Terminology Criteria for Adverse Events. The median follow-up period for the surviving patients was 49.8 months (range, 5.9-194.7).

Results

Twenty-nine (17%) patients developed RN at a median time of 5 months (range, 1-26), most of them (n=17; 59%) being asymptomatic (grade 1). Grade 2, 4 and 5 toxicities occurred in 8, 2 and 2 patients, respectively. Eighteen (11%) patients developed WML at a median time of 14.5 months (range, 2-62), most of them (n=13; 72%) being asymptomatic (grade 1). WML Grade 2 and 3 toxicities occurred in 4 and 1 patients, respectively. The 5-year RN-free and WML-free survival was 83% and 87%, respectively. In univariate analysis, neo-adjuvant (p=0.025) or any (p=0.03) chemotherapy, hydrocephalus before PT (p=0.035), and ependymoma (p=0.026) histology were significant predictors of RN.

Conclusions

Children treated with PT demonstrated a low prevalence of symptomatic RN (7%) or WML (3%) compared to similar cohorts treated with either proton or photon radiation therapy. Pre-PT chemotherapy or any chemotherapy administration, ependymomal tumors and hydrocephalus as an initial symptom were significant risk factors associated with RN.

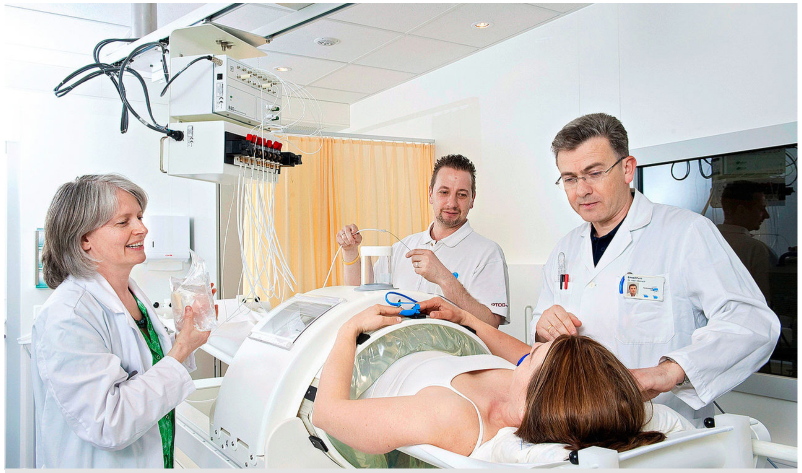
This evaluation was done in a cooperation between Inselspital Bern and PSI by a resident staying one year at PSI. The results were presented this year at the SIOP-conference in Washington and will be published soon.

Reference

Bojaxhiu et al. Radiation Necrosis and White Matter Lesions in Pediatric Patients with Brain Tumors treated with Pencil Beam Scanning Proton Therapy. Int J Rad Onc Biol Phys (accepted for publication)

Radio-Oncology News

Combination of proton therapy and hyperthermia in selected tumor types show promising results



Hyperthermia unit in the radiation oncology department at Kantonsspital Aarau. Preparation of a treatment session by the team (left to right): N.Lomax, O. Timm, Dr. E. Puric

The combination of hyperthermia with radiation therapy has led to higher response rates in different tumor types as sarcomas, cervical cancer, breast cancer, rectal cancer, melanomas or bladder cancer. In Switzerland there are only few institutions offering hyperthermia therapy, the largest of them is the radiation oncology department of Kantonsspital Aarau (head: Prof. Stephan Bodis).

The Center for Proton Therapy CPT at PSI has a close collaboration with KSA, among others in the framework of a prospective phase I/II clinical trial (HYPROSAR-study, NCT01904565) on the treatment of soft tissue sarcomas. Sarcomas arise often in the soft tissue of the extremities or the trunk. A resection would lead either to an amputation or a very mutilating disfigurement and often it is not possible to remove the whole tumor especially in the area of the trunk. The alternative treatment is radiation therapy. But the applicable dose with conventional radiation therapy is often limited due to the delicate localisations of the tumors surrounded by sensitive healthy organs. The beneficial physical behaviors of protons compared with photons that are used in conventional radiation therapy allow delivering higher doses in the tumor area without overdosing the surrounding organs at risk. The synergy of proton therapy with hyperthermia leads to maximal tumor-cytotoxic effect in the cancer. Hyperthermia for deep seated tumors is generated by the exposure to electromagnetic waves in form of microwaves. It is applied via regional deep hyperthermia and heats up the tumor tissue to temperatures in the range of 41.5-42.5°C. Hyperthermia at these temperatures enhances the radiation induced damage in the tumor cell. This thermal sensitizing effects increase on one hand the sensitivity of hypoxic, nutritionally deficient tumor cells in low pH, on the other hand it inhibits the radiation induced DNA damage repair capacity of the tumor cells.

Based on the experience with the HYPROSAR-study the use of proton therapy with hyperthermia was introduced in clinical practice for selected large inoperable sacral chordomas which usually show unsatisfactory local tumor control rates even when treated with high dose proton therapy. Up to now 5 patients were treated within a preliminary feasibility treatment protocol. Proton therapy was delivered in a simultaneous boost treatment concept, meaning that the macroscopic gross tumor received a higher total dose than the surrounding area with microscopic spread in the same number of treatment sessions. This leads to a hypofractionated irradiation of the gross tumor with higher single fraction dose, which especially in radio-resistant tumors show additional positive effect. With this concept the treatment lasts 5 ½ weeks with 5 treatment sessions per week. Hyperthermia is given once a week before or after proton therapy. Early results in these patients are encouraging with no higher grade acute and late toxicities. Early follow-up imaging showed either slight regression or stable tumor situation. Initial clinical pretreatment symptoms showed clear decrease during follow up in all patients. The implementation of a clinical trial protocol is currently under discussion.

These early results on sacral chordomas have been submitted to the annual meeting 2018 of the European Society for Radiotherapy&Oncology (ESTRO) next spring in Barcelona, Spain.

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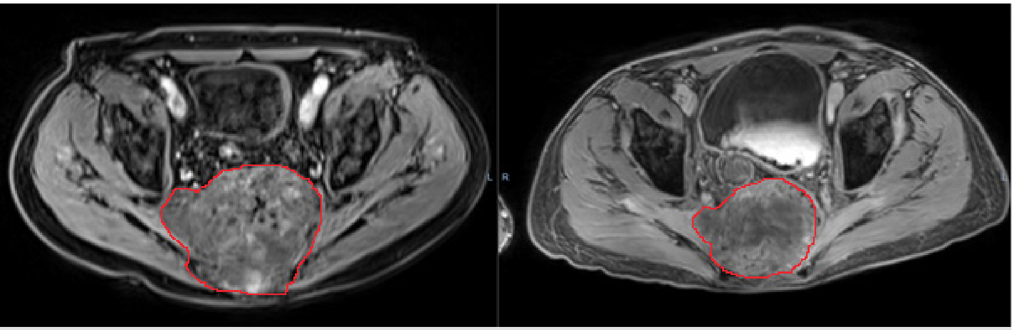

MRI's of the pelvis of a 73 year old patient with a sacral chordoma. MRI before (left image) and 9 months after combined hyperthermia and proton therapy (right image) showing a clear decrease of tumor size.

Medical-Physics News

Reduced spot numbers for PBS proton therapy shortens delivery time without dosimetric plan compromise.

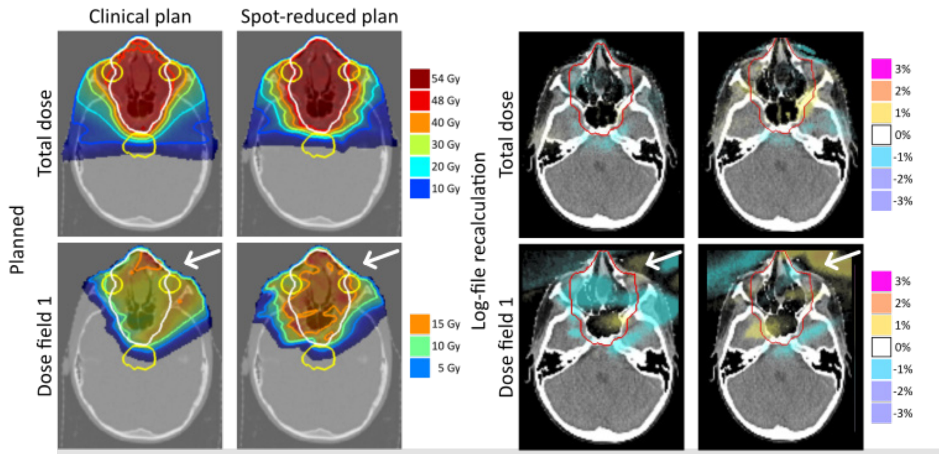

Figure 1: Planned dose distributions and log-file recalculations (delivered-planned) for the total dose and the dose of field 1 for the clinical plan (left hand-side) and the spot-reduced plan (right-hand side).

Purpose

The degeneracy of spot-scanned proton therapy treatment plans can be exploited to shorten delivery times, by reducing the number of proton spots (i.e. pencil beams) while maintaining dosimetric plan quality. Because a strongly reduced number of spots can potentially affect the treatment delivery, we performed an extensive investigation to assess the deliverability, delivery accuracy, robustness and actual delivery time reduction of a spot-reduced treatment plan.

Material and methods

For one patient treated in the sinonasal region, a 'spot-reduced plan' was generated using Erasmus-iCycle (Erasmus MC Cancer Institute, Rotterdam, Netherlands) for which the dosimetric plan quality was equal or better than the clinical plan generated using PSIplan (PSI, Villigen, Switzerland).

Table 1. Characteristics of the clinical plan and the corresponding spot-reduced plan.

	Clinical plan	Spot-reduced plan
Beams / fields	4*	4*
Energy layers	199	195 (-2%)
Spots	26069	1540 (-94%)
Average delivery time per field (s)	55.8	19.5 (-65%)

** Identical beam arrangement*

For both plans, the same 4-beams arrangement was used with 4mm lateral spot spacing, 2.5mm energy layer spacing and a 4.2cm water-equivalent pre-absorber. The planning target volume was 280 cm3 and received a homogeneous dose from each field. For the spot-reduced plan, the number of spots was minimized using the 'pencil beam resampling' technique, which involves repeated inverse optimization, while adding in each iteration randomly selected spots and excluding low-weighted spots until the plan quality deteriorates. Machine steering files were generated and both treatment plans were delivered on our PBS Gantry 2 at PSI, comparing the delivery time per field, measured dose profiles in water and recalculated dose distributions using log-files. In addition, simulations were performed to compare the robustness against random errors in individual spot position and against systematic errors in patient setup (±3mm along 3 axes) and proton range (±3%).

Results

The number of spots was reduced by 94% from 26069 in the clinical plan to 1540 in the spot-reduced plan. The spot-reduced plan was found to be deliverable and the delivery time per field was shortened by 65% on average from 56 s to 20 s (Table 1). The measured dose profiles showed differences between delivered and planned dose of 2.9%-4.3% (as standard deviation of the linear correlation) for the spot-reduced plan and ‹2% (standard deviation) for the clinical plan. For both plans, the log-file recalculated dose was within ±1% of the planned dose for 100% of the voxels (96% and 98% on average for the individual fields of the spot-reduced or clinical plan, respectively) (Figure 1). The robustness simulations showed that random spot position errors of ≤0.5mm resulted in 94%/100% of voxels passing the ±1% criterion for the spot-reduced/clinical plans, respectively. Surprisingly, the spot-reduced plan was less sensitive to rigid setup and range errors, with a target mean dose reduction of 0.4% in the worst case scenario, compared to a 2.4% reduction for the standard plan. The increased dose to organs at risk was of 2.6%/20.4% as maximum dose to the brainstem in the worst case scenario for the spot-reduced and standard plan, respectively.

Conclusion

Compared with the clinical plan, spot number could be reduced by 94%, without compromising the dosimetric plan quality, which resulted in a substantial delivery time reduction of 65% on average per field. Although the spot-reduced plan was more sensitive to delivery uncertainties, the accuracy of total delivered dose was well within clinical tolerance.

This work has been submitted to the annual meeting 2018 of the European Society for Radiotherapy-&Oncology (ESTRO) next spring in Barcelona, Spain.

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