Paul Scherrer Institut
Center for Proton Therapy
Newsletter #33_01/2025

Dear Reader

Welcome to this first 2025 edition of our SpotOn+ Newsletter. Liquid biopsies (LB) present an emerging field that combines advanced imaging technologies, artificial intelligence (AI), and molecular biology to enhance the detection and monitoring of cancers applied to our patients, adults and children alike, that present mostly with sarcomas, brain tumors, skull-base tumors or lymphomas. LBs from patients planned for proton therapy were compared to healthy volunteers. We have observed that chromatin biomarkers enable us to correctly distinguish mononuclear cells from healthy and cancer patients by their chromatin organization profiles. Additionally, we also observed that chromatin organization of these cells showed tumor-specific characteristics, which allowed to distinguish cells from meningioma, glioma and head and neck cancer populations with an accuracy of 69% to 89%. These results should be independently confirmed but the potential exists of monitoring residual disease by identifying chromatin abnormalities in these circulating mononuclear cells.

In the second article, we assess the potential association of proton radiation's dose rate (DR) with toxicity. Radiation-induced adverse events of the optic apparatus, mainly in the pre-chiasmatic aspect of the optic nerve or the chiasma, have been observed rarely after treatment of brain tumors with proton therapy, that could not be explained by the traditional dose- or LET metrics. Importantly, dose rates are usually higher with pencil beam scanning, when compared to passive scattering delivery. As the former delivery paradigm

has been introduced (and advocated) to the clinics by PSI, it is of paramount importance to seek any association with DR and toxicity in patients treated at PSI. Two patients with visual radiation-induced toxicity were compared to patients with no toxicity. Of note, LET-related metrics were not noticeably different between the two groups of patients. None of the non-toxicity patients were exposed to DR above 3.7 GyRBE/s, whereas the two patients with toxicity has this DR threshold delivered to the optic nerve. Importantly, high dose rate regions were spatially overlapping with Gd+/T1 hyper-intense lesions on the brain MRI. This topic will be discussed with several other institutions in a close meeting in Boston this Spring.

That being said, I hope this newsletter is of interest to you. I take the opportunity to wish you all a Happy New Year!

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

Radio-Oncology News

Imaging and AI based chromatin biomarkers for diagnosis and therapy evaluation from liquid biopsies

Background

Multiple genomic and proteomic studies have suggested that peripheral blood mononuclear cells (PBMCs) respond to tumor secretomes and thus could provide possible avenues for tumor prognosis and treatment evaluation. We hypothesized that the chromatin organization of PBMCs obtained from liquid biopsies, which integrates secretome signals with gene expression programs, provides efficient biomarkers to characterize tumor signals and the efficacy of proton therapy in tumor patients.

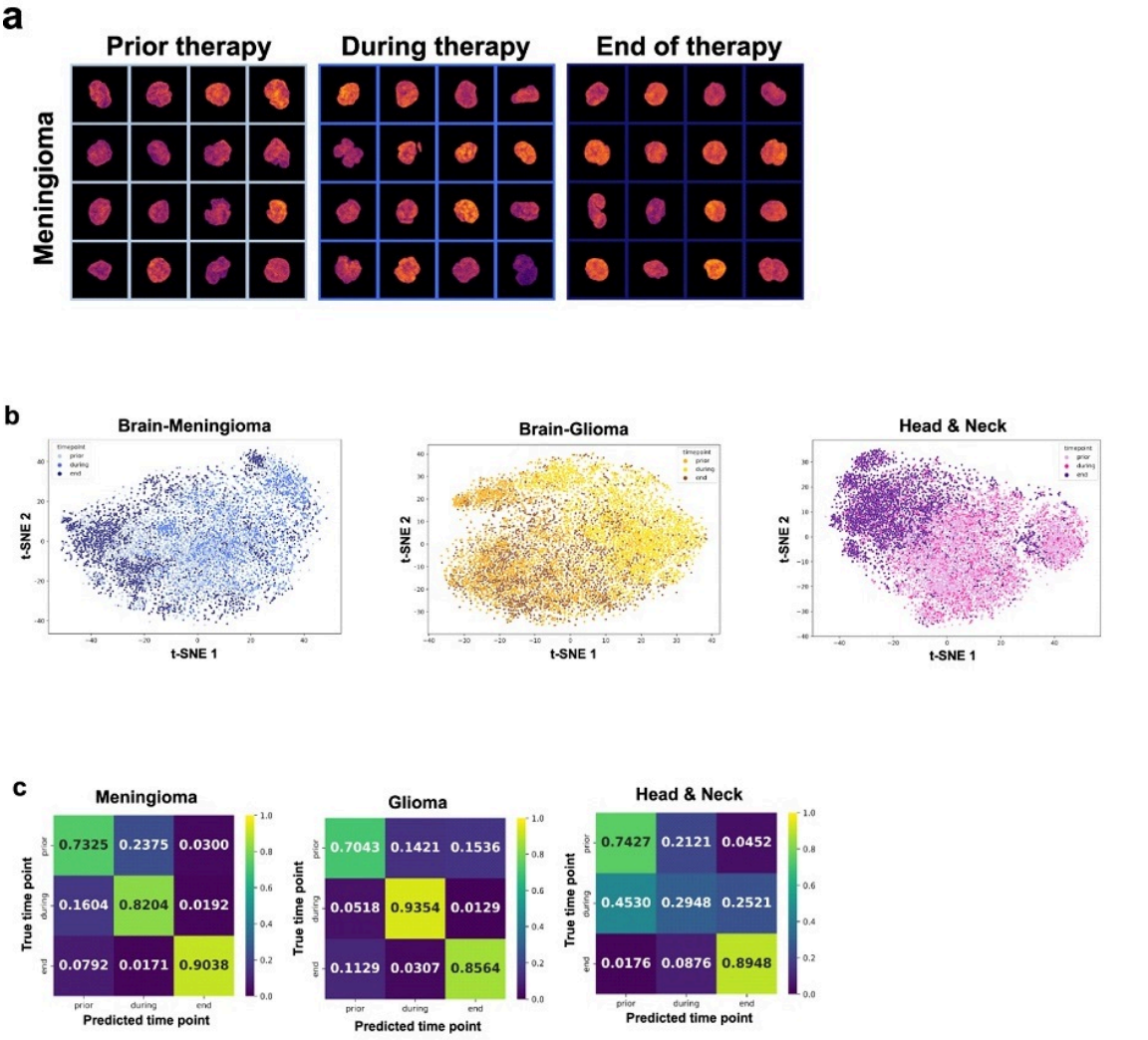
Materials and Methods

Blood samples of 10 healthy volunteers and 30 tumor patients, i.e. glioma, meningioma and head and neck tumor patients (n=10 each) were collected prior, during and at the end of proton therapy. PBMCs were extracted from the

obtained blood samples via density-gradient centrifugation, fixed and immunofluorescently stained and imaged using a confocal microscope.

Results

We show that chromatin imaging of PBMCs combined with machine learning methods provides a robust and predictive chromatin biomarkers. We show that such chromatin biomarkers enable us to accurately distinguish PBMCs from healthy and cancer patients solely by their chromatin organization profiles. We then find that the chromatin organization of PBMCs shows tumor-specific characteristics, which allows us to distinguish between PBMCs from meningioma, glioma and head and neck cancer populations with an accuracy of 75%, 69% and 89%, respectively. Further the chromatin states of the PBMCs seemed to primarily differ between treatment time points as seen in a tSNE visualization (Fig.). Concordantly, a random forest classifier (RFC) could accurately distinguish between PBMCs of the different treatment time points across all tumor groups with classification accuracies of 0.82 (+/-0.09) for meningioma, 0.83 (+/-0.12) for glioma and 0.64 (+/-0.10) for head and neck tumor patients' PBMCs.



a Visualization of 16 representative single-nuclei images of PBMCs of meningioma patients obtained from the study population prior to, during and at the end of proton therapy. **b** Visualization of the chrometric profiles of the PBMCs ($n = 7200$) of the meningioma, glioma and head and neck tumor population using a tSNE plot. Each point represents a single PBMC which is coloured accordingly to separate PBMCs from samples obtained prior to, during and at the end of proton therapy. **c** Average of the row-normalized confusion matrices corresponding to the performance of a RFC trained on

the task to distinguish between PBMCs of the different treatment timepoints given their chrometric profiles and evaluated in a leave-one-patient-out cross-validation scheme.

Conclusion

Collectively, we identified that PBMCs morphological and chromatin condensation features are potential liquid biomarkers for cancer type differentiation and to monitor the efficacy of proton therapy.

This work has been recently published (Challa et al. 2023).

Medical-Physics News

Possible association of dose rate and the development of late visual toxicity for patients with intracranial tumours treated with pencil beam scanned proton therapy

Background and purpose

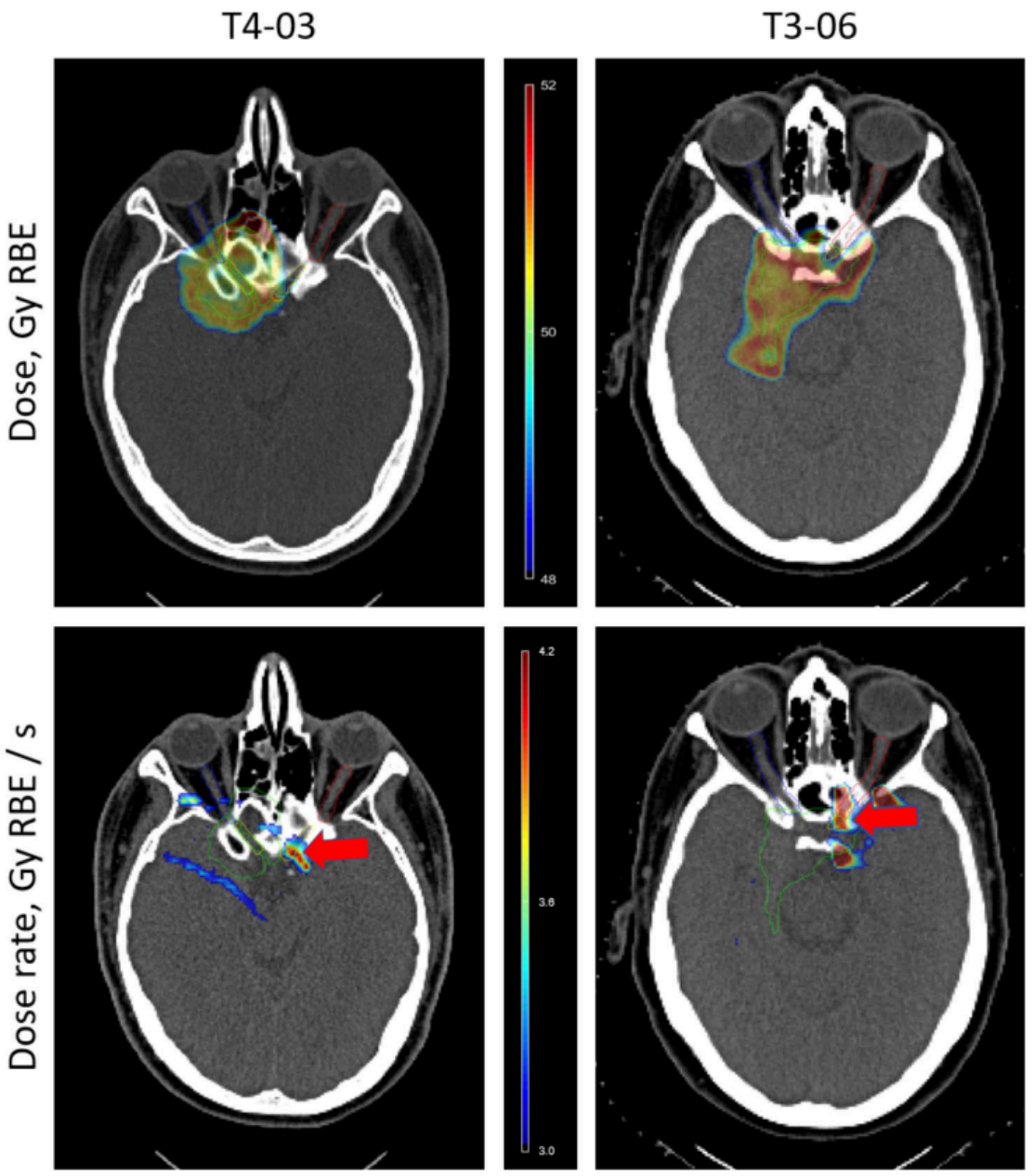
Rare but severe toxicities of the optic apparatus have been observed after treatment of intracranial tumours with proton therapy. Some adverse events have occurred at unusually low dose levels and are thus difficult to understand considering dose metrics only. When transitioning from double scattering to pencil beam scanning, little consideration was given to increased dose rates observed with the latter delivery paradigm. We explored if dose rate related metrics could provide additional predicting factors for the development of late visual toxicity.

Materials and Methods

Radiation-induced intracranial visual pathway lesions were delineated on MRI for all index cases. Voxel-wise maximum dose rate (MDR) was calculated for the two index patients with observed optic nerve toxicities (CTCAE grade 3 and 4), and 6 similar control cases. Additionally, linear energy transfer (LET) related dose enhancing metrics were investigated.

Results

For the two index cases, which developed toxicities at low dose levels (mean, 50 Gy_{RBE}), some dose was delivered at higher instantaneous dose rates. While optic structures of non-toxicity cases were exposed to dose rates of up to 1 to 3.2 Gy_{RBE}/s, the pre-chiasmatic optic nerves of the two toxicity cases were exposed to dose rates above 3.7 Gy_{RBE}/s. LET-related metrics were not substantially different between the index and non-toxicity cases.



Overlay of dose and voxel wise maximum dose rate (MDR) distributions on CT images of the two toxicity cases (T4-03 and T3-06). Dose rate distributions are shown for the fields contributing the highest MDR values. The maximum dose rate distribution above 3 GyRBE/s threshold is shown. High dose rate areas overlap with pre-chiasmatic left optic nerve areas, which developed radiation induced optic neuropathy (RION) on the follow-up MR images. The optic chiasm is shown in yellow, left and right optic nerves are shown in red and blue, respectively, CTV is shown in green, and area of RION is indicated with a red arrow. The dose and dose-rate colourwashes are displayed at the centre of the figure.

Conclusions

Our observations reveal large variations in instantaneous dose rates experienced by different volumes within our patient cohort, even when considering the same indications and beam arrangement. High dose rate regions are spatially overlapping with the radiation induced toxicity areas in the follow up images. At this point, it is not feasible to establish causality between exposure to high dose rates and the development of late optic apparatus toxicities due to the low incidence of injury.

This work has been recently published (Meijers et al. 2024).

Imprint

Editor
Dr. Ulrike Kliebsch

Chairman
Prof. Damien C. Weber

Chief Medical Physicist
Prof. Tony Lomax

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Contact

Paul Scherrer Institut
Center for Proton Therapy
CH-5232 Villigen PSI
protonentherapie@psi.ch
www.protontherapy.ch
Tel. +41 56 310 35 24
Fax +41 56 310 35 15