Rotating Frame Relaxation Measurements in Prostate Cancer Model

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Introduction Rotating frame relaxations ($T_{1\rho}$ and Relaxation Along a Fictitious Field (RAFF) T_{RAFFn}[1,2]) have shown to be quantitative MRI markers to follow up disease progression, including brain and myocardial ischemia[3,4] and to follow up response to therapy[5]. T_{RAFF2} has been shown excellent correlation with cell density in rat glioma model, which makes it potential biomarker to follow up cancer therapy outcome. In this study, rotating frame relaxation times T_{RAFF2}, T_{RAFF4}, $T_{1\rho,CW}$, $T_{1\rho,adiab}$ and $T_{2\rho,adiab}$ were measured in subcutaneous prostate cancer (PC3-RFP) tumors in several time points.

Materials and Methods Prostate cancer cells expressing red fluorescence protein (PC3-RFP, Anticancer Inc., USA) were implanted in right hind limbs of 11 nude mice. The tumor growth was monitored for three weeks using optical imaging and MRI. The mice were anesthetized with 1.5 % isoflurane in ($70\%N_2$:$30\%O_2$) and imaged once a week up to 3 weeks after the implantation first at IVIS Illumina and then during two following days at 7T Bruker Pharmascan using volume transmitter and surface receiver coil. The parameters for fluorescence based optical imaging were the following: Exposure time: auto / 1 s, Binning: medium, F/Stop: 2, Excitation filter: 535 and 465 (background) and Emission filter: DsRed. The MRI scans consisted of T_{RAFF2} and T_{RAFF4} (RAFF2 or 4-pulses[1] pulse train length of 0 - 36 ms, $\gamma B_1/(2\pi)$ = 1250 Hz for RAFF2 and 648 Hz for RAFF4), $T_{1\rho,CW}$ ([2]spin-lock time=0 - 45.4 ms, $\gamma B_1/(2\pi)$=1250 Hz), $T_{1\rho,adiab}$ (train of AFP pulses, train length 18 -72 ms), $T_{2\rho,adiab}$ (3 ms AHP excitation pulse before AFP pulse trains as with $T_{1\rho,adiab}$, then 3 ms AHP back pulse), and for comparison T_2 (adiabatic Hahn double echo preparation with TE = 8 - 22 ms), and T_1 (saturation recovery with TR = 200 - 5000 ms). We monitored also B_1 (altering hard pulse lengths between 0.2 and 1.6 ms). All data were acquired from one axial slice placed on the largest tumor cross section. Fast spin echo sequence (TR = 4 s, effective TE = 8 ms, ETL = 8, FOV = 30x15 mm^2, matrix size 256x128, and slice thickness of 1 mm) with fat suppression was used as readout imaging sequence. In addition, T_2 weighted anatomical images covering the whole tumor were obtained for assessing tumor volumes (TR = 2500 ms, effTE = 33 ms, ETL = 8, matrix size 256x256, FOV = 30x30 cm^2, 15 slices). ROIs representing the tumor and skeletal muscle were hand drawn for further analysis based on T_2 weighted images.

Results and Discussion

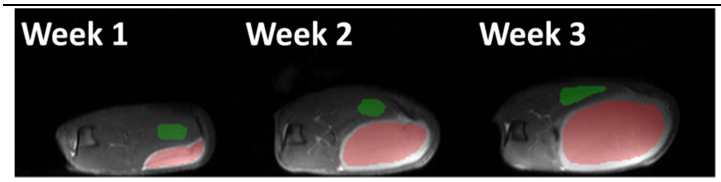

Figure 1. Representative illustration of tumor growth in T_2-weighted images from representative single mouse showing the tumor size in three time points. Skeletal muscle (green) and tumor tissue (red).

Table 1. Relaxation times for tumor and skeletal muscle in three time points (mean±SD [ms]).

	Week 1		Week 2		Week 3	
Parameter	Tumor	Muscle	Tumor	Muscle	Tumor	Muscle
T_{RAFF2}	122±18	48±2	112±4	48±2	111±3	49±3
T_{RAFF4}	403±36	181±9	397±27	185±10	402±16	180±13
$T_{1\rho,CW}$	84±15	32±2	74±2	32±2	75±2	33±3
$T_{1\rho,adiab}$	27±0.2	28±0.5	27±0.2	28±1	27±0.2	29±1
$T_{2\rho,adiab}$	69±14	29±2	64±2	29±2	64±2	30±2
T_2	72±21	35±2	72±6	36±2	73±3	37±3
T_1	2461±157	2084±38	2523±52	2129±46	2487±40	2095±7

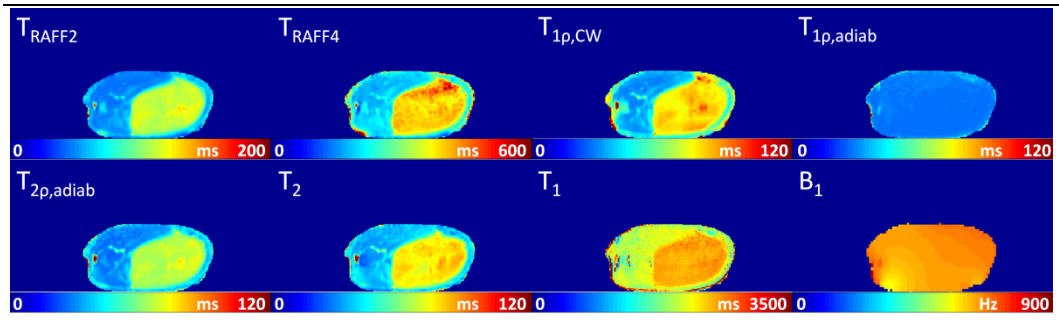

Figure 2. Rotating frame relaxation times T_{RAFF2}, T_{RAFF4}, $T_{1\rho,CW}$, $T_{1\rho,adiab}$ and $T_{2\rho,adiab}$, conventional relaxation times T_1, T_2 and for control B_1 maps shown in the same mouse as in **Fig.1** three weeks after tumor cell implantation.

Tumor growth from week 1 to 3 is well visualized on the T_2 weighted images (**Fig. 1**). The averages of relaxation times over the tumor area in single slice was significantly longer compared to the muscle area with all methods used, except with $T_{1\rho,adiab}$ (**Fig. 2, Table 1**). There was a significant decrease from week 1 to weeks 2 and 3 in $T_{1\rho,CW}$ and T_{RAFF2} values (1-way ANOVA, $p<0.05$). Other relaxation times did not change significantly during tumor growth. Most likely decrease is related to lower cell density of the tumors in the first time point, especially in small tumors. The present data serve as baseline measurements of MRI relaxation time constants for upcoming therapy follow up study. Anticancer therapy induced cell death in the tumors is assumed to be shown as longer relaxation times, opposite to found decrease in $T_{1\rho,CW}$ and T_{RAFF2}.

References 1. Liimatainen T et al. MRM 2010, 2. Liimatainen T et al. ISMRM 2012, 3. Gröhn et al. MRM 1999, 4. Musthafa HNS et al. MRM 2012, 5. Hakumäki et al. Cancer Gene Ther 2002.

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