Relaxation-compensated CEST imaging of the APT predicts therapy response and progression-free survival in patients with glioma at baseline before radiotherapy at 3T

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INTRODUCTION: Chemical exchange saturation transfer (CEST) MRI can be applied to use endogenous compounds, such as peptides and semi-solid macromolecules, as imaging contrasts. However, CEST-contrasts are heavily dependent on the field strength and the applied metrics for contrast reconstruction from the Z-spectrum[1]. Therefore, the purpose of this study was to compare the predictive value of different CEST contrast on patients' therapy response in a larger clinical cohort of patients with glioma before radiotherapy.

METHODS: 81 patients with diffuse glioma prospectively underwent 3T CEST imaging of the APT and ssMT at baseline MRI before radiotherapy, applying Lorentzian-fit- and asymmetry-based reconstruction metrics first described by Zou et al. ($APTw_{asym}$)[2], Mehrabian et al. (MT_{const})[3] and Goerke et al. (APT_{MTRRex} and MT_{MTRRex})[4]. Whole tumor (WT) volumes were segmented on contrast-enhanced $T1w_{CE}$ and T2w-FLAIR images (Fig. 1). Therapy response at the first follow-up (1st FU) four to six weeks after the completion of radiotherapy, progression-free survival (PFS) and overall survival (OS) were assessed. Statistical testing included receiver-operating-characteristic (ROC) and Kaplan-Meier analyses.

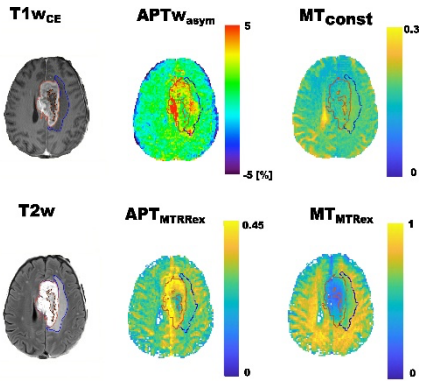

Fig.1: Exemplary $T1w_{CE}$, T2w-FLAIR, $APTw_{asym}$, MT_{const}, APT_{MTRRex} and MT_{MTRRex} contrast maps for a patient with progressive disease at the 1st FU.

RESULTS: ROC analyses for the association with therapy response at the 1st FU yielded area under the curve (AUC) values of 0.65 for the $APTw_{asym}$ (p=0.07), AUC=0.52 for the MT_{const} (p=0.82), AUC=0.72 for the APT_{MTRRex} (p=0.01***; Fig. 2) and AUC=0.55 for the MT_{MTRRex} (p=0.58). Kaplan-Meier analyses for the association with PFS yielded hazard ratios (HR) of 1.01 for the $APTw_{asym}$ (p=0.89), HR=1.54 for the MT_{const} (p=0.21), HR=2.75 for the APT_{MTRRex} (p<0.01***) and HR=1.44 for the MT_{MTRRex} (p=0.29). For OS HR were 1.50 for the $APTw_{asym}$ (p=0.30), HR=1.80 for the MT_{const} (p=0.14), HR=1.76 for the APT_{MTRRex} (p=0.15) and HR=1.21 for the MT_{MTRRex} (p=0.68).

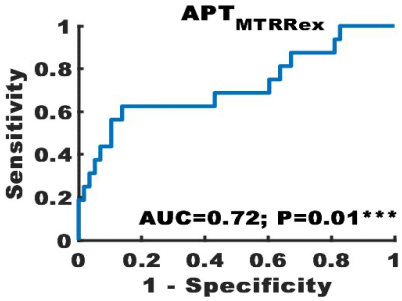

Fig.2: ROC for the association of the APT_{MTRRex} at baseline imaging with therapy response at the 1st FU.

DISCUSSION: In this study, an association of the APT_{MTRRex} with therapy response and PFS was observed, whilst none of the other contrasts demonstrated an association with the assessed clinical outcomes. These findings do not contradict the results from prior studies performed in the same cohort that demonstrated greater association of the $APTw_{asym}$ and MT_{const} with therapy response and survival in the early post-radiotherapy interval, since these studies were based on follow-up MRI instead of baseline scans at the time of initial diagnosis [5, 6]. Different CEST contrasts have varying contributions from other exchange-related effects, direct water saturation and T1, which are all influenced by edema and subcellular macromolecules in the extracellular space[1]. Therefore, differences in the prognostic values of CEST contrasts before and early after radiotherapy might be related to radiation-induced disruption of the blood-brain barrier and tissue necrosis. The missing association with OS in this study might be related to the relatively short mean follow-up time of 18.7 months (min. 0.6 and max. 64.9).

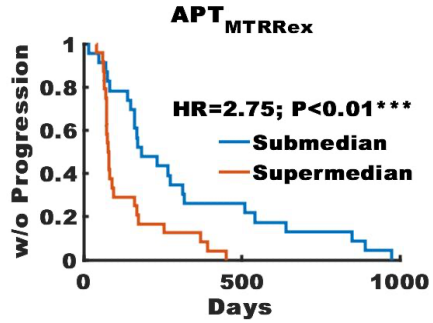

Fig.3: Kaplan-Meier curve for the association of the APT_{MTRRex} at baseline imaging with PFS.

CONCLUSION: The APT_{MTRRex} is a promising contrast in patients with glioma at baseline before radiotherapy. However, larger confirmatory studies (e.g. in multicenter trials) with longer follow-up intervals are warranted.

ACKNOWLEDGMENTS: This study was funded by a grant from the German Research Foundation (grant No. 445704496).

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