PAUL SCHERRER INSTITUT
PSI

SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #27_12/2022

Dear Reader,

Welcome to this last edition of our SpotON+ Newsletter in 2022. You will find on the following page the clinical results of children and adolescents/young adults treated with cranio-spinal irradiation (CSI) using pencil beam proton therapy. PSI has been treating these cancer patients with a very specific field arrangement that is unique to PSI and which has evolved with time (Gantry 1 and then Gantry 2). Most of these patients were treated for medulloblastoma and ependymoma and most were treated with up-front CSI (ca. 77%). The median dose delivered to the spinal axis and to the tumor bed was 24 and 54 Gy, respectively. The estimated 2 year-local control and overall survival was 86% and 85%, respectively. Importantly, the majority of failures were distant CNS, with or without a local treatment failure. Only 1/8 (1.4%) local failure was considered a marginal failure, which is important to point out knowing the sharp dose fall-off of protons. The late toxicity rate was minimal, with an estimated 2-year high-grade toxicity free survival of 93%. These results are in line with those published by other groups and support the safety and efficiency of protons delivered with PSI's technique to these young patients.

The second article relates to hearing loss after proton therapy delivered for skull-base tumors. Fifty-one patients (median age, 50 years) with pre- and post-hearing tests were retrospectively assessed. Importantly, one of the eligibility criteria was that no chemotherapy prior/during or after proton therapy should have been delivered to these patients. Significant risk factors for hearing loss were patient's age, follow-up time and mean cochlear dose in Gy(RBE). We observed that each additional Gy to the cochlea resulted in a 0.34 dB increase in hearing loss. Needless to say, these data show that cochlear dose should keep as low as reasonable possible, which is achievable usually with protons.

Lastly, we report an interesting analysis from Florian Amstutz, PhD student in our institution. He is also working with the Medical Physics group of USZ under the leadership of Jan Unckelbach. Proton therapy, as a unique radiation delivery modality, is delivered however to less than 1% of patients worldwide and even less so in Switzerland. In the endeavour to 'democratize' proton therapy (i.e. making the delivery of protons to more patients and/or new indications), delivering dual photon and proton radiotherapy, on various mix, tailored to the individual 'needs' of lung cancer patients was assessed. This comparative planning analysis, with endpoints such as NTCP among others, used planning CTs acquired in deep-inspiration breath-hold (DIBH) and repeated CTs from treatment days 2, 16, and 31 acquired in three different DIBH of each day. Amstutz et al. have shown that combined treatment plans did improve plan quality compared to photons only. Moreover, low and medium doses to organs at risk were reduced, leading to lower NTCP estimates for three investigated side effects. Combined photon and proton irradiation has thus the potential to increase the accessibility of lung cancer patients to the benefits of proton therapy.

That being said, I hope that this newsletter was of interest to you and I wish you all a merry 'Xmas and happy new year

Sincerely,

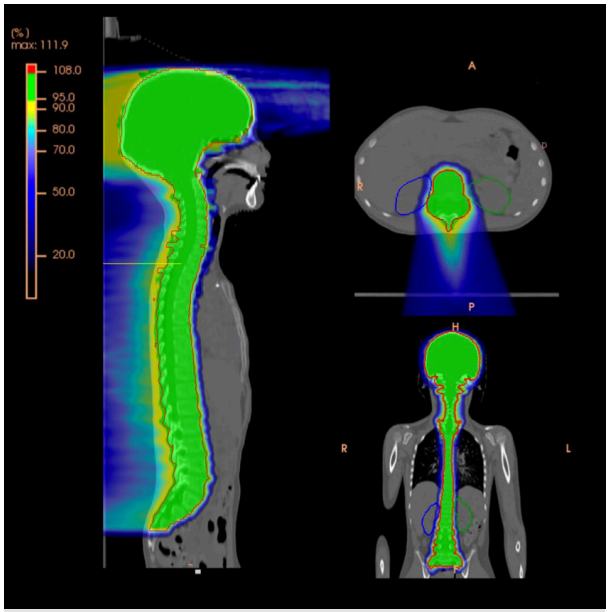
Prof. Damien C. Weber,
Chairman Center for Proton Therapy,
Paul Scherrer Institute

Radio-Oncology News

Early Outcome after Craniospinal Irradiation with Pencil Beam Scanning Proton Therapy for Children, Adolescents and Young Adults with brain tumors

Background and methods

Craniospinal irradiation (CSI) is an essential treatment component to achieve cure for some brain tumors in children and young adults/adolescents (C-AYAs). Pencil beam scanning proton therapy (PBSPT) allows for a minimization of the dose delivered to organs at risk and the brain integral dose and, thus, potentially also allows a reduction of radiation-induced adverse events. The aim of this study was to report 2-year clinical outcome in a cohort of C-AYA treated with PBSPT. Medical records of C-AYAs who received CSI with PBSPT between January 2004 and January 2021 were reviewed. CSI was applied as adjuvant or definitive treatment for primary or recurrent tumors. Induction, concomitant and maintenance chemotherapy was administered in 49.3%, 8.5% and 53.5% of patients, respectively. Time to local failure (LF), distant failure (DF), death and grade (G) 3 late toxicity were calculated to asses local control (LC), distant control (DC), overall survival (OS) and G3 toxicity-free survival. Toxicities were defined according to CTCAE 5.0. A survival analysis using Kaplan-Meier method and log-rank test was performed.



Radiation dose distribution of an 8-years old child with a medulloblastoma treated with PBSPT at our institution

Results

Between 2004 and 2021 71 C-AYA received CSI with PBSPT at our institution. Medulloblastoma (59.2%) was the most frequent diagnosis, followed by ependymoma (11.3%) and germ cell tumors (8.5%). Sixteen (22.5%) patients received PT for a recurrent tumor. Thirty-four (47.9%) patients were metastatic, of which 13 (38.2%) had spinal metastases. Overall, surgery was performed in 60 (84.5%) patients, of which 38 (53.5%) had a gross total resection. Median total radiation dose was 54 GyRBE in 1.8 GyRBE per fraction. CSI and boost median doses were 24 GyRBE and 30.6 GyRBE, respectively.

With a median follow-up of 24.5 months (range, 2-195), 2-year LC, DC and OS were 86.3%, 80.5% and 84.7%, respectively. Four patients (5.6%) had LF only, 11 had DF only (15.5%) and 4 (5.6%) had both. Median time to LF and DF was 24.2 and 10.7 months, respectively. Of the 8 patients with LF (including patients with both DF and LF), 7 (87.5%) were in-field and one (1.4%) was marginal. Twelve (16.9%) patients died, all of them due to progressive disease.

On univariate analysis, patients with a recurrent tumor had worse 2-year LC (95% vs. 44%, p <0.0001), DC (88% vs. 54%, p= 0.004) and OS (89% vs. 70%, p= 0.003) than those treated with upfront PBSPT at diagnosis. Inferior outcomes were also observed for metastatic patients in terms of 2-year DC (66% vs. 92%, p= 0.009) and OS (74% vs. 94%, p= 0.012), but not for LC (75% vs. 93%, p=0.187) when compared to non-metastatic patients.

Four (5.6%) patients developed late G≥ 3 toxicity. G3 toxicity cases consisted of cataract (n=1), CNS radiation necrosis (n=1) and a case of a G3 stroke (n=1) developed in a patient with previous vascular disease (Moya Moya disease). There was one (1.4%) case of a G4 CNS radiation necrosis of the brainstem. Two-year freedom from G≥ 3 late toxicity was 92.6% (95% CI, 79.9% - 97.9%). No patient developed a secondary malignancy after PBSPT.

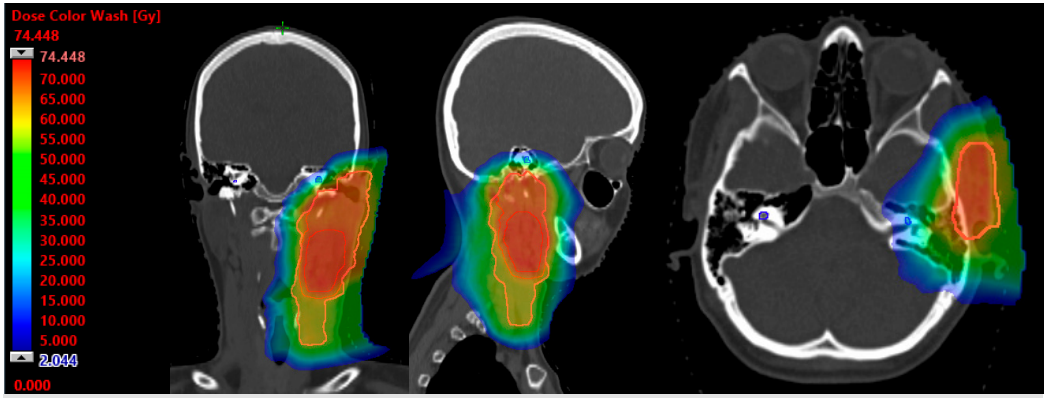
Conclusions

This study provides a detailed analysis of the early clinical outcomes of a cohort of C-AYAs with brain tumors referred to receive CSI with protons using a pencil beam scanning only delivery paradigm. Excellent 2-year LC, DC and OS rates were observed, which are consistent with recent reports investigating the use of CSI with protons among children and AYAs. Of note, patients with recurrent or metastatic tumors at the start of PT were found to have a worse outcome. Our acute toxicity data points to an adequate tolerance of the treatment. It is noteworthy that at two years, the reported actuarial freedom from G≥ 3 toxicity was greater than 90%. This data compares favorably with previous studies and supports the safety and efficacy of proton CSI for the control of CNS tumors.

This work has recently been published (Vazquez et al. 2022)

Radio-Oncology News

Hearing Loss in Cancer Patients with Skull Base Tumors undergoing Pencil Beam Scanning Proton Therapy: A Retrospective Cohort Study



Colour wash of a SIB proton plan of a patient with recurrent adenoid cystic carcinoma of the left parotid gland with perineural infiltration of the facial nerve. The dose levels were 70, 66, and 54.12 Gy (RBE). The left cochlea is shown in blue and is near the 66 Gy (RBE) target area. Nevertheless, a median dose of just 37 Gy (RBE) was achieved.

Background

Most patients with skull base tumors require radiation therapy as part of their overall treatment, preferably with protons. However, vital and healthy organs such as the cochlea are often located in the immediate anatomical vicinity of the tumor. Radiation-induced hearing loss is a severe adverse effect that significantly decreases the affected patient's quality of life. To assess the frequency and severity of changes in hearing after proton therapy, we performed a retrospective study in patients undergoing pencil beam-scanning proton therapy (PBS-PT) for skull base tumors.

Material and Methods

This retrospective analysis included fifty-one patients (median 50 years (range,13-68)) treated with PBS-PT for skull base tumors treated between 2003 and 2017 who had at least one pre- and one post-treatment audiometry test. Pure tone averages (PTAs) were determined before (baseline) and after PBS-PT as the average hearing thresholds at frequencies of 0.5,1,2 and 4 kHz. Hearing changes were calculated as PTA differences between pre-and post-PBS-PT. Higher values of PTA indicate inferior hearing, and an increase in PTA over time suggests a worsening of the hearing threshold. A linear mixed-effects model was used to assess the relationship between PTA at follow-up and baseline, cochlea radiation dose intensity, increased age, and years after PBS-PT.

Results

All patients had histologically confirmed chordoma (n=24), chondrosarcoma (n=9), head and neck tumors (n=9), or meningioma (n=3), with a mean tumor dose of 71.1Gy (RBE) (range, 52.0-77.8). None had distant metastases at diagnosis. No chemotherapy was delivered. The overall mean cochlea dose for all ears was 37.1 Gy (RBE) (SD 22.5). Patients with unilaterally localized tumors had a significantly higher mean dose to the ipsilateral cochlea (59.4 Gy (RBE), SD 16.4) than on the contralateral side (13.4 Gy (RBE); SD 12.29; p<0.001). Also, the ipsilateral cochlear dose of lateralized tumors was higher than in both cochleas in midline tumors (59.4 Gy vs. 37.1.Gy (RBE)). The median time to first follow-up was 11 months(IQR, 5.5-33.7), and the median overall follow-up time was 26 months (IQR 14 - 69). A median of 2 (IQR 1-3, range 1-11 tests) follow-up audiometric tests were performed. PTA increased significantly by 8.7 dB from a median of 15 dB (IQR 10.0-25) at baseline to 23.8 (IQR 11.3–46.3) at the first follow-up, indicating an impairment of hearing sensitivity (p<0.001). This impairment was more pronounced in the ipsilateral ears of patients with lateralized tumors (32.5 dB) than in patients with midline tumors (28.9 dB). In the linear mixed effect model, baseline PTA (Estimate 0.80, 95%CI 0.64 to 0.96, p=<0.001), patient's age (0.30, 0.03 to 0.57, p=0.029), follow-up time (2.07, 0.92 to 3.23,p=<0.001) and mean cochlear dose in Gy(RBE) (0.34, 0.21 to 0.46,p=<0.001) were all significantly associated with an increase in PTA at follow-up.

Discussion and Conclusion

In our study, a gradual relationship was observed between the applied cochlear dose and the deterioration of hearing sensitivity, measured as PTA: Each additional Gy to the cochlea resulted in a 0.34 dB increase in hearing loss. An exciting aspect of our study is that none of the included patients received chemotherapy. This is where our study differs from others, in which primarily concomitant chemotherapy was given, which is a contributing factor for ototoxicity. We have shown that the applied dose to the cochlea has an independent effect on hearing loss after PBS-PT. Therefore, we believe it is impossible to define a safe dose for the cochlea that will reliably prevent ototoxicity after PBS-PT. This fact should be understandably explained to patients so they are sufficiently informed to give informed consent for radiation.

This work has been recently published (Bachtiary et al. 2022)

Medical-Physics News

Combined proton-photon therapy for non-small cell lung cancer

Background

Locally advanced non-small cell lung cancer (NSCLC) remains a challenging indication for conventional photon radiotherapy. Proton therapy has the potential to improve outcomes. However, despite the rapid increase in proton therapy facilities worldwide, proton therapy slots remain a limited resource. Optimally combined proton-photon therapy (CPPT) might increase accessibility to proton therapy for such a patient cohort. For this CPPT treatment, protons and photons are simultaneously optimized and delivered in the same fraction. This approach allows adding a fixed horizontal proton beam line (FHB) to a conventional photon Linac room. The FHB could reduce the costs compared to a gantry, while the photon Linac compensates for the lost flexibility. This study aimed to investigate the potential benefits of CPPT for NSCLC and inspect the impact of anatomical changes on a CPPT treatment.

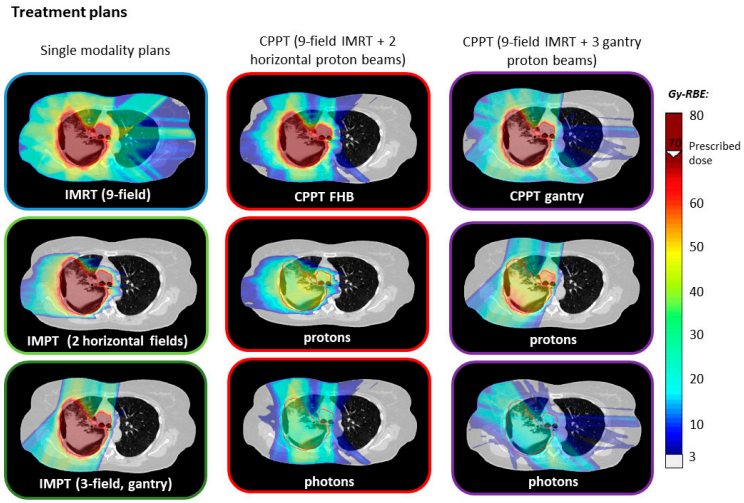
Materials and Methods

This treatment planning study investigated a cohort of seven locally advanced NSCLC patients. Each patient had a planning CT acquired in deep-inspiration breath-hold (DIBH) and nine repeated CTs from treatment days 2, 16, and 31 acquired in three different DIBH of each day. This image acquisition scheme allowed for two adaption treatment planning strategies. In the non-adaptive strategy, the treatment plans were optimized on the planning CT only and recalculated on the repeated CTs. For the adaptive approach, for each imaging day, a plan was optimized on one DIBH and recalculated on the repeated CTs from the remaining two DIBHs. Two different CPPT plans were optimized, one using the FHB and another with a gantry. As a reference, an IMRT plan with 9-equispaced fields was planned. Finally, to compare CPPT also to the IMPT-only plans, one IMPT FHB and one IMPT gantry plan were optimized. All the plans were additionally robustly optimized with range uncertainty scenarios of ±3%, ±5%, and ±7% HU scaling. The plan quality was compared on the dosimetric level (e.g. DVHs, dose parameters) and with normal tissue complication probabilities (NTCPs).

Results

The CPPT treatment plans improve plan quality compared to IMRT. Low and medium doses to organs at risk (OARs) are reduced, leading to lower NTCP estimates for three investigated side effects. Over all patients, the average reduction from IMRT to CPPT was for radiation pneumonitis -5.2%, for esophageal toxicity -6.6%, and for 2-year mortality -2.5%. IMPT or CPPT with a gantry could slightly improve the plan quality in some cases, however, the cost reduction would be lost.

The inter-fractional changes primarily impact the target coverage of CPPT and IMPT treatments, while the OARs were considerably less affected by these changes. On the other hand, with the adaptive treatment strategy, the target coverage of CPPT remained of good quality, even when having the variability between the breath-holds included. On the other hand, range robust optimization can only help to recover target coverage for CPPT partly. Additionally, in such a scenario, the photon component is substantially increasing, compromising the benefit of CPPT.



Treatment plan examples for Patient 1. Including the single modality plans on the left (IMRT, IMPT FHB, IMPT gantry) and the CPPT plans with their respective proton and photon contribution.

Conclusions

CPPT is potentially increasing the accessibility of NSCLC patients to the benefits of proton therapy. In addition, the combined treatment shows improved dose distributions compared to IMRT. Compared to IMPT-only plans, plan quality is only reduced for some patients and OARs. Furthermore, with CPPT, NTCP reductions are observed for radiation pneumonitis, ≥ grade 2 esophageal toxicity and for 2-year mortality compared to IMRT. CPPT partly reduces the sensitivity of the plans to anatomical changes compared to complete proton treatments. Nevertheless, with more extensive inter-fractional changes present, CPPT needs adaptive strategies to preserve target coverage.

This study has been recently published (Amstutz et al. 2022)

Imprint

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