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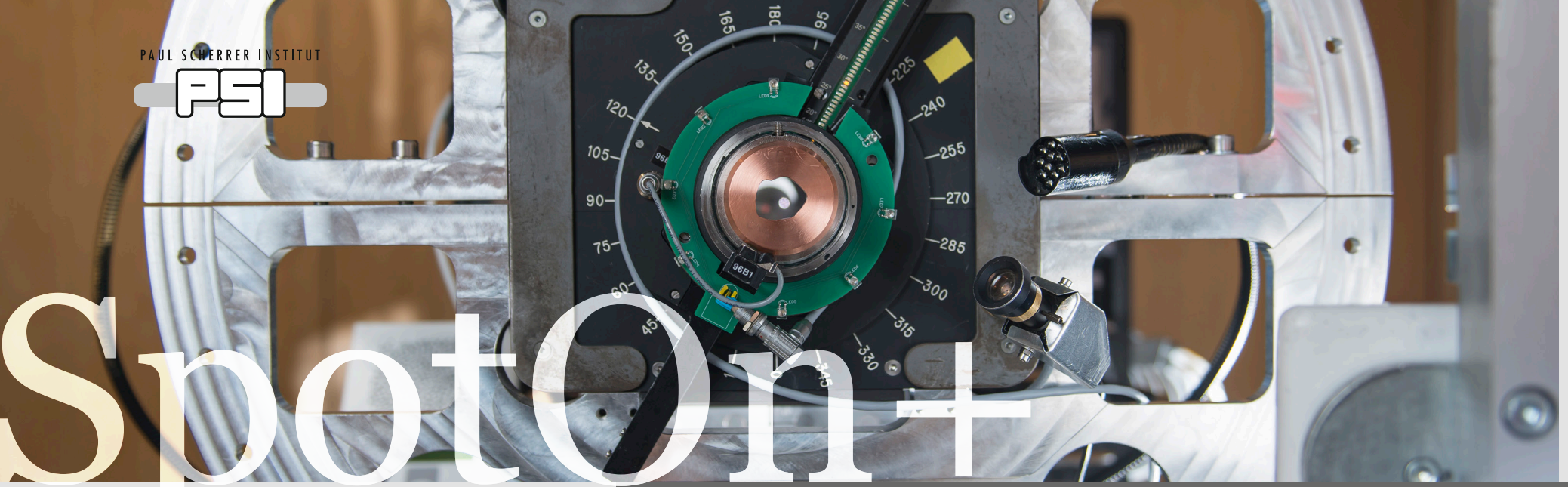


SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #21_11/2020

Dear Reader,

In this edition, the clinical prognostic factors for late toxicity of proton therapy delivered to para-papillary choroidal melanomas are detailed in a large cohort of 310 patients treated at the PSI. These are challenging patients as the tumor is in direct vicinity of the macula. Only two (0.6%) recurrences were observed after a median follow-up time of 120 months. Not surprisingly, only 64 patients (21%) maintained a good visual acuity for at least 5 years following treatment. The majority of patients (79%) had thus poor visual outcome, including the two with a recurrence treated with repeated proton therapy and enucleation. Age was an independent negative prognostic factor for visual outcome on multivariate analyses and so was the location of the posterior tumor border. Other independent prognostic factors included the amount of irradiation delivered to the optic disc and to the macular surface, with a cutoff of 30 GCE. This series, analyzed in collaboration with the Hôpital Ophtalmique Jules Gonin, showed excellent tumor control with one patient out of five having a good visual outcome after proton therapy.

The following article reports on the clinical outcome and quality of life (QoL) of children and adolescents with brain tumors treated with proton therapy. The main histologies were ependymoma, glioma and craniopharyngioma. Over 70% of patients received chemotherapy. With a median follow-up time of › 50 months, treatment failures were observed in one patient out of three. The 5-year overall survival and local control were 79.9% and 72.1%, respectively. High-grade ≥G3 CTCAE late toxicity occurred unfrequently and the estimated 5-year toxicity-free survival was 91.0%. Statistical analyses showed that age ≤3 years at PT and chemotherapy were a significant predictor of high-grade toxicity. Interestingly, children aged ≥5 years self-rated QoL higher than their parents (proxy assessment). In summary, the outcome of these young patients was excellent after PT and few of them presented with late ≥G3 toxicity.

Finally, the treatment of lung cancer were benefit from dose escalation with very conformal radiation therapy (i.e. proton therapy). A phase III trial (RTOG 1308) is currently accruing to see if protons, as opposed to photons, result in an increased therapeutic ratio. Of note, PSI in collaboration with the Kantonspital Aarau will participate in this trial in Q1 2021. The issues of treating moving targets treated with a dynamic beam have been already mentioned in several SpotOn+ newsletters. Here, we report the deformable image registration (DIR) uncertainty for inter-fractional dose accumulation of proton therapy delivered to lung cancers. There are several DIR algorithms that enable one to accumulate the dose on the reference planning CTs. The team of Tony Lomax has shown that the dose degradation caused by anatomical changes were more pronounced than the uncertainty of employing different DIRs for dose accumulation. Importantly, the results of accumulated doses with multiple DIRs provide a good representation of dose degradation caused by anatomy changes. These results are of critical importance to understand how the steep dose gradients achievable with intensity modulated proton therapy perform with motion. That being said, I hope this newsletter was of interest to you and I wish all of you all the best in these challenging COVID-19 times.

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

Radio-Oncology News

Long-term visual outcome of parapapillary choroidal melanoma patients treated with proton therapy

Introduction

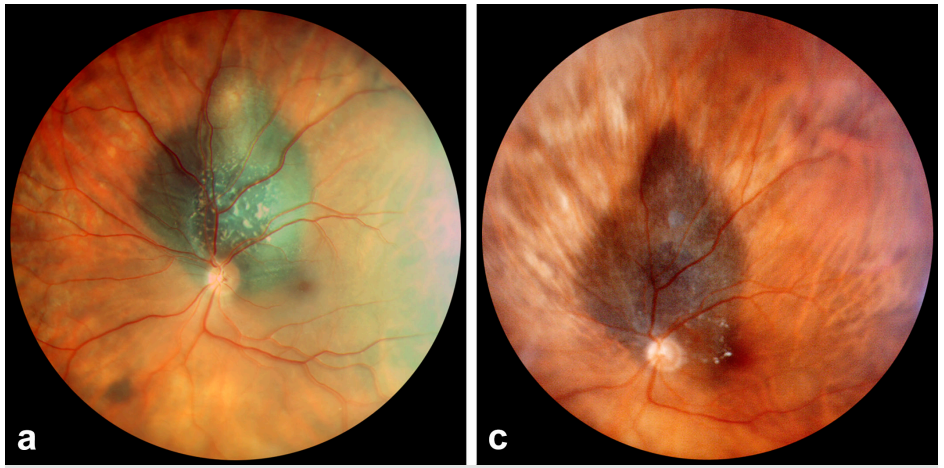
Parapapillary choroidal melanoma (pcM) is treated with external beam proton therapy (PT) to decrease the risk of a local recurrence through geographical miss. However, the indication for conservative PT of pcM is still challenged, because irradiation of the optic disc is correlated with a higher risk of complications as a result of direct neuropathic effects and a radiation-induced vasculopathy, leading to loss of useful vision and even secondary enucleation. In our study we investigated important predictive factors for long-term vision by comparing patients with excellent long-term vision after proton therapy to all other patients.

Methods

A best corrected visual acuity (BCVA) of ≤ 0.2 logMAR (≥ 0.6 decimal) for at least 5 years following PT was considered as a 'good long-term' visual acuity (VA). Our study compared patient, ocular and tumor characteristics at baseline (pre-treatment), PT parameters, as well as follow-up BCVA and ocular complications of patients with a good long-term VA, allocated to the "good visual outcome" (GVO) group, with those of the remaining patients, representing the "poor visual outcome" (PVO) group. In total, 310 patients, treated between 1984 and 2005, could be included in the analyses. All patients underwent tantalum clip surgery under general anesthesia at the Jules-Gonin Eye Hospital (HOJG, Lausanne) for tumor location. PT was planned and delivered at the Paul Scherrer Institute (PSI, Villigen), using the EYEPLAN software program and a custom-modeled head holder for immobilization. A total dose of 54.5 Gy, corresponding to 60 CGE, was delivered in 4 fractions of 15 CGE on 4 consecutive days. Follow-up examinations took place at HOJG, Lausanne.

Results

Out of 310 pcM patients who had received PT, 64 patients (21%) maintained a VA of ≤ 0.2 logMAR (≥ 0.6 decimal) for at least 5 years following treatment and were therefore allocated to the GVO group, while the remaining 246 patients (79%) entered the PVO group. In the latter, two patients presented a recurrence at 8 and 9 years following PT and were treated with a second PT, followed in the latter case by a secondary enucleation 3 years later. The overall mean follow-up was 120.8 ± 48.8 months (range 54.0–295.0), with no significant statistical difference between the two groups ($P = 0.053$). The GVO group was on average five years younger, and older age at the time of PT was identified as an independent risk factor ($P = 0.04$) for poor long-term visual outcome in multivariate analyses. The location of the posterior tumor border was strongly correlated with long-term visual outcome. That is, whether the tumor abutted the optic disc (GVO vs. PVO: 34% vs. 52%; $P < 0.001$), or was positioned temporally to the fovea (25% vs. 49%; $P < 0.001$), or at a closer distance to the fovea ($P < 0.001$), increased significantly the probability of a poor long-term visual outcome Interestingly, only the tumor location relative to the fovea remained significant with a distance of less than 0.6 mm from the fovea resulting as an independent negative predictor for maintaining good long-term VA. While the multivariate analysis identified both the % of irradiation delivered to the optic disc and to the macular surface as two independent negative predictors for maintaining long-term vision, it also highlighted the relative importance of irradiation delivered to the macula ($P < 0.001$), rather than the optic disc ($P = 0.02$).



Parapapillary choroidal melanoma (left eye) maintaining useful vision following proton therapy. a: Panoramic fundus photo in a 71-year-old female at initial presentation with loss of VA to 0.6 decimal related to a secondary macular detachment. c: Eleven years after radiation therapy, the tumor borders are under control on panoramic fundus photography, with some lipid exudates close to the macular border.

Conclusions

Out of 310 successfully treated small- and medium-sized pcM patients, one in five maintained a VA ≤ 0.2 logMAR (≥ 0.6 decimal) for at least five years following PT. Independent negative predictors for maintaining a useful long-term vision were older age, tumor proximity to the fovea, and the volume of the optic disc and macula receiving at least 30 CGE, the latter being the most significant risk factor.

The results of this collaboration project between HJOG and PSI were published recently (Pica et al. 2020).

Radio-Oncology News

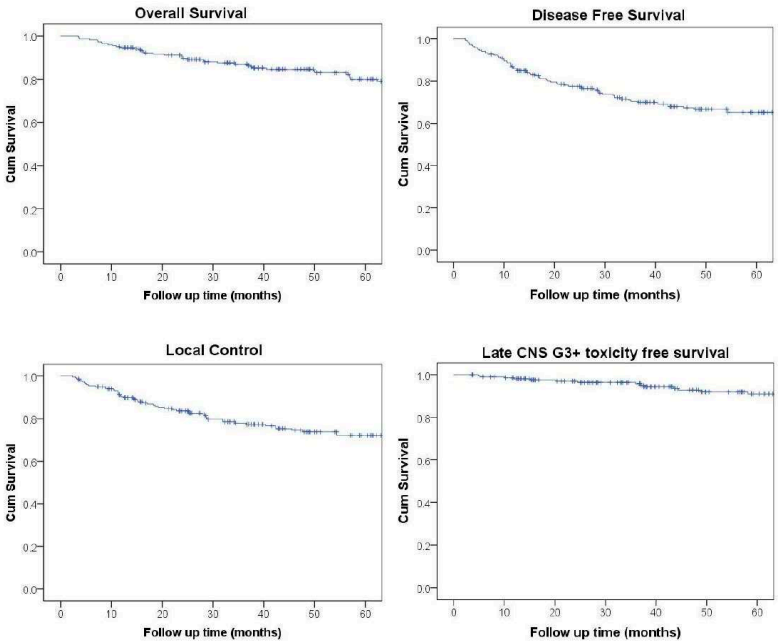
Clinical outcome and quality of life in children with primary brain tumors treated with proton therapy

Background

Long-term treatment-related toxicity may substantially impact well-being, quality of life (QoL), and health of children/adolescents with brain tumors (CBTs). Strategies to reduce toxicity include pencil beam scanning (PBS) proton therapy (PT). The dosimetric advantages of protons over conventional radiotherapy (CRT) make them the preferred irradiation modality in CBTs. Favorable neuropsychological outcomes after PT have been demonstrated over CRT, but comprehensive long-term data for PBS use in CBTs is scarce. The aim of this study is to report long-term clinical outcomes and QoL in a large cohort of CBTs treated with PBS-PT and to assess prognostic factors related to these clinical outcomes.

Procedure

We retrospectively reviewed 221 PBS-treated CBTs aged <18 years on a scanning gantry. Acute toxicities were documented weekly during PT. Documentation on long-term clinical and radiological follow-up (FU) performed by referring physicians was obtained by our study and research office. Overall-free (OS), disease-free (DFS), and late-toxicity–free survivals (TFS), local control (LC) and distant (DC) brain/spinal control were calculated using Kaplan-Meier estimates (figure). Prospective QoL reports from 206 patients (proxies only for patients ≤4 years, proxies and patients for patients ≥5 years) were descriptively analyzed.



Figur: Kaplan Meier curves for Overall Survival, Disease Free Survival, Local Control and Late CNS ≥G3 toxicity-free survival.

Results

Median age at diagnosis and at PT start were 3.1 (range, 0.3-17.7) and 4.1 years (range, 0.8-18.2), respectively. Overall, 59% patients were males. The main histologies were ependymoma (n = 88; 39.8%), glioma (n = 37; 16.7%), craniopharyngioma (n = 22; 10.0%), atypical teratoid/rhabdoid tumor (ATRT) (n = 21; 9.5%) and medulloblastoma (n = 15; 6.8%). One hundred sixty (72.4%) patients received chemotherapy; in 38 (17.2%) cases concomitantly with PT. Median PT dose was 54 Gy (relative biological effectiveness) (range, 18.0-64.8). Median follow-up was 51 months (range, 4-222).

Treatment failure was observed in 74 of 221 (33.5%) patients. Isolated local failure was the most common pattern (n = 47; 63.5%). During the FU period, 43 (19.5%) patients died. The 5-year OS, DFS, LC, and DC (95% CI) were 79.9% (74-85.8), 65.2% (59.8-70.6), 72.1% (65.4-78.8), and 81.8% (76.3-87.3), respectively. Late PT-related ≥G3 toxicity occurred in 19 (8.6%) patients. The 5-year ≥G3 TFS was 91.0% (86.3-95.7).

Patients aged ≤3 years at PT (P = .044) or receiving chemotherapy (P = .043) experienced more ≥G3 toxicity. ATRT histology independently predicted distant brain failure (P = .046) and death (P = .01).

Three (1.4%) secondary malignancies were observed. Two children diagnosed with posterior fossa ependymoma at <3 years of age developed glioblastoma within the high-dose region, 8 and 10 years after PT, respectively. A third patient was diagnosed with acute myeloid leukemia 51 months after PT.

Patients aged ≥5 years self-rated QoL higher than their parents (proxy assessment). Both reported lower social functioning and cognition after PT than at baseline, but near-normal long-term global well-being. QoL was well below normal before and after PT in children ≤4 years.

Conclusions

The outcome of CBTs was excellent after PBS in this large cohort with long-term FU and compares favorably to photon series data. Few patients had late ≥G3 toxicity. ATRT histology was an independent predictor for distant brain failure and for death, but long-term survivors diagnosed with this brain tumor were also observed, thus justifying treatments approaches reducing long-term toxicity risk such as PBS. Patients aged <5 years showed worse QoL and toxicity outcomes and more research is warranted to increase therapeutic ratio, particularly in this age group.

The results of this retrospective study have been recently published (Tran et al. 2020).

Medical-Physics News

Deformable image registration uncertainty for inter-fractional dose accumulation of lung cancer proton therapy

Introduction

Non-small cell lung cancer (NSCLC) patients can particularly benefit from the steep dose gradients achievable with intensity modulated proton therapy. However, they show typically large anatomical changes during treatment, which causes large dose degradations. This makes recalculation or adaption necessary. For a comprehensive evaluation, report and review, the applied treatment dose can be accumulated on the reference (planning) CT using deformable image registration (DIR). Nowadays, many clinically used treatment planning systems have DIR algorithms implemented. Unfortunately, different clinically used DIR algorithms give different results. Due to the lack of ground truth, the errors and variations of these DIR algorithms are hard to quantify and the dosimetric effect of these DIR uncertainties on the accumulated dose are unknown. Therefore, we have investigated differences in the accumulated dose by using six different clinically available and used DIR algorithms for NSCLC patients in presence of inter-fractional anatomy variations.

Materials and methods

Proton treatment plans with 66 Gy-RBE to the planning target volume (PTV) were optimized for seven NSCLC patients. For each patient, nine repeated CTs were acquired and first registered rigidly to the planning CT. All CTs were acquired in visually guided deep-inspiration breath-hold. Therefore, as a simplification, the dose was recalculated on each CT as if it was delivered in a static, single breath hold. For a dose accumulation, all CTs were registered deformably using six different clinically used DIR algorithms. Two were open source algorithms from plastimatch (Demon and B-spline), and four were commercial algorithms implemented in clinical software: one from Mirada, one from Velocity and two from Raystation (Anaconda and Morpheus). The recalculated doses from each repeated CT were warped back to the planning CT using the corresponding six DIR algorithms. Fraction doses warped with the same DIR were summed up to six different accumulated dose distributions per patient, and compared to the initial planned dose.

Results

An evaluation of the localization of dose differences showed that most relevant dose differences between the DIRs were located in the regions of the dose gradient (Figure). However, also within the tumor differences of up to 20% were observed just depending on the choice of the DIR algorithm for dose accumulation. A separation of the effects of anatomical changes and DIR uncertainty showed that the PTV-V95 of accumulated doses decreased by 16% on average over all patients caused by anatomical changes. The variations due to DIR selection was 8.7%. A good agreement between the dose degradation caused by anatomical changes and the dose degradation calculated by averaging all DIRs was found (differences of only 1.6%).

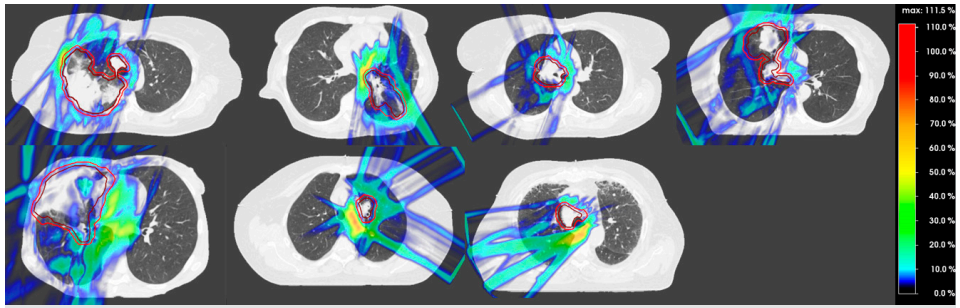


Figure: Voxel-wise maximum-minimum differences of accumulated treatment doses with six different DIR algorithms for seven NSCLC patients. Most dose differences are located in dose gradients, however, also within the tumor severe dose differences were observed

Conclusions

The dose degradation caused by anatomical changes was more pronounced than the uncertainty of employing different DIRs for dose accumulation. The averaged results of accumulated doses with multiple DIRs provide a good representation of dose degradation caused by anatomy. However, the variations in the accumulated dose with DIRs can be substantial, so the use of only one DIR algorithm for dose accumulation is not advisable.

The results of this work have been recently published (Nenoff et al. 2020).

Imprint

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