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Center for Proton Therapy :: Paul Scherrer Institut :: #22_03/2021

Dear Reader,

Radiation-induced optic neuropathy (RION) is a feared complication of radiation therapy in brain and head and neck patients. In this edition, Köthe et al. assessed 216 patients treated with PBS proton therapy at PSI. Importantly, all patients received at least 45 GyRBE to the optic apparatus. After a median follow up time of 5 years, high-grade (i.e. ≥ 2 CTCAE version 5) toxicity was observed in 6.5% of cases. Statistical analysis revealed that older age, female gender, arterial hypertension and tumor abutment to the optic apparatus were all risk factors for RION. Interestingly, no dosimetric parameters were associated with an increased risk of RION. For patients presenting these risks, such as meningioma patients, we currently assess the localization of heavily-weighted spots (i.e. >40% of the maximum weight in a field as displayed in PSIplan) on a routine basis and perform LET and/or RBE analysis in selected cases. Of note, the potential risk for meningioma patients were already highlighted in a paper published in 2018 by Murray et al. In this analysis, optic events were observed in 7/96 (7.3%) cases, although the majority of toxicities were cataracts. As a result, we rarely prescribed doses › 50.4 and 60 GyRBE for benign and non-benign meningiomas, respectively, and usually deliver a fractional dose of 1.8 GyRBE. The following article reports on the dosimetric analysis of local failures for skull base tumors treated with proton therapy. Although local failure is a rare event for chondrosarcoma, 30 local failures with skull-base chordomas (sbChs) were observed during follow-up, which represent the majority (86%) of treatment failures in the base of skull for these two entities. The mean proportion of recurrence volumes covered by the initial target structures (overlap) was ca. 50% for the initial GTV, ranging from 0% (surgical pathway recurrence) to 86% (local failure). In the multivariate analysis, histology PTV volume and GTV‹66GyRBE, were all independent prognostic factors for local tumor control. The latter factor stresses the need of very conformal radiation therapy with a remarkable dose-fall off in order to keep GTV‹66GyRBE as low as possible. Noteworthy, we have observed only one (0.7%) surgical pathway recurrence in our cohort of sbCh patients. Although this is a classical event, with a reported prevalence of up to 1.3%, it is definitively a rare event that does not mandate to include in the high-dose targets the surgeons access to the tumor. Finally, the results of a SNF grant (Ultrasound-guided PBS proton beam tracking in lung cancer) are reported here. Krieger et al. have reconstructed the tumour and lung motion using a statistical motion model and liver ultrasound (US) as a real-time motion surrogate and studied the feasibility of PBS tracking for the management of lung cancer. Simultaneous lung 4D-MR and liver US images were acquired for five volunteers in free breathing after IRB approval. Then deformation vector fields were extracted from each 4DMRI and used to generate 10 synthetic 4DCT datasets from a static lung patient CT. As shown with the DVHs in the Fig on page 4, both 2D and 3D tracking improved the CTV coverage substantially, when compared to unmitigated motion. The conclusion of this analysis is, that the liver-US-based motion model is accurate enough for the use in PBS tracking for proton therapy. These results are both timely and necessary, as PSI with the Kantonsspital Aarau will randomise its first patient in the phase III RTOG 1308 trial assessing the value of protons in the management of advanced NSCLCs in Q2 2021. We will keep the community informed when this important trial will be activated in Switzerland. That being said, I hope that this newsletter was of interest to you and I wish all of you all the best in these challenging COVID-19 times. Stay safe and happy vaccination.

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

Radio-Oncology News

Combining Clinical and Dosimetric Features in a PBS Proton Therapy Cohort to Develop a NTCP Model for Radiation-Induced Optic Neuropathy

Background

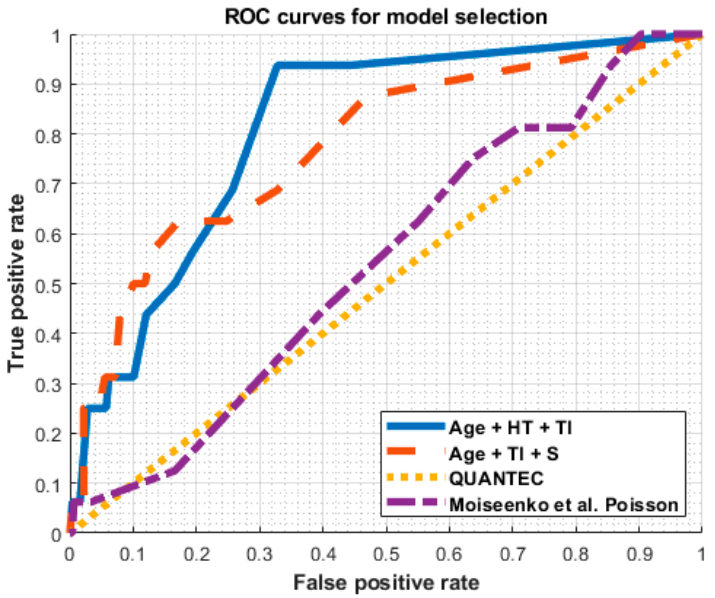
Following radiation therapy to tumours in proximity of the optic apparatus, some patients can suffer from radiation-induced optic neuropathy (RION), a rare, yet severe side effect that can lead to visual impairment or even blindness. Because of the scarcity of data on this rare complication, the interplay of delivered dose and clinical patient characteristics is not fully understood. Although risk factors, such as older age or various dose metrics have been reported, few models exist allowing for a quantification of the risk of this side effect prior to proton therapy. It was the goal of this study to test existing photon-based normal tissue complication probability (NTCP) models against a cohort of patients treated for tumors in the head region and received high dose of protons to the optic apparatus, thereby at risk for RION. We propose a NTCP model combining dose metrics and clinical patient characteristics.

Methods and Materials

The study was conducted based on a cohort of 216 patients treated for skull base or head and neck cancer with pencil beam (PBS) proton therapy at PSI between 1999 and 2014. Inclusion criteria were adult age, no chemotherapy, sufficient follow-up and a minimum of 45 Gy_{RBE} to the optic apparatus. Patients in the cohort were followed up sufficiently long to detect RION (median 5 years), which was diagnosed in 14 patients (6.5%) with ≥ grade 2 (CTCAE 5.0). The data was evaluated on published classical dosimetry-based NTCP models developed on photon cohorts, such as a Lyman-Kutcher-Burman formulation in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) review. Furthermore, extensive statistical analyses including elimination of strongly cross-correlated variables, bootstrapping methods and cross-validation were employed to develop a robust NTCP model that includes clinical parameters as well as plan dosimetry.

Results

Predictive performance and classification ability of the published photon models were limited on our proton cohort. The prevalent risk factors emerging from the statistical analysis encompassed older age, female gender, arterial hypertension and tumor abutment of the optic apparatus. The two best trivariable models based on age, tumor involvement and hypertension or gender showed good ability of classification and calibration. No dosimetric parameter was explicitly included in the best performing NTCP models. However, in agreement with the literature, RION toxicity was not observed below doses of 45 Gy_{RBE} to the optic apparatus. Therefore, the developed models are applicable only to patients with high dose to the optic structures, implicitly accounting for dosimetry. While high dose is the main trigger for RION onset, above a certain threshold, clinical variables such as age, gender or hypertension determine the likelihood of RION toxicity. Furthermore, a trend towards a volume effect in the optic structures was detected which could open up to optimized planning approaches with particle therapy, targeting patients with increased risk for RION with highly conformal treatments.



Receiver operating characteristic (ROC) curves for two published photon-based and two multivariate RION NTCP models built on the PSI proton database. Classification ability, represented as the area under the curve, is greatly improved for the models including age, hypertension (HT), tumor involvement (TI) and gender (S) as opposed to the dosimetry-based QUANTEC and Poisson models.

Conclusion

While high (› 45 Gy_{RBE}) dose to the optic apparatus is a prerequisite for the incidence of RION based on our assessment, clinical patient characteristics such as age, gender, hypertension or an involvement of the tumour in the optic structures are the deciding factor for the onset of this complication. Furthermore, a slight trend towards a volume effect was detected which could favor proton therapy to minimize RION toxicity risk for high-risk subjects.

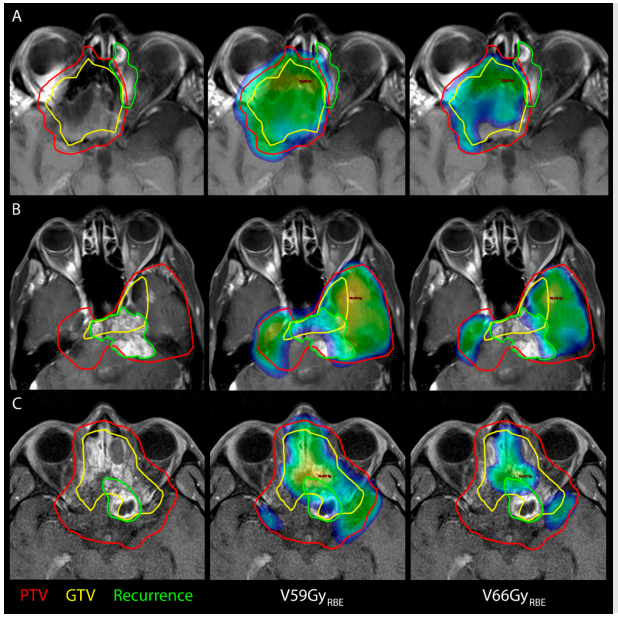
The research leading to these results has received funding from the Strategic Focal Area “Personalized Health and Related Technologies (PHRT)” of the ETH Domain and was recently published (Köthe et al 2021).

Radio-Oncology News

Dosimetric analysis of local failures in skull-base chordoma & chondrosarcoma following PBS proton therapy

Background

Chordoma (Chor) and chondrosarcoma (ChoSa) of the skull base are rare bone tumors which are often located in close proximity to critical organs at risk (OAR), making complete surgical resection of these tumors challenging and postoperative high-dose radiotherapy necessary in most cases. Particle beam radiotherapy offers critical advantages compared to photon irradiation in these patients, as it is able to deliver high curative doses even to target volumes in close proximity to OARs, based on their finite range in tissue (Bragg-Peak), as well as an overall lower integral radiation dose delivered to the patient.
However, despite combined modality treatment involving surgery and adjuvant radiotherapy, a relevant percentage of Chor and ChoSa patients develop a local recurrence (LR), which is most likely explained by the locally aggressive growth pattern. Prognostic parameters to assess the risk of local failure are lacking, but could help in the clinical decision-making process.
This study therefore aimed to analyze patterns of recurrence and correlate local control with a detailed dosimetric analysis.



Three examples of in-field recurrences (green) or marginal failures, together with the initial GTV (yellow) and PTV_{high} (red) structures and dose distribution. The dose of 66 Gy_{RBE} corresponds to the 95% covering isodose (D95) in most cases. Example (**A**) shows a marginal failure in the ethmoid/frontal sinus due to lack of elective coverage in this area. In the example (**B**), the initial PTV_{high} nearly completely covers the recurrence but because of the brainstem OAR constraint, the dose distribution is compromised in this area (right image). (**C**) shows a marginal failure because of chiasm OAR constraints.

Methods

222 patients were treated with proton radiotherapy for Chor (n=151) and ChoSa (n=71) at the PSI between 1998-2012. All patients underwent surgery, followed by pencil-beam scanning (PBS) proton therapy to a mean dose of 72.5 ± 2.2 Gy_{RBE}. A retrospective patterns of recurrence analysis was performed: LR were contoured on follow-up MRI, registered with planning-imaging and the overlap with initial target structures (GTV, $PTV_{high\text{-}dose}$, $PTV_{low\text{-}dose}$) was calculated. DVH parameters of planning structures and recurrences were calculated and correlated with LR using univariate and multivariate cox regression.

Results

After a median follow-up of 50 months (range, 4–176), 35 (16%) local failures were observed, 5 (7%) in ChoSa and 30 (20%) in Chor patients. Follow-up MRI imaging, which was the basis for diagnosis of LR, was available for 27 (77%) of these 35 recurring patients. The overlap of the local failures with the initial target structures GTV, high-dose PTV_{high} and low-dose PTV_{low} was calculated. Only one recurrence was located completely outside the initial PTV and was identified as a surgical pathway recurrence. The mean proportion of recurrence volumes covered by the initial target structures (overlap) were 48% for the initial GTV, ranging from 0% (surgical pathway recurrence) to 86% (local failure). The initial PTV_{high} covered a mean of 70% of the recurrence volumes, ranging from 0% to 100%. The larger PTV_{low} covered a mean of 83% of recurrence volumes, ranging from 0% to 100%.

In addition to the patterns of recurrence analysis, individual DVH parameters of initial planning structures and recurrences were calculated and correlated with local failure.
In the multivariate analysis, histology (Chor vs ChoSa, p=0.009), PTV volume (p=0.045) and GTV ($V<66Gy_{RBE}$, p=0.022), (CI=0.67) were significant and independent prognostic factors for local tumor control. The GTV volume receiving less than 66GyRBE could differentiate between a 5-year local control rate of 65% ($GTV<66Gy_{RBE}$ >3cc) and 77% ($GTV<66Gy_{RBE}$ <3cc) for Chor and between 86% ($GTV<66Gy_{RBE}$ >3cc) and 97% ($GTV<66Gy_{RBE}$ <3cc) for ChoSa patients. The PTV volume could differentiate between a 5-year local control rate of 57% (PTV >120cc) and 78% (PTV <120cc) for Chor and between 73% (PTV >120cc) and 97% (PTV <120cc) for ChoSa patients.

Conclusion

This study was able to identify prognostic DVH parameters, associated with the risk of local recurrence in chordoma and chondrosarcoma patients treated with proton therapy. We have shown that the residual tumor volume and the coverage of the PTV was of paramount importance. These metrics may be used for clinical decision making when treating these challenging patients, although confirmatory results are required.

This work has been recently published (Basler et al. 2020)

Medical-Physics News

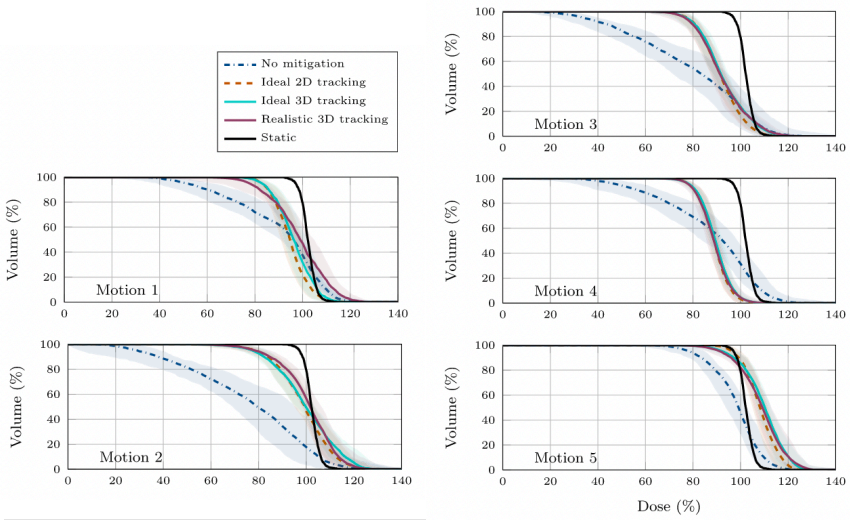
Ultrasound-guided PBS proton beam tracking in lung using a statistical motion model

Introduction

Pencil beam scanned proton therapy (PBS) naturally lends itself to tumour tracking, because the beam position is continuously adjusted during the treatment. In order to follow the tumour with the beam, the deformable 3D motion of the entire patient geometry needs to be known in real-time due to the protons' sensitivity to changes in the beam path. This is impossible with current online image-guided radiotherapy (IGRT) approaches, which is why motion models are needed. In this study, we reconstructed the tumour and lung motion using a statistical motion model and liver ultrasound (US) as a real-time motion surrogate and studied the feasibility of PBS tracking based on our model's predictions.

Materials and Methods

Simultaneous lung 4DMR and liver US images were acquired for five volunteers in free breathing over 7-11 min each, resulting in 690-1500 variable 4DMR volumes with corresponding US images per volunteer. Deformation vector fields (DVF) were extracted from each 4DMRI and used to generate 10 synthetic 4DCT datasets from a static lung patient CT. Each dataset contained 99-159 full breathing cycles, and the corresponding DVFs were considered to represent the ground truth motion for each 4DCT dataset. A patient-specific motion model based on a principal component analysis to reduce the complexity, an autoregression for temporal prediction, and Gaussian process regression for correlation was trained by correlating the MR and US images of each volunteer. Based on the corresponding US signals, this model was then used to predict DVFs of the lung for 26s motion (predicted motion), which were excluded for the model training. A two-field PBS plan was optimised on the CTV +2mm of the reference CT. Deformable 2D and 3D beam tracking was simulated by adapting the pencil beam positions laterally and in depth (only for 3D tracking) based on either the ground truth or the predicted motions, while using the ground truth motion as input for the 4D dose calculations. The ground truth spot adaptions represent ideal tracking, whereas using the predicted motions for spot adaptations represents realistic tracking. The resulting 4D dose distributions were compared in terms of dose volume histograms (DVH) and dose homogeneity (D5-D95%) within the CTV.



Dose volume histograms for all tracking scenarios, compared to the worst-case reference of unmitigated motion (blue, dashed-dotted) and the best-case reference of no motion (black, solid).

Results

Compared to unmitigated motion, both 2D and 3D tracking improved the CTV coverage substantially, as seen in the figure. Furthermore, ideal and realistic tracking provided similar results, indicating that the liver-US-based motion model is accurate enough for the use in PBS tracking. However, none of the tracking scenarios was able to reproduce the steep fall-off of the static dose calculation's DVH. Moreover, in the case of pronounced tumour deformation, the dose level for tracking can be shifted towards higher or lower doses (Motions 3-5). Indeed, the dose homogeneity in terms of D5-D95% is improved for tracking compared to unmitigated deliveries, independent of the type of tracking. Again, the static dose homogeneity could not be reproduced by tracking.

Conclusion

Our US-based motion model is a promising IGRT approach to guide 3D proton beam tracking in real-time if patient specific models are first created based on the simultaneous pre-treatment acquisition of 4DMRI and liver US. However, in order to further mitigate residual patient/motion specific effects, it will be necessary to combine tracking with other motion mitigation techniques such as rescanning or 4D optimisation to fully restore the dose homogeneity close to the static case.

This study has recently been published (Krieger et al 2021).

Imprint

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