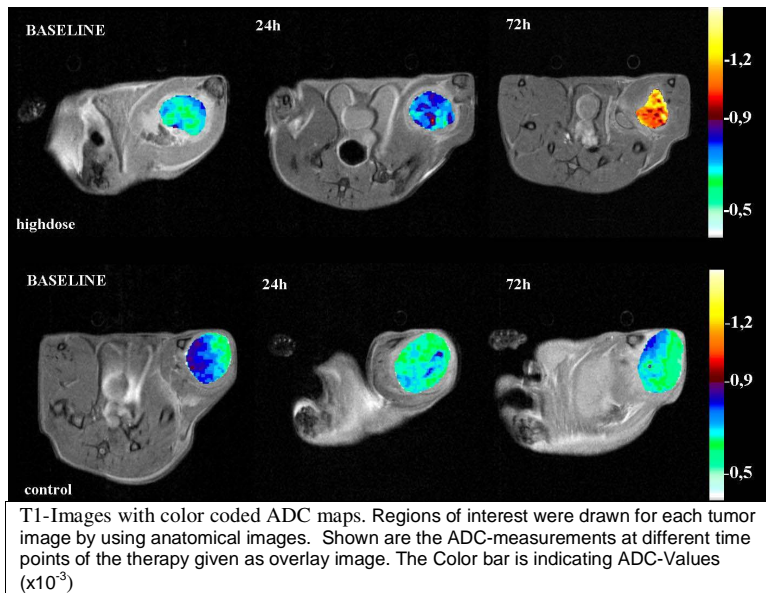# Diffusion weighted imaging as predictor of therapy response in animal model of Ewing-Sarcoma

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Introduction:

Traditionally assessment of the effectiveness of cancer therapy relies on comparison of tumour images acquired before and after therapeutic intervention by inspection of cross-section images to evaluate changes in tumour size. Additionally, Diffusion weighted imaging (DWI) has proved to be a valuable tool in monitoring the effect of chemotherapy in clinical as well as in preclinical studies [1], especially early assessment of treatment induced changes using DWI seems to be a promising tool in the evaluation of novel therapies [2]. Ewing's sarcoma (ES) is the second most common bone tumor in children and adolescents. High dose chemotherapy followed by autologous stem cell rescue has been demonstrated to be associated with higher cure rates than conventional chemotherapy in relapsed patients. The goal of this Study was to evaluate diffusion-weighted magnetic resonance (MR) imaging for monitoring dose dependent tumour response in mouse-xenograft model of Ewing's Sarcoma after administration of Treosulfan in different dosages

T1-Images with color coded ADC maps. Regions of interest were drawn for each tumor image by using anatomical images. Shown are the ADC-measurements at different time points of the therapy given as overlay image. The Color bar is indicating ADC-Values (x10^{-3})

Materials and Methods:

To compare the anti-tumor effect of high dose and low dose Treosulfan in mice, Ewing's sarcoma bearing NOD/SCID-mice were randomized to one single intraperitoneal treatment with either high-dose-Treosulfan (2500mg/kg), low-dose-Treosulfan (1500mg/kg) or vehicle (DMSO/20%). The experiments were done in mice either bearing tumors of Ewing's sarcoma cell line TC71 or CHP-100. 29 mice were imaged using a 9,4 Tesla animal Scanner (BioSpec 94/20, Bruker, Ettlingen, Germany). Mice were anesthetized under spontaneous breathing conditions using isoflurane. Heart rate and respiration rate were continuously monitored and gating was used to reduce moving and blood flow artefacts during the scan. The MRI–Protocol consisted of a localizer sequence, a T1-weighted RARE sequence to outline the Tumor and a T2-weighted RARE sequence to detect necrotic areas within the Tumor. (T1-RARE: TR/TE/FA 350ms/5.4ms/40°; T2-RARE: TR/TE/FA: 4200ms/36ms/180°, both sequences: FOV 30x30mm; matrix 256x256, in plane resolution of 117 x 117µm). Slice thickness and distance was 1mm. DW-MRI echo-planar sequence was performed with a wide range of b-values (b = 0, 100, 200, 400, 600, 800 and 1000 sec/mm2). The following parameters were used for this sequence: TR = 3000 ms, TE = 30 ms, matrix size of 128x128, 4 averages. Apparent diffusion coefficient (ADC) maps were calculated from the native diffusion images with the built-in software tools of the MRI scanner. The contrast of tumour tissue vs. muscle tissue depicted with T2-weighted images and diffusion-weighted images were evaluated by means of ROI-measurements. Altogether three ROIs were placed in solid parts of the tumour tissue as determined by the T2-measurements. The findings were also correlated using histopathology to determine the rate of microscopic necrosis in the tumor. Total tumor volumes were calculated from sets of contiguous images by summing products of area measurements and slice thickness using MIPAV, a freely available medical image processing software package from the National Institutes of Health (Bethesda, USA) Histopathology was performed to correlate ADC findings with Cellviability using HE staining.

Results and Discussion:

24h after baseline, no significant difference between the high-dose and the low-dose group was found, whereas we observed a marked increase in relative tumor volume in the Control group versus the treated groups (Fig. 1 and 2 Cellline CHP-100, given as relative change in percent compared to baseline). At 72h after baseline, the tumors in the control group had further grown significantly, measuring now more than 200% compared to the initial volume at baseline. Compared to the measurements at 24h after the administration of Treosulfan, the tumor volumes in the high dose group and in the low dose group were significantly different. The tumor volumes in the high dose group were reduced (92% vs. 111, 5% of the initial volume at baseline) whereas we observed an increase of the tumor volume in the low dose group (141% (72h) vs. 105, 7% (24h) of the initial volume at baseline. In our study, treatment response of Ewing's sarcoma to different dosages of Treosulfan was evaluated using diffusion weighted imaging We found a relationship between an increase in signal in ADC maps and the effectivity of the chemotherapy which could be detected before morphological changes indicated a difference in the tumor response. Moreover, because DWI is a non invasive technique that can easily be adapted to clinical routine, inclusion of DWI in phase 1 and 2 clinical trials would provide a powerful tool to detect treatment efficacy, which is especially valuable in dose escalation protocols.

Conclusion: In addition to basic relaxation-weighted MR imaging and volumetric measurements, diffusion-weighted MR imaging was used to discriminate between the effects of high or low dose therapy of Treosulfan monitoring the therapy inVivo.

References: 1. Schubert, M.I., et al., *Diffusion-weighted magnetic resonance imaging of treatment-associated changes in recurrent and residual medulloblastoma: preliminary observations in three children.* Acta Radiol, 2006. 47(10): p. 1100-4. **2**. Lee, K.C., et al., *An imaging biomarker of early treatment response in prostate cancer that has metastasized to the bone.* Cancer Res, 2007. 67(8): p. 3524-8.
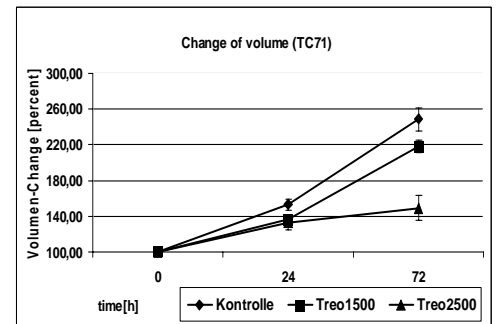
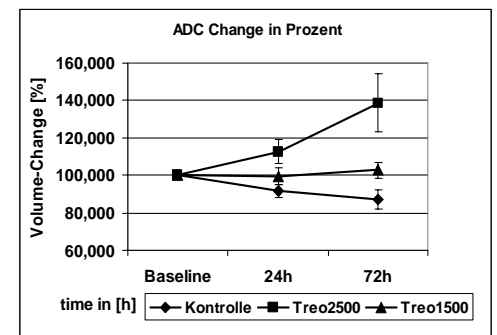Figure 1: Change of Tumor-Volume during Therapy (Cellline, CHP-100)

Figure 1: Change of ADC during Therapy (Cellline, CHP-100)