OSCILLATING GRADIENT DIFFUSION MRI AS A BIOMARKER FOR EARLY DETECTION OF RADIATION THERAPY RESPONSE

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Target audience: Researchers interested in the application of novel DWI methods to detect cancer response to radiation therapy.

Purpose: To investigate the ability of oscillating gradient diffusion (OGSE) methods to detect tumour response to radiation therapy in a mouse model and compare detection characteristics between OGSE and standard PGSE methods.

Introduction: DWI methods have been shown to be sensitive to cellular changes caused by cancer and its treatment. However, in radiation therapy treatment the ADC values assessed by standard DWI methods generally show a weak and relatively late increase, which limits their value as a biomarker for radiation treatment response [1]. Due to their ability to selectively assess changes in diffusion restrictions on a sub-cellular level, novel OGSE methods are promising as a biomarker for therapy response [2]. This study investigates the value of OGSE DWI in gaining information about the response of tumours (glioblastoma) to radiation therapy in a mouse model.

Methods: A cos-OGSE sequence, as described in [3] (OGSE-C1), was implemented on a BioSpec Avance III 94/20 system equipped with BGA-12S HP gradients (G_{max}=660mT/m, dG/dt_{max}=4570Tm/s) and 72-mm quad-RF-coil. Nude mice were inoculated with U87 glioblastoma cells and randomly divided into a control and radiation group (3 animals each). The latter was treated by full head irradiation with 2 Gy/24h for 15 consecutive days (overall 30Gy) using a self-contained X-ray system (X-RAD 320) from day 11 after tumour implantation. During the course of treatment MR Imaging was performed at 6 timepoints overall using the following schedule {day -2(0Gy), day 2(4Gy) , day 7(14Gy), day 9(18Gy), day 12(24Gy), day 36(30Gy)}. The MRI protocol consisted of an anatomical T2w TurboRARE scan, OGSE DWI and PGSE DWI. DWI parameters: FoV: 1.5x1.5cm, Matrix: 64x64, Resolution: 234x234 µm, Slice Thickness: 2mm + 0.2mm gap, 3 slices, TE = 70.2ms, TR= 2500ms, 1 b-value=600 s/mm^2 and 1 b=0 reference scan in 3 diffusion directions, 2 averages, scantime per DWI scan 19min, *OGSE:* f=200Hz, δ = 30ms, Δ = 34ms, effective diffusion time = 1.25ms, *PGSE*: Δ=20ms δ=5ms, effective diffusion time = 18ms. ADC maps were calculated for each oscillation frequency by mono-exponential fitting of $S = So \times \exp(-ADC \times b)$ and co-registered with the first timepoint using ITK. Cancer tissue was delineated by an elliptical ROI on the anatomical image of the first timepoint, which was transferred to all other timepoints for statistical analysis.

Results: Fig. 1 shows OGSE ADC maps and anatomical T2w scans from a typical animal in the radiation group. During the course of radiation, the average OGSE ADC in the tumour increased significantly (DADC(t) ~ 10-50%) in all treated animals. The ADC in control ROIs (control animals and contralateral ROIs in treated animals) remained unchanged. Fig. 2 shows the average ADC in a tumour ROI and a contralateral ROI for one irradiated and one control animal. The ADC in tumour ROIs generally exhibited a non-linear behaviour, showing a significant step increase between 14 Gy and 18 Gy of radiation dose. ADC values in OGSE tumour tissue ROIs in untreated animals and prior to treatment consistently showed significantly (~40%) higher average ADC values than normal tissue. Compared to the standard PGSE method, OGSE showed a significantly larger ADC difference between tumour and normal tissue, as well as a stronger and earlier ADC increase after irradiation (data not shown).

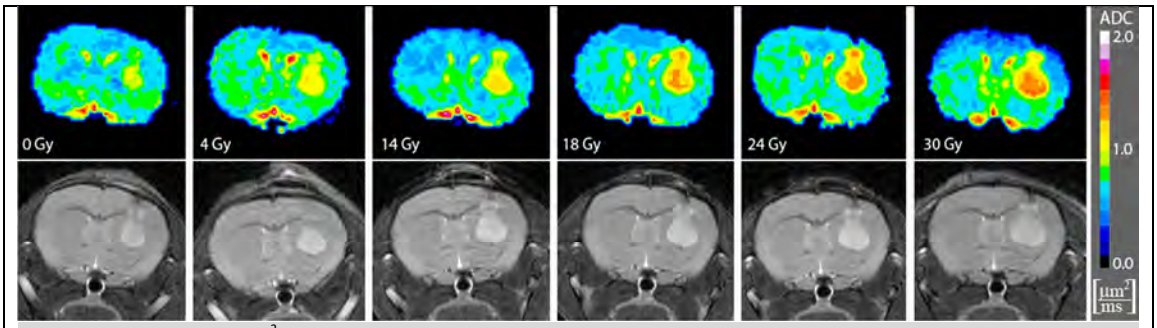

Fig. 1: OGSE ADC maps [µm^2/ms] of U87 inoculated mouse brains after consecutive irradiation treatment and corresponding anatomical T2w tumour images. Tumour ADC shows marked increase after 14 Gy radiation dose, no volume change in T2w

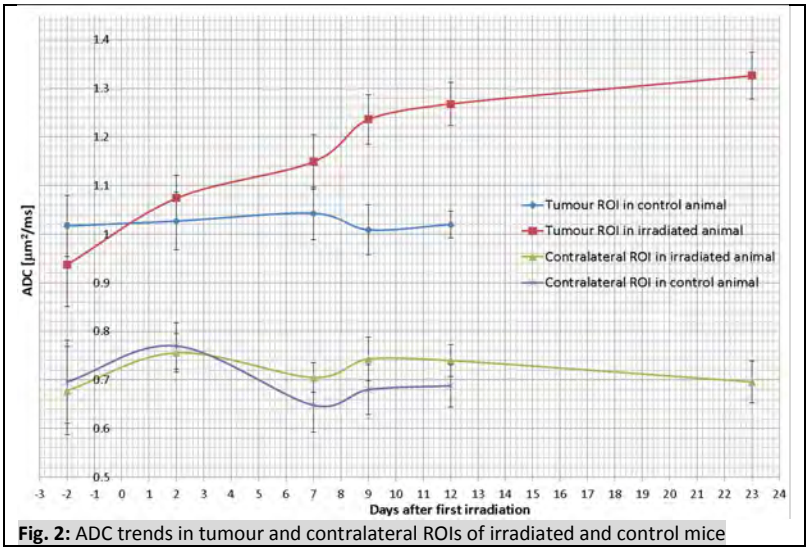

Fig. 2: ADC trends in tumour and contralateral ROIs of irradiated and control mice

Discussion and Conclusion: In our glioblastoma model, OGSE appears to be sensitive to early structural changes after radiation therapy. Here, OGSE proved more sensitive to these changes than standard PGSE. This makes the method a potentially valuable tool for assessing early response in single- or multi-fraction radiation treatment. Increased sensitivity can probably be attributed to the selectivity of OGSE to changes in sub-cellular restrictions. Further investigation and modelling is needed to explain this behaviour on a biophysical basis.

References: [1] Mardor et al.: *Journal of Clinical Oncology 21* (2003), [2] Does et al.: *Magnetic Resonance in Medicine 49* (2003), [3] Colvin et al.: *Magnetic Resonance Imaging 29* (2011)