Comparison of $T_{1\rho}$ and diffusion response following chemotherapy in mouse EL4 tumors at 9.4 T

M. I. Kettunen[1], D-E. Hu[1], K. M. Brindle[1]
[1]Department of Biochemistry, University of Cambridge, Cambridge, United Kingdom

Introduction

Diffusion MRI provides an early and apparently universal marker of therapy-induced cell death in tumors [1]. A potential limitation of diffusion MRI is its sensitivity to motion, due to the large diffusion gradients required. Spin-lock ($T_{1\rho}$) MRI has been shown recently to detect the early effects of therapy in rat BT4C gliomas and mouse RIF-4 tumors [2-4]. In contrast to diffusion, $T_{1\rho}$ MRI is less sensitive to motion and might therefore be a useful alternative to diffusion measurements in situations where diffusion MRI could be challenging. To assess this, we investigated the utility of spin-lock and diffusion MRI to detect response to chemotherapy in mouse EL4 lymphomas.

Methods

Female C57BL/6 mice (n=19) were injected subcutaneously with $5x10^6$ EL-4 cells. Tumor cell death was induced with a single i.p injection of etoposide (34 mg/kg) and cyclophosphamide (50 mg/kg) once the tumors had grown to a size of ~1 cm^3. For MRI experiments, animals were anesthetized with intraperitoneal injection of Hypnorm/Hypnovel/dextrose-saline(4%:0.18%) in a 5:4:31 ratio (10 ml/kg body weight). MRI was performed before treatment and daily after treatment until the tumors had disappeared.

All MRI experiments were performed at 9.4 T using a quadrature volume coil. The ADC was measured using a navigator-echoed spin-echo pulse sequence (TR = 1.5 s, TE = 26 ms, with four b-values between 5–1017 s/mm^2). $T_{1\rho}$ was measured using adiabatic spin-lock pulses (spin-lock field 0.2 G, 5 spin-lock times between 10 and 90 ms) in a front of FLASH imaging sequence (TR = 5.5 ms, TE = 2.1 ms, 10 s delay between images). T_1 and T_2 were also measured using inversion recovery-FLASH (10 inversion times between 50 ms and 10 s) and spin-echo (four TEs between 10 and 80 ms) pulse sequences, respectively. Regions of interest within the tumors were analysed to produce parameter histograms and the mean ± SD for the $T_{1\rho}$ and ADC values.

Results

Before treatment, $T_{1\rho}$ provided a clear contrast between normal and tumor tissue (Fig 1). Following treatment, the ADC increased by 20%, however the mean $T_{1\rho}$ value did not change significantly during the observation period (Table 1). Furthermore, histogram analysis did not reveal any changes in the distribution of $T_{1\rho}$ values after treatment (Fig 2).

Discussion

The current results suggest that while spin-lock MRI shows strong contrast between tumor and normal tissue, it may not always be sensitive to treatment response following chemotherapy. It may not, therefore, be a general alternative to diffusion measurements and its applicability needs to be tested further.

The differences between these current observations and the $T_{1\rho}$ therapy-studies reported previously [2-4] could be due to several factors. In vivo $T_{1\rho}$ is known to show field-dependency as a function of both the B_1-field [5] and the main magnetic field, B_0 [6,7]. Previous studies of therapy response have been performed at B_0 fields of 4.7 T or lower, using B_1-fields in the range 0.1 to 2 G, while the current study was performed at 9.4 T using a B_1 field of 0.2 G. This could alter the sensitivity of $T_{1\rho}$ and needs to be assessed. Alternatively it is possible that $T_{1\rho}$ responses vary depending on the tumor model. For example, in the current model the tumor start to shrink early on following treatment. From this point of view, it is interesting to note that the ADC increased after the therapy showing it is more sensitive to tissue changes related to cell death than other studied MR parameters.

References

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Table 1. MR parameters before and after treatment

	ADC ($*10^{-3}$ mm^2/s)	$T_{1\rho}$ (ms)	T_2 (ms)	T_1 (ms)
Pre-treatment (n=12)	49 ± 4	53 ± 2	37 ± 1	2480 ± 50
Day 1 (n=10)	62 ± 4**	53 ± 1	33 ± 2**	2450 ± 70
Day 2 (n=7)	61 ± 10**	54 ± 2	35 ± 4	2290 ± 110**
Day 3 (n=6)	72 ± 14**	51 ± 2	29 ± 2	2070 ± 110**

** p<0.01 (Student's t-test corrected for multiple comparisons)

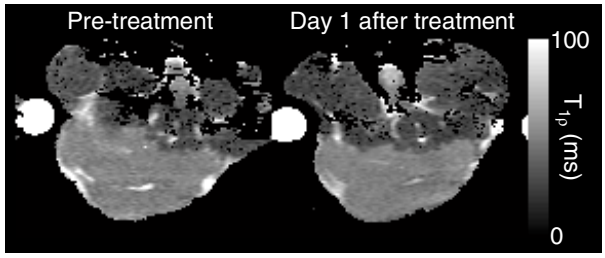

Figure 1. $T_{1\rho}$-maps before treatment and one day after chemotherapy.

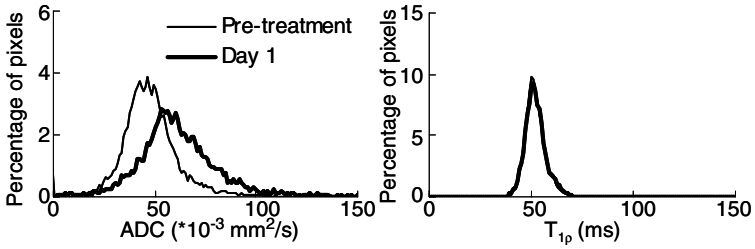

Figure 2. Parameter histograms for ADC and $T_{1\rho}$ before and one day after the treatment. Note that no change in $T_{1\rho}$ was observed following treatment (the histograms overlap) while ADC distribution shifted towards higher values.